U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: El-Hattab AW, Scaglia F. Deoxyguanosine Kinase Deficiency. 2009 Jun 18 [Updated 2023 Feb 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Deoxyguanosine Kinase Deficiency

Synonyms: DGUOK Deficiency; *DGUOK*-Related Mitochondrial DNA Depletion Syndrome, Hepatocerebral Form

Ayman W El-Hattab, MD, FAAP, FACMG[1] and Fernando Scaglia, MD, FAAP, FACMG[2]

Created: June 18, 2009; Updated: February 9, 2023.

Summary

Clinical characteristics

The two forms of deoxyguanosine kinase (DGUOK) deficiency are a neonatal multisystem disorder and an isolated hepatic disorder that presents later in infancy or childhood. The majority of affected individuals have the multisystem illness with hepatic disease (jaundice, cholestasis, hepatomegaly, and elevated transaminases) and neurologic manifestations (hypotonia, nystagmus, and developmental delay) evident within weeks of birth. Those with isolated liver disease may also have renal involvement, and some later develop mild hypotonia. Progressive hepatic disease is the most common cause of death in both forms.

Diagnosis/testing

The diagnosis of DGUOK deficiency is established in a proband by the identification of biallelic pathogenic variants in *DGUOK* on molecular genetic testing.

Management

Treatment of manifestations: Care is best provided by a multidisciplinary team. Feeding therapy and/or gastrostomy tube as needed for feeding issues; developmental and education support. Children with cholestatic liver disease may require formulas with enriched medium-chain triglyceride content and fractional meals with enteral nutrition at night for adequate nutrition. Cornstarch for those with symptomatic hypoglycemia; supplementation with fat-soluble vitamins and essential fatty acids; routine immunizations for affected individuals and household contacts to prevent viral illness. Liver transplantation has been used to treat individuals without neurologic involvement or with minimal neurologic involvement. Treatment of hepatocellular carcinoma per oncologist; social work support and care coordination as needed.

Author Affiliations: 1 Professor, Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; Email: elhattabaw@yahoo.com. 2 Professor, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas; Email: fscaglia@bcm.edu.

Surveillance: Monitor fasting blood sugar during infancy; neurologic and developmental assessment at each visit; assess weight gain, nutritional status, and serum concentrations of ALT, AST, GGT, bilirubin, albumin, and coagulation profile at each visit; AFP and abdominal ultrasound every three months; urinalysis and urine amino acids at each visit in those with isolated hepatic disease; assess family needs at each visit.

Genetic counseling

DGUOK deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the *DGUOK* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Deoxyguanosine kinase (DGUOK) deficiency (*DGUOK*-related hepatocerebral mitochondrial DNA depletion syndrome) **should be suspected** in individuals with a combination of the following clinical, supportive laboratory, and liver biopsy findings.

Clinical features. Early infantile manifestations include the following:

- Liver disease. Jaundice, cholestasis, and hepatomegaly, progressing to liver failure
- Neurologic manifestations. Hypotonia, nystagmus, and developmental delay

Supportive laboratory findings

- Lactic acidosis and hypoglycemia
- Elevated transaminases alanine aminotransferase and aspartate aminotransferase
- In some individuals, elevated serum gammaglutamyltransferase, alpha fetoprotein, and ferritin [Dimmock et al 2008b]
- In most individuals, plasma amino acid profile showing elevated tyrosine, phenylalanine, and methionine [Leanza et al 2008, Mudd et al 2012]

  Note: (1) Elevated serum concentration of tyrosine or phenylalanine can be detected on newborn screening in the majority of neonates with multisystem DGUOK deficiency. (2) Infants with DGUOK deficiency do not excrete succinylacetone in the urine, whereas urinary excretion of succinylacetone is diagnostic for tyrosinemia type 1. (3) When transient, elevation of serum concentration of tyrosine may be falsely attributed to transient tyrosinemia of the newborn [Lee et al 2009].

Liver biopsy findings

- Liver histology typically reveals cholestasis, but may show microsteatosis, fibrosis, giant cell hepatitis, or cirrhosis. Electron microscopy may reveal an increase in the number of mitochondria and abnormal cristae, findings common to all hepatocerebral mitochondrial DNA (mtDNA) depletion syndromes [Dimmock et al 2008b, Al-Hussaini et al 2014].
- Mitochondrial DNA content in liver tissue of affected individuals is typically less than 20% of matched control mtDNA content. The liver typically shows a combined deficiency of electron transport chain complexes I, III, and IV [Dimmock et al 2008b].

Establishing the Diagnosis

The diagnosis of DGUOK deficiency is established in a proband by the identification of biallelic pathogenic (or likely pathogenic) variants in *DGUOK* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *DGUOK* variants of uncertain significance (or of one known *DGUOK* pathogenic variant and one *DGUOK* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing does not. Children with the distinctive clinical and laboratory findings of neonatal multisystem disease are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype of isolated hepatic disease indistinguishable from many other inherited disorders with liver disease are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of neonatal multisystem disease due to DGUOK deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *DGUOK* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: Targeted analysis for pathogenic variants can be performed first in individuals of Druze ancestry (see Table 6).

- **A multigene panel** that includes *DGUOK* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders with liver disease, molecular genetic testing approaches can include a combination of **comprehensive genomic testing** (exome sequencing, genome sequencing) or **gene-targeted testing** (multigene panel):

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.
- **A multigene panel** that includes *DGUOK* and other genes of interest (see Differential Diagnosis) may also be considered.

Table 1. Molecular Genetic Testing Used in Deoxyguanosine Kinase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DGUOK	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Deoxyguanosine kinase (DGUOK) deficiency presents in the majority of affected individuals as neonatal multisystem disease and in the minority of affected individuals later in infancy or childhood as isolated hepatic disease. Affected sibs with the same pathogenic variants have exhibited both multisystem disease and isolated hepatic disease with divergent long-term outcomes. To date, more than 100 individuals have been identified with pathogenic variants in *DGUOK* [El-Hattab et al 2017]. The following description of the phenotypic features associated with this condition is based on these reports.

Neonatal Multisystem Disease

Most affected infants have lactic acidosis and hypoglycemia in the first week of life. Within weeks of birth, all infants with this form of disease have hepatic disease and neurologic dysfunction.

Neurologic manifestations include hypotonia, developmental delay, and typical rotary nystagmus developing into opsoclonus. Neurologic features, particularly profound hypotonia, significant developmental delay, and nystagmus, are associated with poor long-term outcomes [Dimmock et al 2008a].

Brain MRI is usually normal. However, subtentorial abnormal myelination and globus pallidus hyperintensity have been reported [Brahimi et al 2009].

Liver involvement includes jaundice, cholestasis, hepatomegaly, and elevated transaminases. Hepatic dysfunction progresses in the majority of children, causing neonatal- or infantile-onset liver failure with ascites, edema, and coagulopathy [Dimmock et al 2008b, Al-Hussaini et al 2014, Sezer et al 2015, McKiernan et al 2016, Bychkov et al 2021, Doğulu et al 2021, AlMenabawy et al 2022].

The prognosis for neonatal multisystem disease is poor; most affected children die of liver failure before age four years [Sezer et al 2015].

Isolated Hepatic Disease

A minority of affected children initially present in infancy or childhood with isolated hepatic disease manifesting as jaundice, cholestasis, hepatomegaly, and elevated transaminases. Compared to neonatal multisystem disease, this form is associated with a less severe and later-onset liver disease. The liver disease, occasionally induced by a viral illness, is typically progressive and can lead to liver failure. However, hepatic disease has undergone reversal in one individual with isolated liver disease [Mousson de Camaret et al 2007, Dimmock et al 2008b].

One individual with isolated liver disease subsequently developed hepatocellular carcinoma [Freisinger et al 2006, Grabhorn et al 2014].

Although neurologic manifestations are typically absent, long-term follow up suggests that individuals with isolated hepatic disease may subsequently develop mild hypotonia, and some may also have renal involvement manifesting as proteinuria and aminoaciduria [Dimmock et al 2008a].

Other Less Frequent Manifestations

The following variable phenotypes have occasionally been reported:

- Noncirrhotic portal hypertension with onset during infancy or childhood [Vilarinho et al 2016]
- Neonatal hemochromatosis [Hanchard et al 2011, Pronicka et al 2011]
- Adult-onset myopathy presenting with limb weakness, ophthalmoplegia, and ptosis [Ronchi et al 2012]
- Juvenile-onset myopathy presenting with weakness and fatigability [Buchaklian et al 2012]
- Adult-onset myopathy and parkinsonism presenting with ptosis, ophthalmoplegia, weakness, rigidity, and bradykinesia [Caporali et al 2018]

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations are evident among individuals with *DGUOK* pathogenic missense variants. Affected sibs with the same *DGUOK* missense variants have exhibited divergent long-term outcomes. Similarly, diverse long-term outcomes have been observed in affected individuals from unrelated families harboring the same missense variants. These findings suggest that in individuals with pathogenic missense variants, the genotype and/or family history may not be helpful in predicting long-term outcome.

In contrast, two null variants have been typically associated with multisystem disease and a more severe clinical phenotype [Dimmock et al 2008b].

There is no clear correlation between *DGUOK* pathogenic variants and outcome after liver transplantation. Affected individuals with the same genotype can show good response with liver transplantation or a very poor outcome [Jankowska et al 2021].

Prevalence

No large population-based studies have evaluated the prevalence of mitochondrial DNA (mtDNA) depletion in general or DGUOK deficiency specifically. More than 100 individuals with DGUOK deficiency have been

reported [El-Hattab et al 2017]. DGUOK deficiency is one of the most common causes of hepatocerebral mtDNA depletion syndromes and is estimated to account for 15%-20% of all individuals diagnosed with mtDNA depletion syndromes [Sezer et al 2015].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DGUOK*.

Differential Diagnosis

Multisystem Disease

The neonatal multisystem form of deoxyguanosine kinase (DGUOK) deficiency needs to be differentiated from other mitochondrial DNA (mtDNA) depletion syndromes, a genetically and clinically heterogeneous group of primarily autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs. Table 2 includes the currently known mtDNA depletion syndromes.

Mitochondrial DNA depletion syndromes occur as a result of defects in mtDNA maintenance caused by pathogenic variants in nuclear genes that function in either mitochondrial nucleotide synthesis (*TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, *TYMP*, and *ABAT*) or mtDNA synthesis (*POLG*, *TWNK*, *TFAM*, and *RNASEH1*).

Mitochondrial DNA depletion syndromes are phenotypically classified into hepatocerebral (encephalohepatopathic), encephalomyopathic, neurogastrointestinal encephalopathic, encephaloneuropathic, and myopathic forms [El-Hattab & Scaglia 2013].

Table 2. Mitochondrial DNA Depletion Syndromes

Phenotype [1]	Gene	Disorder / Phenotype	Additional Common Manifestations [2]
Hepatocerebral (Encephalo-hepatopathic)	*DGUOK*	DGUOK deficiency	DD, hypotonia, nystagmus, lactic acidosis
	POLG	Alpers-Huttenlocher syndrome	DD, psychomotor regression, epilepsy, hearing impairment
	MPV17	MPV17 deficiency	DD, hypotonia, poor weight gain, hearing impairment, lactic acidosis
	TFAM	Encephalohepatopathy (OMIM 617156)	IUGR, hypoglycemia
	TWNK	Encephalohepatopathy (OMIM 271245)	DD, hypotonia, lactic acidosis

Table 2. continued from previous page.

Phenotype [1]	Gene	Disorder / Phenotype	Additional Common Manifestations [2]
Encephalo-myopathic	*ABAT*	Encephalomyopathy w/↑ GABA (OMIM 613163)	DD, hypotonia, epilepsy, ↑ GABA in plasma, urine, & CSF
	FBXL4	FBXL4 deficiency	DD, hypotonia, epilepsy, hearing impairment, lactic acidosis
	OPA1	Encephalomyopathy (OMIM 616896)	DD, HCM, optic atrophy
	RNASEH1	Encephalomyopathy (OMIM 616479)	Ophthalmoplegia, ptosis, ataxia
	RRM2B	*RRM2B* encephalomyopathic MDMD	DD, hypotonia, GI dysmotility, renal tubulopathy
	SUCLA2	SUCLA2 deficiency	DD, hypotonia, dystonia, hearing impairment, ↑ methylmalonic acid
	SUCLG1	SUCLG1 deficiency	DD, hypotonia, hearing impairment, ↑ methylmalonic acid
Neurogastro-intestinal encephalopathic	*POLG*	MNGIE type 4B	GI dysmotility, cachexia, peripheral neuropathy, ophthalmoplegia, muscle weakness, leukoencephalopathy [3]
	RRM2B	MNGIE type 8B	
	TYMP	MNGIE type 1	
Myopathic	*AGK*	Sengers syndrome (OMIM 212350)	Hypotonia, HCM, cataracts
	MGME1	Myopathy (OMIM 615084)	Ptosis, ophthalmoplegia
	TK2	TK2 deficiency	Hypotonia, loss of acquired motor skills
Encephalo-neuropathic	*TWNK*	Infantile-onset spinocerebellar ataxia	Hypotonia, hearing impairment

CSF = cerebrospinal fluid; DD = developmental delay; GI = gastrointestinal; HCM = hypertrophic cardiomyopathy; IUGR = intrauterine growth restriction; MDMD = mitochondrial DNA maintenance defect; MNGIE = mitochondrial neurogastrointestinal encephalopathy

1. Within each phenotypic category, mtDNA depletion syndromes are ordered by relative prevalence.

2. Common manifestations seen in addition to the primary phenotype (i.e., in addition to encephalohepatopathy, encephalomyopathy, etc.).

3. Leukoencephalopathy is not present in *POLG*-related neurogastrointestinal encephalopathy.

Isolated Hepatic Disease

The differential diagnosis of isolated hepatic disease due to DGUOK deficiency includes other genetic and non-genetic age-specific causes of cholestatic liver disease.

Genetic causes

- Alagille syndrome
- Cystic fibrosis
- Galactosemia
- Tyrosinemia type 1
- Citrin deficiency
- Inborn errors of bile acid synthesis (See Pediatric Genetic Cholestatic Liver Disease Overview, Table 2.)
- Alpha-1 antitrypsin deficiency
- Niemann-Pick disease type C
- Wolman disease (See Lysosomal Acid Lipase Deficiency.)

- Peroxisomal biogenesis disorders (See Rhizomelic Chondrodysplasia Punctata Type 1 and Zellweger Syndrome Spectrum.)
- Progressive familial intrahepatic cholestasis (See ATP8B1 Deficiency and Pediatric Genetic Cholestatic Liver Disease Overview.)

Non-genetic causes

- Extrahepatic biliary atresia
- Choledochal cyst
- Hypothyroidism
- Total parenteral nutrition cholestasis
- Neonatal hemochromatosis

Management

No clinical practice guidelines for deoxyguanosine kinase (DGUOK) deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DGUOK deficiency, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Deoxyguanosine Kinase Deficiency

System/Concern	Evaluation	Comment
General	Measurement of plasma lactate & fasting blood sugar	In those w/neonatal multisystem disease
Neurologic	• Comprehensive neurologic exam • Developmental/cognitive assessment • Brain MRI may be considered.	
Hepatic	• Eval of hepatic status by physician familiar w/care of children w/liver failure • Initial testing should incl measurement of serum concentrations of ALT, AST, GGT, bilirubin, albumin, & coagulation profile. • Nutritional assessment by dietician w/experience in managing children w/hepatic failure	
	Abdominal ultrasound & AFP to screen for HCC	AFP is a sensitive, but not specific, marker to differentiate HCC from nonmalignant liver disease. [1]
Renal	Urinalysis & urine amino acids to evaluate for renal involvement	In those w/isolated hepatic disease
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of DGUOK deficiency to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

AFP = alpha fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gammaglutamyltransferase; HCC = hepatocellular carcinoma; MOI = mode of inheritance

1. Although the value of a highly elevated serum AFP in the detection of hepatocellular carcinoma in DGUOK deficiency is not known, the possibility of hepatocellular carcinoma should be considered in individuals with a solid tumor detected by abdominal ultrasound examination *and* a highly increased serum AFP concentration [Freisinger et al 2006].

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management requires a multidisciplinary team including specialists in hepatology, neurology, child development, nutrition, and clinical genetics (see Table 4).

Table 4. Treatment of Manifestations in Individuals with Deoxyguanosine Kinase Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Hypotonia / Feeding issues	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	For those w/neonatal multisystem disease
Hepatic disease / Nutrition	Mgmt per hepatologist & dietician w/experience in liver disease • Formulas w/enriched medium-chain triglyceride content may provide better nutritional support for infants w/cholestasis than formulas w/predominantly long-chain triglycerides. [1] • Cornstarch may ↓ symptomatic hypoglycemia in those w/isolated hepatic disease. • Fractional meals & enteral nutrition at night can result in good nutritional control. [2] • Supplementation w/fat-soluble vitamins & essential fatty acids. [1]	• Liver transplantation in selected persons w/ DGUOK deficiency is not contraindicated, esp in those w/o or w/minimal neurologic abnormalities. • Liver transplantation was performed in 20 persons w/DGUOK deficiency at age 1-18 mos. Ten individuals (50%) died 1-21 mos after transplant from procedure-related complications (renal insufficiency, intraventricular hemorrhage, sepsis, pulmonary hypertension, or peritonitis). Among survivors, 8 presented w/good psychomotor development &/or mild hypotonia, 1 presented w/moderate cognitive impairment, & 1 presented w/severe psychomotor impairment. [3]
	Routine immunizations (incl influenza vaccine) for all persons w/DGUOK deficiency & their household contacts	Hepatic disease can be induced by viral illness.
Hepatocellular carcinoma	Treatment per oncologist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

1. Feranchak & Sokol [2007]
2. Dimmock et al [2008b]
3. Jankowska et al [2021]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

No clinical guidelines for surveillance are available. To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Deoxyguanosine Kinase Deficiency

System/Concern	Evaluation	Frequency
General	Monitor fasting blood sugar.	During infancy
Neurodevelopment	• Neurologic assessment • Assess developmental progress (particularly gross motor skills) & educational needs.	At each visit in those w/ neonatal multisystem disease
Hepatic function & hepatocellular carcinoma	• Assess weight gain & nutritional status. • Monitor serum concentrations of ALT, AST, GGT, bilirubin, albumin, & coagulation profile.	At each visit
	AFP & abdominal ultrasound to monitor for HCC	Every 3 mos

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Renal disease	Urinalysis & urine amino acids for proteinuria & aminoaciduria	At each visit in those w/isolated hepatic disease
Family/Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

AFP = alpha fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gammaglutamyltransferase; HCC = hepatocellular carcinoma

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Deoxyguanosine kinase (DGUOK) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *DGUOK* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *DGUOK* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *DGUOK* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

- Although penetrance of DGUOK deficiency is probably complete, age of onset and severity of the clinical symptoms vary, even in the same family. Affected sibs sharing the same pathogenic variants have exhibited both multisystem disease and isolated hepatic disease with divergent long-term outcomes.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with DGUOK deficiency would be obligate heterozygotes for a pathogenic variant in *DGUOK*. To date, however, fertility is unknown, as no affected individuals have reproduced.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DGUOK* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *DGUOK* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if both partners are of the same ethnic background. A *DGUOK* founder variant has been identified in individuals of Druze heritage (see Table 6).

Prenatal Testing and Preimplantation Genetic Testing

Once the *DGUOK* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for DGUOK deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org
- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca

- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  www.childliverdisease.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Deoxyguanosine Kinase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DGUOK	2p13.1	Deoxyguanosine kinase, mitochondrial	DGUOK database	DGUOK	DGUOK

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Deoxyguanosine Kinase Deficiency (View All in OMIM)

251880	MITOCHONDRIAL DNA DEPLETION SYNDROME 3 (HEPATOCEREBRAL TYPE); MTDPS3
601465	DEOXYGUANOSINE KINASE; DGUOK

Molecular Pathogenesis

DGUOK encodes the mitochondrial enzyme deoxyguanosine kinase (DGUOK), which mediates the first step of the mitochondrial purine nucleoside salvage pathway as it phosphorylates deoxyguanosine and deoxyadenosine to deoxyguanosine monophosphate (dGMP) and deoxyadenosine monophosphate (dAMP), respectively.

Missense, nonsense, and splice site variants result in a reduction or absence of DGUOK enzyme activity, which causes an imbalance of the mitochondrial deoxynucleotide pools. Because the mitochondria depend heavily on the salvage pathway for the supply of deoxynucleotides, DGUOK deficiency results in impaired mitochondrial DNA (mtDNA) synthesis and mtDNA depletion [El-Hattab et al 2017].

Mechanism of disease causation. Loss of function

Table 6. Notable *DGUOK* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_080916.2 NP_550438.1	c.255delA	p.Ala86ProfsTer13	Founder variant in Druze population [Mandel et al 2001]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author History

David Dimmock, MD; Medical College of Wisconsin (2009-2016)
Ayman W El-Hattab, MD, FAAP, FACMG (2016-present)
Fernando Scaglia, MD, FAAP, FACMG (2009-present)
Lee-Jun Wong, PhD; Baylor College of Medicine (2009-2023)

Revision History

- 9 February 2023 (sw) Comprehensive update posted live
- 22 December 2016 (bp) Comprehensive update posted live
- 18 June 2009 (et) Review posted live
- 10 February 2009 (fs) Original submission

References

Literature Cited

Al-Hussaini A, Faqeih E, El-Hattab AW, Alfadhel M, Asery A, Alsaleem B, Bakhsh E, Ali A, Alasmari A, Lone K, Nahari A, Eyaid W, Al Balwi M, Craig K, Butterworth A, He L, Taylor RW. Clinical and molecular characteristics of mitochondrial DNA depletion syndrome associated with neonatal cholestasis and liver failure. J Pediatr. 2014;164:553-9.e1-2.

AlMenabawy N, Hassaan HM, Ramadan M, Ehsan Abdel Meguid I, Ahmed El Gindy H, Beetz C, Selim L. Clinical and genetic spectrum of mitochondrial DNA depletion syndromes: a report of 6 cases with 4 novel variants. Mitochondrion. 2022;65:139–44. PubMed PMID: 35750291.

Brahimi N, Jambou M, Sarzi E, Serre V, Boddaert N, Romano S, de Lonlay P, Slama A, Munnich A, Rötig A, Bonnefont JP, Lebre AS. The first founder DGUOK mutation associated with hepatocerebral mitochondrial DNA depletion syndrome. Mol Genet Metab. 2009;97:221–6. PubMed PMID: 19394258.

Buchaklian AH, Helbling D, Ware SM, Dimmock DP. Recessive deoxyguanosine kinase deficiency causes juvenile onset mitochondrial myopathy. Mol Genet Metab. 2012;107:92–4. PubMed PMID: 22622127.

Bychkov IO, Itkis YS, Tsygankova PG, Krylova TD, Mikhaylova SV, Klyushnikov SA, Pechatnikova NL, Degtyareva AV, Nikolaeva EA, Seliverstov YA, Kurbatov SA, Dadali EL, Rudenskaya GE, Illarioshkin SN, Zakharova EY. Mitochondrial DNA maintenance disorders in 102 patients from different parts of Russia: Mutational spectrum and phenotypes. Mitochondrion. 2021;57:205–12. PubMed PMID: 33486010.

Caporali L, Bello L, Tagliavini F, La Morgia C, Maresca A, Di Vito L, Liguori R, Valentino ML, Cecchin D, Pegoraro E, Carelli V. DGUOK recessive mutations in patients with CPEO, mitochondrial myopathy, parkinsonism and mtDNA deletions. Brain. 2018;141:e3. PubMed PMID: 29228108.

Dimmock DP, Dunn JK, Feigenbaum A, Rupar A, Horvath R, Freisinger P, Mousson de Camaret B, Wong LJ, Scaglia F. Abnormal neurological features predict poor survival and should preclude liver transplantation in patients with deoxyguanosine kinase deficiency. Liver Transpl. 2008a;14:1480–5. PubMed PMID: 18825706.

Dimmock DP, Zhang Q, Dionisi-Vici C, Carrozzo R, Shieh J, Tang LY, Truong C, Schmitt E, Sifry-Platt M, Lucioli S, Santorelli FM, Ficicioglu CH, Rodriguez M, Wierenga K, Enns GM, Longo N, Lipson MH, Vallance H, Craigen WJ, Scaglia F, Wong LJ. Clinical and molecular features of mitochondrial DNA depletion due to mutations in deoxyguanosine kinase. Hum Mutat. 2008b;29:330–1.

Doğulu N, Tuna Kırsaçlıoğlu C, Köse E, Ünlüsoy Aksu A, Kuloğlu Z, Kansu A, Eminoğlu FT. The clinical variations and diagnostic challenges of deoxyguanosine kinase deficiency: a descriptive case series. J Pediatr Endocrinol Metab. 2021;34:1341–7. PubMed PMID: 34167177.

El-Hattab AW, Craigen WJ, Scaglia F. Mitochondrial DNA maintenance defects. Biochim Biophys Acta Mol Basis Dis. 2017;1863:1539–55. PubMed PMID: 28215579.

El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013;10:186–98. PubMed PMID: 23385875.

Feranchak A, Sokol R. Medical and nutritional management of cholestasis in infants and children. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children*. 3 ed. New York, NY: Cambridge University Press; 2007:190-231.

Freisinger P, Fütterer N, Lankes E, Gempel K, Berger TM, Spalinger J, Hoerbe A, Schwantes C, Lindner M, Santer R, Burdelski M, Schaefer H, Setzer B, Walker UA, Horváth R. Hepatocerebral mitochondrial DNA depletion syndrome caused by deoxyguanosine kinase (DGUOK) mutations. Arch Neurol. 2006;63:1129–34. PubMed PMID: 16908739.

Grabhorn E, Tsiakas K, Herden U, Fischer L, Freisinger P, Marquardt T, Ganschow R, Briem-Richter A, Santer R. Long-term outcomes after liver transplantation for deoxyguanosine kinase deficiency: a single-center experience and a review of the literature. Liver Transpl. 2014;20:464–72. PubMed PMID: 24478274.

Hanchard NA, Shchelochkov OA, Roy A, Wiszniewska J, Wang J, Popek EJ, Karpen S, Wong LJ, Scaglia F. Deoxyguanosine kinase deficiency presenting as neonatal hemochromatosis. Mol Genet Metab. 2011;103:262–7. PubMed PMID: 21478040.

Jankowska I, Czubkowski P, Rokicki D, Lipiński P, Piekutowska-Abramczuk D, Ciara E, Płoski R, Kaliciński P, Szymczak M, Pawłowska J, Socha P. Acute liver failure due to DGUOK deficiency-is liver transplantation justified? Clin Res Hepatol Gastroenterol. 2021;45:101408. PubMed PMID: 32278775.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Leanza L, Ferraro P, Reichard P, Bianchi V. Metabolic interrelations within guanine deoxynucleotide pools for mitochondrial and nuclear DNA maintenance. J Biol Chem. 2008;283:16437–45. PubMed PMID: 18417473.

Lee NC, Dimmock D, Hwu WL, Tang LY, Huang WC, Chinault AC, Wong LJ. Simultaneous detection of mitochondrial DNA depletion and single-exon deletion in the deoxyguanosine gene using array-based comparative genomic hybridisation. Arch Dis Child. 2009;94:55–8. PubMed PMID: 19103789.

Mandel H, Szargel R, Labay V, Elpeleg O, Saada A, Shalata A, Anbinder Y, Berkowitz D, Hartman C, Barak M, Eriksson S, Cohen N. The deoxyguanosine kinase gene is mutated in individuals with depleted hepatocerebral mitochondrial DNA. Nat Genet. 2001;29:337–41. PubMed PMID: 11687800.

McKiernan P, Ball S, Santra S, Foster K, Fratter C, Poulton J, Craig K, McFarland R, Rahman S, Hargreaves I, Gupte G, Sharif K, Taylor RW. Incidence of primary mitochondrial disease in children younger than 2 years presenting with acute liver failure. J Pediatr Gastroenterol Nutr. 2016;63:592–7. PubMed PMID: 27482763.

Mousson de Camaret B, Taanman JW, Padet S, Chassagne M, Mayençon M, Clerc-Renaud P, Mandon G, Zabot MT, Lachaux A, Bozon D. Kinetic properties of mutant deoxyguanosine kinase in a case of reversible hepatic mtDNA depletion. Biochem J. 2007;402:377–85. PubMed PMID: 17073823.

Mudd SH, Wagner C, Luka Z, Stabler SP, Allen RH, Schroer R, Wood T, Wang J, Wong LJ. Two patients with hepatic mtDNA depletion syndromes and marked elevations of S-adenosylmethionine and methionine. Mol Genet Metab. 2012;105:228–36. PubMed PMID: 22137549.

Pronicka E, Węglewska-Jurkiewicz A, Taybert J, Pronicki M, Szymańska-Dębińska T, Karkucińska-Więckowska A, Jakóbkiewicz-Banecka J, Kowalski P, Piekutowska-Abramczuk D, Pajdowska M, Socha P, Sykut-Cegielska J, Węgrzyn G. Post mortem identification of deoxyguanosine kinase (DGUOK) gene mutations combined with impaired glucose homeostasis and iron overload features in four infants with severe progressive liver failure. J Appl Genet. 2011;52:61–6. PubMed PMID: 21107780.

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, et al. 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. PubMed PMID: 25741868.

Ronchi D, Garone C, Bordoni A, Gutierrez Rios P, Calvo SE, Ripolone M, Ranieri M, Rizzuti M, Villa L, Magri F, Corti S, Bresolin N, Mootha VK, Moggio M, DiMauro S, Comi GP, Sciacco M. Next-generation sequencing reveals DGUOK mutations in adult patients with mitochondrial DNA multiple deletions. Brain. 2012;135:3404–15. PubMed PMID: 23043144.

Sezer T, Ozçay F, Balci O, Alehan F. Novel deoxyguanosine kinase gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome. J Child Neurol. 2015;30:124–8. PubMed PMID: 24423689.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Vilarinho S, Sari S, Yilmaz G, Stiegler AL, Boggon TJ, Jain D, Akyol G, Dalgic B, Günel M, Lifton RP. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. Hepatology. 2016;63:1977–86. PubMed PMID: 26874653.

License