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Dihydrolipoamide Dehydrogenase (DLD) Deficiency: A Case Report

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Case Report

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Abstract

Background: Dihydrolipoamide dehydrogenase deficiency (DLDD) is a rare autosomal-recessive mitochondrial disorder that may present as episodic hepatic crises with full recovery between attacks, leading to delayed diagnosis.
Case presentation: A 7-year-old boy from Jordan had recurrent monthly episodes of abdominal pain and vomiting with intermittent jaundice. Episodes were associated with ketotic hypoglycemia, transaminitis, and coagulopathy; liver biopsy showed mild steatohepatitis with early fibrosis. Whole-exome sequencing identified a homozygous DLD c.685G>T (p. Gly229Cys) variant, confirming hepatic-predominant DLDD. Management started with dextrose-containing intravenous fluids and supportive care and the patient remains well between episodes with hepatology follow-up.

In conclusion, This report expands the geographic representation of hepatic-predominant DLDD and emphasizes that recurrent vomiting/abdominal pain with ketotic hypoglycemia, episodic liver dysfunction, and recovery between crises should prompt early molecular testing—particularly in consanguineous families—to reduce diagnostic delay and avoid unnecessary invasive procedures.

Introduction

Dihydrolipoamide dehydrogenase deficiency (DLDD) is a rare inherited metabolic disorder transmitted in an autosomal recessive pattern, characterized by remarkable clinical heterogeneity, variable age of onset, and a wide range of disease severity among affected individuals (1). Despite its rarity, DLDD represents a clinically significant condition due to its potentially life-threatening metabolic decompensations and lack of a definitive curative therapy (1, 2).

The disorder results from pathogenic variants in the DLD gene located on chromosome 7q31.1, which encodes the E3 subunit of several mitochondrial multienzyme complexes. These include the pyruvate dehydrogenase complex (PDH), α-ketoglutarate dehydrogenase complex (KGDH), branched-chain α-keto acid dehydrogenase complex (BCKDH), as well as the glycine cleavage system (2, 3). Consequently, DLD deficiency disrupts multiple critical metabolic pathways, leading to impaired oxidative metabolism and energy production.

Clinically, dihydrolipoamide dehydrogenase deficiency is classically categorized into three major phenotypic variants. The early-onset neurologic phenotype typically presents in infancy with hypotonia, failure to thrive, recurrent hypoglycemia, progressive encephalopathy, and severe intermittent lactic acidosis, often associated with high morbidity and mortality. A second, hepatic-predominant phenotype is characterized by episodic liver dysfunction with vomiting, abdominal pain, ketotic hypoglycemia, transaminitis, and coagulopathy, frequently triggered by catabolic stress and followed by near-complete recovery between episodes. Finally, a myopathic or adult-onset phenotype has been described, presenting later in life with exercise intolerance, myopathy, or isolated hepatic involvement, sometimes without significant neurological manifestations. Considerable overlap and intra-familial variability exist among these phenotypes, underscoring the complexity of genotype–phenotype correlations in DLD deficiency (3, 5).

Isolated liver involvement has been reported, with presentations ranging from the neonatal period to as late as the third decade of life. Hepatic manifestations are frequently preceded by nonspecific symptoms such as nausea and vomiting and are often accompanied by encephalopathy (2, 3). Acute metabolic crises are commonly associated with laboratory abnormalities, including elevated serum lactate, increased hepatic transaminases, and hyperammonemia (5). Metabolic decompensations are commonly precipitated by catabolic stressors such as fever, infection, or fasting, which overwhelm compromised mitochondrial energy metabolism and may lead to lactic acidosis and organ dysfunction (5, 8, 12).

Genetically, both homozygous and compound heterozygous pathogenic variants in the DLD gene have been reported (3). Early molecular studies identified missense mutations such as K37E and P453L, as well as insertion mutations including InsA105, further establishing the genetic diversity underlying the disease (6). To date, Recent larger series have expanded the published experience in DLD deficiency; notably, the largest report focused on the hepatic phenotype described 52 patients, detailing laboratory patterns and therapeutic approaches (8).

From an epidemiological perspective, the highest carrier frequency has been observed in the Ashkenazi Jewish population, estimated at 1:94 to 1:110, with a disease prevalence ranging from 1:35,000 to 1:48,000 (4). In contrast, DLDD appears to be considerably less prevalent in other populations, including Mediterranean populations, although precise incidence rates remain unknown (4).

Currently, no definitive curative treatment exists for DLDD. Management primarily focuses on preventing acute metabolic decompensation through dietary modifications and supplementation with vitamins and cofactors, such as thiamine, riboflavin, and lipoic acid, with variable clinical responses reported (1, 2). Recent case reports have highlighted potential benefits of targeted supplementation in selected patients, underscoring the importance of early recognition and individualized management strategies (1).

Given the rarity of DLDD and its wide phenotypic variability, reporting additional pediatric cases is essential to enhance understanding of its clinical presentation, diagnostic challenges, and therapeutic outcomes. In this context, our case report discusses a pediatric patient from Jordan presenting with the hepatic form of DLDD, contributing valuable insight into disease manifestation in underreported populations.

Case Presentation

Table 1 should appear here: Liver Function Tests and Random Blood Glucose.

Table 2 should appear here: Arterial Blood Gas and Metabolic Tests.

Table 3 should appear here: Genetic Analysis Results.

A 7-year-old boy was admitted to a tertiary hospital with several days of abdominal pain, recurrent non-projectile vomiting and jaundice. He was born to healthy consanguineous parents and had two healthy siblings. His development was normal, with no reported complications during the neonatal or infantile periods. There was no family history of recurrent vomiting or other significant medical conditions.

The patient had a history of recurrent attacks requiring frequent hospital admissions. Symptoms initially began at the age of six years and were characterized by recurrent vomiting, abdominal pain, and occasional fever, most of these attacks were attributed to URTI like tonsillitis or otitis media and treated accordingly. During some of these episodes (Where the LFT was done) the patient noted to have variable degree of mild to moderate liver enzyme elevations. However, given that the liver enzyme returned back to normal between episodes it was assumed to be caused by the infection. Till one episode in which the patient had clinically evident jaundice and laboratory investigations revealed markedly elevated liver enzymes (multiple thousands). Consequently, he was referred to a tertiary care center for further evaluation.

- An extensive diagnostic workup was conducted to investigate the recurrent episodes and liver enzyme elevations, including autoimmune, metabolic (including Wilson's disease), and infectious studies, all of which were unremarkable. Imaging studies were also performed and came back normal. First liver biopsy done and was normal, LFT return backed to normal. Subsequently the patient presented again with the same picture, initial investigations this time showed mild metabolic acidosis, mild lactic acidosis, hypoglycemia and ketone in urine(up to + 3), Laboratory findings during acute episodes demonstrated variable elevations in liver enzymes, coagulopathy, hypoglycemia, and metabolic abnormalities, as summarized in (Tables 1 and 2) a second liver biopsy done 6th months later and biopsy demonstrated mildly active steatohepatitis with mild macrovesicular steatosis (10–15%) and stage 1/4 fibrosis.
- At the age of seven years, whole exome sequencing (WES) revealed a homozygous pathogenic variant in the DLD gene, confirming the diagnosis of dihydrolipoamide dehydrogenase deficiency(Table3).
- Over time, the patient experienced recurrent hospitalizations, typically every 6–8 weeks, each lasting approximately one week. Between episodes, he returned to his baseline state of health. Supportive management included intravenous dextrose-containing fluids and antibiotics when upper respiratory tract infection was suspected. The patient was also strictly advised to avoid fasting, avoid foods high in branched amino acids (BCAAs) and encourage high fat- low carbohydrate diet, and was maintained on regular vitamin supplementation (Riboflavin B2, thiamine B1 and levocarnitine)

Table 1
Liver Function Tests and Random Blood Glucose

Test	Result Range during the attacks	Reference Range.
AST	50–3627 U/L	10–50 U/L
ALT	55 – 2941 U/L	10–50 U/L
Prothrombin Time (PT)	14.6–26.5 sec	11–14 sec
Activated PTT	25.9–40 sec	21.5–31.9 sec
Random Blood Glucose	2.4-6.0 mmol/L	≥ 3.9 mmol/L

Table 2
Arterial Blood Gas and Metabolic Tests

Test	Result Range during the attacks	Reference Range
pH	7.35–7.41	7.35–7.45
PCO_2	28.9–46.5 mmHg	35–45 mmHg
HCO_3	15.3–25.6 mmol/L	22–26 mmol/L
PO_2	30.3–110.5 mmHg	80–100 mmHg
O_2 Saturation	54.8–77.7%	95–100%
Plasma Lactate	3.3–3.9 mmol/L	0.5–2.2 mmol/L
Alpha-Amylase	118–135 U/L	30–110 U/L
Ammonia	35–65 µmol/L	15–45 µmol/L

Table 3
Genetic Analysis Results (Whole Exome Sequencing)

Gene	Variant	Zygosity	Clinical Significance
DLD	Pathogenic variant (specific nucleotide and amino acid change)	Homozygous	Consistent with autosomal recessive dihydrolipoamide dehydrogenase deficiency

Table 4
Timeline

Date / period	Milestone	Key details
Apr 2024	First symptomatic episode + initial hospitalization	Scleral icterus + abdominal pain + high-grade fever (39–40°C) + recurrent vomiting/anorexia; hospitalized ~ 15 days; hepatitis panel negative; abdominal US showed splenomegaly → referred for further evaluation.
2024 (monthly; ~1 week/episode)	Recurrent attacks	Monthly episodes with consistent abdominal pain + vomiting; sometimes preceded by tonsillitis; repeated ED visits with supportive management (IV fluids/analgesics). Extensive viral, autoimmune, metabolic work up was done In one episode Hypoglycemia (RBS 2.4 mmol/L), ketonuria (+ 3), elevated ALP/AST/ALT with mildly elevated direct bilirubin, and prolonged PT/PTT documented .
Pre-molecular diagnosis (date not specified)	Liver biopsy #1 and #2	Biopsy #1 normal; biopsy #2: mildly active steatohepatitis + macrovesicular steatosis (10–15%) + stage 1/4 fibrosis.
04 Feb 2025	WES sample collected	EDTA blood collected for clinical exome
11 Mar 2025	WES report issued	Homozygous pathogenic DLD variant NM_000108.5:c.685G > T (p.Gly229Cys); consistent with DLD/E3 deficiency (OMIM 246900); no additional clinically significant variants reported
Follow-up period	Subsequent episodes	Episodes recur every 6–8 weeks

Discussion

Dihydrolipoamide dehydrogenase (DLD) deficiency is a rare autosomal recessive mitochondrial disorder caused by pathogenic variants in the DLD gene, which encodes the E3 subunit shared by several mitochondrial multienzyme complexes, including the pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (α-KGDH), and branched-chain α-ketoacid dehydrogenase (BCKDH) complexes (2, 3). Owing to the central role of this enzyme in mitochondrial oxidative metabolism, DLD deficiency results in a broad and heterogeneous clinical spectrum involving the liver, central nervous system, and skeletal muscle (3). Multi-omics analysis of fibroblasts from DLD-deficient patients reveals disrupted mitochondrial metabolism, including altered one-carbon metabolism and serine catabolism, underscoring profound bioenergetic dysfunction beyond standard enzyme deficiency (15).

In the present report, we describe a child with a predominantly hepatic phenotype, characterized by recurrent episodes of abdominal pain, vomiting, hypoglycemia, ketonuria, intermittent transaminitis, and coagulopathy, with complete clinical recovery between episodes and preserved neurodevelopment. Preserved neurodevelopment in this patient is consistent with previously described hepatic-predominant forms of DLD deficiency, in which neurological involvement may be minimal or absent between metabolic decompensations. To the best of our knowledge, this is among the first reported pediatric cases from Jordan, expanding the geographic and ethnic spectrum of this disorder.

Hepatic involvement is a well-recognized manifestation of DLD deficiency and may range from episodic elevations of liver enzymes to acute liver failure, frequently precipitated by metabolic stressors such as infections, fasting, or other catabolic states (5, 7). Several cohort studies have demonstrated that patients with the hepatic phenotype often experience recurrent, self-limited episodes of liver dysfunction with normalization of biochemical parameters between crises, a clinical course that closely mirrors the presentation observed in our patient (5, 8). Interestingly, recent cohort data indicate that mean hepatic transaminase activity levels in individuals with hepatic DLD deficiency (DLDD) are often relatively low when compared with cohorts of patients presenting with acute liver failure of unknown etiology, suggesting a distinct pattern of hepatocellular injury that may contribute to diagnostic uncertainty during acute episodes (8).

Genotype–phenotype correlations in DLD deficiency remain complex and incompletely understood. Certain pathogenic DLD variants have been associated more frequently with hepatic-predominant phenotypes, particularly among Middle Eastern and Ashkenazi Jewish populations (4, 5). The p.Gly229Cys (p.G229C) variant appears to be the most frequently reported pathogenic DLD mutation in the Middle East and is commonly associated with a hepatic-predominant phenotype (9). Notably, individuals homozygous for the p.Gly229Cys (p.G229C) variant may demonstrate a remarkably wide phenotypic spectrum, ranging from asymptomatic courses to recurrent metabolic decompensations characterized by lactic acidosis and hypoglycemia, even in the absence of overt liver involvement (8). This variability highlights the incomplete penetrance and variable expressivity associated with this mutation and underscores the limitations of predicting clinical severity based solely on genotype (8). Our patient is homozygous for the p.Gly229Cys (p.G229C) variant, which is strongly associated with the hepatic phenotype in reported cohorts, supporting previously reported genotype–phenotype associations (3, 5).

The diagnosis of DLD deficiency is frequently delayed due to its episodic nature and nonspecific clinical manifestations. DLD deficiency can present with a range of manifestations including acute metabolic acidosis, hepatomegaly, hyperammonemia, or normal lactate between crises, making diagnosis challenging due to overlap with other mitochondrial and metabolic disorders (14). Many affected individuals undergo prolonged diagnostic evaluations, including repeated metabolic investigations and invasive procedures such as liver biopsy, prior to the establishment of a definitive molecular diagnosis (2, 5). In our case, the patient experienced multiple hospital admissions and underwent liver biopsies as part of an extensive diagnostic evaluation before whole-exome sequencing confirmed the diagnosis. Formal diagnostic criteria for DLD deficiency have not been established, and diagnosis relies on supportive clinical features and molecular testing, with enzyme assay or fibroblast DLD activity being supportive but of limited utility compared with genetic testing (12). Histopathological findings such as steatohepatitis and early fibrosis, as observed in our patient, have been described in hepatic forms of DLD deficiency and other mitochondrial hepatopathies; however, these findings remain nonspecific and should be interpreted within the appropriate clinical and biochemical context (6, 8). Although elevations in plasma alanine and glutamine and increased urinary lactate excretion on organic acid analysis are frequently observed

in DLD deficiency, these findings are nonspecific. Consequently, conventional biochemical investigations do not provide a single reliable or disease-specific biomarker for the diagnosis of DLDD (11).

The differential diagnosis of recurrent hepatic dysfunction with vomiting and hypoglycemia in childhood is broad and includes viral or autoimmune hepatitis, fatty acid oxidation disorders, and other inborn errors of metabolism. While isolated dysfunction of the BCKDH complex is characteristic of maple syrup urine disease, DLD deficiency uniquely affects multiple mitochondrial enzyme systems, resulting in combined hepatic dysfunction, lactic acidosis, and hypoglycemia. This constellation of features, along with the recurrent nature of hepatic involvement and complete recovery between episodes, is well documented in cohorts of patients with hepatic DLDD and helps distinguish it from other metabolic conditions (5, 8).

Management of DLD deficiency remains primarily supportive and preventive. Key strategies include avoidance of prolonged fasting, early recognition of metabolic decompensation, and prompt correction of metabolic derangements (1, 5). During acute metabolic crises, administration of high-dose intravenous glucose is strongly recommended, as it effectively reverses the catabolic state, suppresses endogenous energy mobilization, and leads to rapid normalization of lactic acidemia, representing a cornerstone of emergency management in DLDD (8). Supplementation with cofactors such as thiamine, riboflavin, and lipoic acid has been reported to provide clinical benefit in selected patients like our patient, although therapeutic responses remain variable (1, 2). Long-term prognosis largely depends on the frequency and severity of metabolic decompensations, with hepatic-predominant forms generally associated with more favorable neurodevelopmental outcomes when recognized and managed early (5). In patients with DLD-E3 deficiency, partial ketogenic diet has been associated with improved survival compared with a historical cohort, although no significant improvement in quality of life was observed, highlighting both potential benefit and limitation of this approach (13).

Published hepatic-predominant DLD deficiency cases commonly feature stress-triggered episodes (infection/fasting/vomiting) with vomiting/abdominal pain, hypoglycemia with ketosis, transient transaminitis/coagulopathy, and variable lactate and ammonia elevations, followed by near-complete intercritical recovery—patterns that can mimic common hepatology differentials and contribute to diagnostic delay (5, 7, 8, 12). Table 5 summarizes representative hepatic-involvement reports/series and shows that our patient's presentation and p.Gly229Cys genotype fit within this spectrum, while also reflecting the practical management approach emphasized across reports: rapid glucose to reverse catabolism during crises, fasting avoidance, and individualized supplementation/nutritional planning with metabolic follow-up (1, 4, 5, 7, 8, 12, 13). The sequence of episodes, investigations (including repeated biopsies), and eventual molecular confirmation in our patient is outlined in Table 4, reinforcing the value of earlier genomic testing in similar recurrent hepatic crises—particularly in consanguineous settings (8, 10, 12).

Table 5
Published DLD deficiency reports/series with hepatic involvement compared with the present case.

Study (Ref)	Design / Region	N / Age	Genotype	Phenotype category	Key hepatic presentation	Key management	Outcome/Not
Present case	Case report / Jordan	1 / 7 y (male)	DLD: p.Gly229Cys, homozygous	Episodic hepatic phenotype	Recurrent vomiting and abdominal pain; ketotic hypoglycemia; transaminitis; coagulopathy	IV dextrose-containing fluids and supportive care; vitamin K; electrolyte correction; empiric antibiotics as indicated	Clinical recovery between attacks; ongoing hepatology follow-up and fibrosis surveillance
Aloulou et al. (2)	Case reports / Tunisia	2 / 11 d (F) and 9 y (M)	DLD: c.685G > T (p.Gly229Cys), homozygous	Episodic hepatic phenotype	Recurrent vomiting with liver dysfunction; episodes may include acute liver failure (coagulopathy) and/or encephalopathy; often triggered by fasting/catabolic stress	Acute: IV glucose and supportive metabolic crisis care; Prevention: fasting avoidance and individualized supplementation/support as reported.	Both survived one with recurrent episodes over years, the oth reported episode-free follow-up with preventive strategy
Brassier et al. (7)	Family case series / France (Algerian consanguineous family)	5 affected in one family: 2 neonatal deaths; 3 adults with crises since infancy	DLD: c.685G > T (p.Gly229Cys), homozygous	Recurrent acute liver failure / Reye-like phenotype	Recurrent episodes since infancy with hypoglycemia, vomiting, abdominal pain and liver failure; may mimic Reye-like syndrome and be overlooked	Supportive crisis management; diagnosis may require enzyme/genetic testing despite "non-suggestive" routine metabolic profiles	Survivors had recurrent cris into adulthoo emphasizes that classic metabolic markers can b absent or sub
Hammann et al. (8)	Multicenter cohort (hepatic form focus)	52 patients	Predominantly p.Gly229Cys (p.G229C); additional genotypes reported.	Hepatic form / episodic hepatic phenotype	Recurrent metabolic decompensations with elevated transaminases; may progress to acute liver failure; commonly triggered by febrile infections and/or fasting; GI symptoms (nausea/vomiting, abdominal pain) common	Supportive + preventive approach across cohort (avoid fasting; rapid carbohydrate/IV glucose during illness; crisis management per metabolic protocols)	Outcome vari across the cohort; genotype-stratified outcomes an complication patterns were reported.
El Masri et al. (9)	Case report / Lebanon	1 / pediatric	Not specified	Severe hepatic crisis with encephalopathy	Acute liver failure with hyperammonemia and encephalopathy during crisis	Supportive and metabolic management as reported in case	Illustrates severe hepati crisis with neurologic involvement; highlights diagnostic challenge in non-endemic settings
Pode-Shakked et al. (5)	Natural history cohort / Israel	53 patients (35 families); onset from birth to 10 y	Common variants include p.Gly229Cys and p.Ile353Thr (among others)	Natural history cohort (mixed phenotypes; hepatic involvement included)	Hepatic involvement reported across the cohort (including episodic crises), overlapping with neurologic/systemic features in some patients.	Supportive care; prevention strategies emphasized (avoid fasting/catabolic stress; early intervention during illness)	Natural histor data emphasi variability, including asymptomati adults and severe pediat disease
Alfarsi et al. (4)	National cohort / Saudi Arabia	8 patients (multiple families; pediatric)	Most commonly c.685G > T (p.Gly229Cys); one novel variant reported	Mixed neurologic-hepatic phenotype	Hepatic involvement in 5/8 (ranging from acute hepatic failure to chronic hepatitis); neurologic involvement reported in 5/8	Supportive care + metabolic management (acute crises and prevention)	Shows broad phenotype ev within one region; both acute and chronic liver involvement reported
Mihaljević et al. (3)	Family case series / Croatia	5 affected siblings (of 9)	c.685G > T (p.Gly229Cys), homozygous in family	Episodic hepatic phenotype (intra-familial variability)	Index child: emesis + mental deterioration + fulminant hepatic failure requiring urgent liver transplant; other siblings variably affected (including milder episodes/asymptomatic)	Acute crisis support; transplant performed for fulminant hepatic failure	Post-transpla course complicated; demonstrates variable expressivity even with san genotype

Study (Ref)	Design / Region	N / Age	Genotype	Phenotype category	Key hepatic presentation	Key management	Outcome/Not
Barak et al. (6)	Adult case report / Israel	1 / 34 y (female)	Not reported	Adult-onset hepatic presentation	Acute hepatitis without cognitive impairment or acidosis (adult presentation)	Supportive care	Demonstrates DLD deficienc can present beyond childhood as isolated acute hepatitis; DOI 10.1016/S016 8278(98)8006 X

Conclusion

This case highlights hepatic-predominant dihydrolipoamide dehydrogenase deficiency as an important and underrecognized cause of recurrent, stress-triggered vomiting and abdominal pain with ketotic hypoglycemia, intermittent transaminitis, and coagulopathy, despite complete recovery between episodes and preserved neurodevelopment. In children—particularly those from consanguineous families—this characteristic episodic pattern should prompt early genomic testing to confirm the diagnosis, reduce delays and unnecessary invasive procedures, and enable preventive strategies (avoidance of fasting, early dextrose during illness, and individualized cofactor supplementation). Ongoing follow-up is essential to monitor liver disease progression and optimize long-term outcomes.

Parent perspective

The patient's parents reported that the recurrent episodes of vomiting, abdominal pain, and repeated hospital admissions over the past year were a significant source of concern, particularly as the child appeared completely well between episodes. They described the period prior to diagnosis as especially distressing due to the absence of a clear explanation and the unpredictable nature of the attacks. Following confirmation of the diagnosis through genetic testing, they expressed relief at finally understanding the cause of their child's condition. They also reported increased reassurance after receiving clear medical guidance, particularly regarding avoidance of fasting and the importance of early medical evaluation during acute episodes.

Declarations

Abbreviations

Not applicable.

Ethics approval and consent to participate

Jordan University of Science and Technology Review Board approval was not required for the publication of this de-identified observational study. However, written consent for participation was obtained from the patient's mother

Consent for publication

Written informed consent was obtained from the patient's mother as the legal guardian for publication of this case report

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

E.A. served as the first author of this case report.N.O. was involved in patient identification and case collection.E.A., N.O., G.M., and A.A. contributed to the acquisition of clinical data, imaging studies, and pathology findings.E.A., M.Z., M.A., and N.O. participated in data analysis and interpretation.K.B. supervised the work and critically reviewed the manuscript for important intellectual content.All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data Availability

The variant reported in this study has been submitted to the ClinVar database under submission ID SUB16179802 and is currently undergoing validation and processing by ClinVar. The submitted record will be made publicly available through the ClinVar portal upon completion of the review and accessioning process by ClinVar. The corresponding ClinVar accession number will be provided once assigned

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