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Epimerase Deficiency Galactosemia

Synonyms: Galactosemia Type III, GALE Deficiency, UDP-Galactose-4'-Epimerase Deficiency

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Summary

Clinical characteristics

Epimerase deficiency galactosemia (GALE deficiency galactosemia) is generally considered a continuum comprising several forms:

- **Generalized.** Enzyme activity is profoundly decreased in all tissues tested.
- **Peripheral.** Enzyme activity is deficient in red blood cells (RBC) and circulating white blood cells, but normal or near normal in all other tissues.
- **Intermediate.** Enzyme activity is deficient in red blood cells and circulating white blood cells and less than 50% of normal levels in other cells tested.

Infants with generalized epimerase deficiency galactosemia develop clinical findings on a regular milk diet (which contains lactose, a disaccharide of galactose and glucose); manifestations include hypotonia, poor feeding, vomiting, weight loss, jaundice, hepatomegaly, liver dysfunction, aminoaciduria, and cataracts. Prompt removal of galactose/lactose from their diet resolves or prevents these acute symptoms. Longer-term features that may be seen in those with generalized epimerase deficiency include short stature, developmental delay, sensorineural hearing loss, and skeletal anomalies. In contrast, neonates with the peripheral or intermediate form generally remain clinically well even on a regular milk diet and are usually only identified by biochemical testing, often in newborn screening programs.

Diagnosis/testing

The diagnosis of epimerase deficiency galactosemia is established in a proband with impaired GALE activity in RBC or other cells and/or biallelic pathogenic variants in *GALE* identified on molecular genetic testing. The degree of GALE enzyme activity impairment in RBC does not distinguish between the clinically severe

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generalized and the milder intermediate or peripheral forms of epimerase deficiency; further enzymatic testing in other cell types such as stimulated leukocytes or EBV-transformed lymphoblasts is required to make that distinction.

Management

Treatment of manifestations: The common acute and potentially lethal symptoms of generalized epimerase deficiency galactosemia are prevented or corrected by a galactose/lactose-restricted diet. Note: Affected individuals may require trace environmental sources of galactose: infants should be fed a formula (e.g., soy formula) that contains trace levels of galactose or lactose. Continued dietary restriction of dairy products in older children is recommended. In contrast, infants with peripheral epimerase deficiency galactosemia are believed to remain asymptomatic regardless of diet; infants with intermediate epimerase deficiency galactosemia may benefit in the long term from early dietary galactose/lactose restriction, but this remains unclear. Standard treatment for developmental delay, skeletal anomalies, poor weight gain / failure to thrive, mature cataracts, and sensorineural hearing loss.

Prevention of primary manifestations: In generalized epimerase deficiency galactosemia, restriction of dietary galactose/lactose appears to correct or prevent the common acute signs and symptoms of the disorder (hepatic dysfunction, renal dysfunction, and mild cataracts), but not the developmental delay or learning impairment observed in some affected individuals. Because of the difficulty in distinguishing peripheral and intermediate forms of epimerase deficiency galactosemia, dietary restriction of galactose/lactose is recommended for all infants with GALE deficiency, relaxing the restriction, as warranted, once a more accurate diagnosis has been confirmed.

Surveillance: Hemolysate gal-1P (galactose-1-phosphate) or urinary galactitol is monitored, especially if the diet is to be normalized. Acceptable levels of RBC gal-1P are not known, but are estimated to be <3.5 mg/100 mL (normal ≤1.0 mg/100 mL) on data from classic galactosemia. Other parameters that warrant monitoring are growth and developmental milestones, vision, and hearing (particularly in those in whom hearing loss has been identified).

Agents/circumstances to avoid: Dietary galactose/lactose in persons with generalized epimerase deficiency galactosemia, certainly as infants and perhaps for life.

Evaluation of relatives at risk: Each at-risk newborn sib should be treated with dietary restriction of galactose from birth while awaiting results of diagnostic testing for epimerase deficiency galactosemia; either molecular genetic testing (if the pathogenic variants in the family are known) or measurement of GALE enzyme activity in RBC (if the pathogenic variants in the family are not known) can be performed.

Genetic counseling

Epimerase deficiency galactosemia is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *GALE* pathogenic variant, each full 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 family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

Epimerase deficiency galactosemia (GALE deficiency galactosemia) is a continuum comprising three forms:

- **Generalized.** Enzyme activity is profoundly decreased in all tissues tested.

- **Peripheral.** Enzyme activity is deficient in red blood cells (RBC) and circulating white blood cells, but normal or near normal in all other tissues.
- **Intermediate.** Enzyme activity is deficient in RBC and circulating white blood cells and less than 50% of normal levels in other cells tested.

Suggestive Findings

Epimerase deficiency galactosemia **should be suspected** in individuals with the following newborn screening results, suggestive clinical features, and supportive laboratory findings while on a normal milk diet.

Newborn screening results

- In states in which the newborn screening program includes measurements of both total galactose (gal+gal-1P) and GALT enzyme activity (see Galactosemia):
  - Total galactose (sum of galactose and galactose-1-phosphate) is elevated; and
  - GALT enzyme activity is normal.
- In states in which total galactose is only measured if GALT enzyme activity is low, an infant with GALE deficiency will have a normal newborn screening result for galactosemia.

Suggestive clinical features

- Hypotonia
- Poor feeding
- Vomiting
- Weight loss
- Jaundice
- Hepatomegaly
- Liver dysfunction
- Cataracts
- No clinical findings (peripheral and intermediate forms of GALE deficiency)

Supportive laboratory findings in an infant drinking breast milk or a dairy milk formula

- Elevated RBC hemolysate gal-1P concentration (normal: 0-1.0 mg/100 mL RBC):
  - As high as 170 mg/100 mL packed RBC in those with generalized epimerase deficiency
  - >30 mg/100 mL packed RBC in those with intermediate or peripheral epimerase deficiency
- Urinary galactose concentrations as high as 116 mmol/L (2.09 g/100 mL, control <30 mg/100 mL)
- Non-glucose reducing substance in the urine (which represents urinary galactose)
- Elevated urinary galactitol concentrations (normal: <94.7 mmol/mol creatinine for age <1 year, <45.3 mmol/mol creatinine for age 1-6 years, <18.4 mmol/mol creatinine for age >6 years)
- Generalized aminoaciduria
- Normal GALT, GALK, and GALM enzyme activities
- Note: If epimerase deficiency galactosemia is suspected, assessment of enzymatic activity for GALT, GALK, and GALM is **not** required prior to pursuing either measurement of GALE enzyme activity or molecular genetic testing for *GALE* (see Establishing the Diagnosis). If Gal-1P is elevated, GALT activity should be tested to rule out classic galactosemia, but GALT testing may be done concurrently with GALE. GALM activity testing may not be clinically available.

Establishing the Diagnosis

A diagnosis of epimerase deficiency galactosemia **is established** in a proband by ONE OR MORE of the following:

- 0.0-8.0 µmol/hr/g hemoglobin (Hb) GALE enzyme activity in red blood cells (RBC) (normal 17.1-40.1 µmol/hr/g Hb) as determined by the traditional spectrophotometric assay
- <0.5 µmol/hr/g Hb GALE enzyme activity in RBC using liquid chromatography/tandem mass spectrometry (normal 2.3-12.7 µmol/hr/g Hb) [Chen et al 2014]
- Identification of biallelic pathogenic (or likely pathogenic) variants in *GALE* 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 *GALE* variants of uncertain significance (or of one known *GALE* pathogenic variant and one *GALE* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing** or a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *GALE* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *GALE* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely 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. (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.

Table 1. Molecular Genetic Testing Used in Epimerase Deficiency Galactosemia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GALE	Sequence analysis [3]	14/16 alleles and 13/14 alleles (~90%) [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Whole-gene sequencing has revealed ostensibly causal *GALE* variants in most persons with biochemically confirmed GALE deficiency who have been studied (e.g., Park et al [2005], Openo et al [2006], reviewed in Berry et al [2020]); however, due to the small number of alleles studied and the biochemical complexity of the diagnosis this estimate may change with time.
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.
6. At the time of this writing, no deletions or duplications involving *GALE* have been reported to cause epimerase deficiency galactosemia.

Additional Testing

GALE enzyme activity can be measured in fibroblasts or lymphoblasts to help distinguish between the generalized, peripheral, and intermediate forms of epimerase deficiency galactosemia; however, to the authors' knowledge this testing is not currently offered on a clinical basis.

Clinical Characteristics

Clinical Description

The clinical severity of epimerase deficiency galactosemia caused by reduced activity of the enzyme GALE [Berry et al 2020] ranges from potentially lethal [Holton et al 1981, Henderson et al 1983, Walter et al 1999, Sarkar et al 2010] to apparently benign [Gitzelmann 1972].

Epimerase deficiency galactosemia can be divided by apparent enzyme activity level in specific cell types into the following three forms: generalized, peripheral, and intermediate (see Diagnosis) [Openo et al 2006]. Note: In all three forms, GALE enzyme activity is deficient in peripheral circulating red and white blood cells.

A key difference between generalized epimerase deficiency galactosemia and intermediate or peripheral epimerase deficiency galactosemia is that individuals with generalized epimerase deficiency galactosemia develop clinical findings on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia remain clinically well, at least in the neonatal period.

Generalized Epimerase Deficiency Galactosemia

Generalized epimerase deficiency galactosemia is rare, with only nine individuals from five families described in the literature [Holton et al 1981, Garibaldi et al 1983, Henderson et al 1983, Sardharwalla et al 1988, Walter et al 1999, Sarkar et al 2010, Dias Costa et al 2017]. Table 2 summarizes the key clinical features of individuals reported with this phenotype.

Table 2. Generalized Epimerase Deficiency Galactosemia: Frequency of Select Features

Feature	# of Persons w/Feature [1]	Comment
Hepatic abnormalities	8/9	May be ameliorated by treatment [2]
Short stature	7/7	In those who survive the neonatal period
Developmental delay	6/6	Incl both children who experienced acute illness before diagnosis & younger sibs who were switched to a low-galactose diet before onset of severe neonatal symptoms
Hypotonia	6/8	May be ameliorated by treatment [2]
Sensorineural hearing loss	4/7	
Micrognathia	4/6	
Flexion deformities of the fingers	3/6	
Hip dysplasia	3/7	
Cataracts	3/8	May be ameliorated by treatment [2]
Renal dysfunction/tubulopathy	1/6	

1. Not all affected individuals were assessed for each feature listed.
2. See Treatment of Manifestations.

Infants with generalized epimerase deficiency galactosemia who are on a diet containing galactose/lactose typically present with symptoms reminiscent of classic galactosemia: hypotonia, poor feeding, vomiting, weight loss, jaundice, hepatomegaly, liver dysfunction (e.g., markedly elevated serum transaminases), aminoaciduria, and cataracts. Renal dysfunction was also noted in one affected individual [Dias Costa et al 2017]. Prompt removal of galactose/lactose from the diet resolves or prevents these acute symptoms [Walter et al 1999, Sarkar et al 2010] (see Management).

Long-term outcome information for persons with generalized epimerase deficiency galactosemia is limited due to the small number of known affected individuals. Some have demonstrated long-term complications that became evident by early childhood (including sensorineural hearing impairment and physical and cognitive developmental delay and/or learning difficulties) while others have not. Confounding factors include the fact that a majority, but not all, of the individuals reported were born to known consanguineous parents, raising the concern that homozygosity for other autosomal recessive alleles – other than *GALE* but perhaps genetically linked to *GALE* – may underlie some of the long-term complications reported. In addition to the features listed in Table 2, other rare features reported in survivors include the following:

- Positional talipes equinovarus [Walter et al 1999]
- Normal puberty with no apparent evidence of premature ovarian insufficiency [Walter et al 1999]
- Dilated cardiomyopathy that responded to standard treatment in one affected sib [Dias Costa et al 2017].

Peripheral Epimerase Deficiency Galactosemia

Neonates with the peripheral form are usually asymptomatic even on a regular milk diet; these infants are only identified following biochemical detection of elevated total galactose on newborn screening.

Children with peripheral epimerase deficiency galactosemia appear to remain asymptomatic even if maintained on a normal milk diet.

Intermediate Epimerase Deficiency Galactosemia

Neonates with the intermediate form are also usually asymptomatic even on a regular milk diet and are only identified through newborn screening. The long-term outcome remains unclear. One affected individual, who was not treated with dietary restriction of galactose/lactose as an infant, experienced delays in both motor and cognitive development that became evident in early childhood [Alano et al 1998, Openo et al 2006]. All other individuals known to have intermediate epimerase deficiency galactosemia have been treated by dietary galactose/lactose restriction, at least in infancy, and thus far those who have been followed appear to remain clinically well.

Genotype-Phenotype Correlations

Because the numbers of individuals reported with molecularly confirmed epimerase deficiency galactosemia are currently limited, it is difficult to make strong genotype-phenotype correlations. However, some *GALE* variants have been associated with mild or severe outcomes in multiple affected individuals.

- Individuals who are homozygous for c.280G>A (p.Val94Met) are likely to have generalized epimerase deficiency galactosemia and have a more severe outcome [Wohlers et al 1999, Dias Costa et al 2017].
- Individuals who have biallelic *GALE* alleles that are each associated with higher residual GALE activity in non-peripheral cells, such as c.770A>G (p.Lys257Arg) and c.956G>A (p.Gly319Glu), are more likely to have asymptomatic peripheral epimerase deficiency [Alano et al 1997, Openo et al 2006]. However, too few individuals have been described to confirm or refute this prediction.

Nomenclature

Some authors refer to the different forms of galactosemia as type I, type II, type III, and type IV galactosemia, in which:

- Type I galactosemia refers to GALT deficiency;
- Type II galactosemia refers to GALK deficiency;
- Type III galactosemia refers to GALE deficiency (epimerase deficiency galactosemia);
- Type IV galactosemia refers to GALM deficiency (galactose mutarotase deficiency) [Timson 2019].

Prevalence

True prevalence figures are unavailable at this time. Generalized epimerase deficiency galactosemia is very rare; however, epimerase deficiency galactosemia detected by newborn screening may be as frequent as about 1:6,700 among African American infants and about 1:70,000 among US infants of European ancestry [Openo et al 2006, Dias Costa et al 2017].

Genetically Related (Allelic) Disorders

Seo et al [2019] reported a consanguineous family in which six individuals had severe thrombocytopenia with dysplastic megakaryocytes. Some affected family members had additional variable hematologic features, including febrile neutropenia and mild anemia. Whole-genome sequencing identified homozygous c.151C>T (p.Arg51Trp) *GALE* pathogenic variants in the affected individuals, which segregated with the phenotype in the family. No other compelling genetic condition was identified that cosegregated with the disease phenotype in this pedigree. Affected individuals in this family had no other clinical features of epimerase deficiency galactosemia, and although recombinant p.Arg51Trp *GALE* was characterized in vitro, enzymatic testing of GALE in biological samples from this family was not completed. Given that some individuals with epimerase deficiency galactosemia have few to no clinical signs, it is unclear if the hematologic phenotype described in this family is related to compromised GALE function in galactose metabolism, or to some other consequence of the biallelic variants found in this family.

Differential Diagnosis

GALT deficiency. Galactosemia caused by deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT) may be divided into three clinical/biochemical phenotypes: (1) classic galactosemia; (2) clinical variant galactosemia; and (3) Duarte (biochemical variant) galactosemia. This categorization is based on: residual erythrocyte GALT enzyme activity; the levels of galactose metabolites (e.g., erythrocyte galactose-1-phosphate and urine galactitol) that are observed both off and on a lactose-restricted diet; and, most importantly, the likelihood that the affected individual will develop acute and chronic long-term complications. Biallelic pathogenic variants in *GALT* are causative; inheritance is autosomal recessive.

- **Classic galactosemia** can result in life-threatening complications including feeding issues, failure to thrive, hepatocellular damage, bleeding, and *E coli* sepsis in untreated infants. If a lactose-restricted diet is provided during the first ten days of life, the neonatal signs usually quickly resolve and the complications of liver failure, sepsis, and neonatal death are prevented; however, despite adequate treatment from an early age, children with classic galactosemia remain at increased risk for developmental delays, speech issues (termed childhood apraxia of speech and dysarthria), and abnormalities of motor function. The vast majority of women with classic galactosemia manifest premature ovarian insufficiency.
- **Clinical variant galactosemia** can result in life-threatening complications in untreated infants including feeding issues, failure to thrive, hepatocellular damage including cirrhosis, and bleeding. It can occur in individuals of any ancestry with low residual GALT enzyme activity, but is perhaps exemplified by the

disease associated with homozygosity for the p.Ser135Leu *GALT* allele that occurs at high frequency in native Africans in South Africa, and to a lesser extent in African Americans. Infants with clinical variant galactosemia may be missed if newborn screening only measures blood total galactose level and not erythrocyte GALT enzyme activity, as the hypergalactosemia is not as marked as in classic galactosemia and breath testing is normal. As in classic galactosemia, if a lactose-restricted diet is provided during the first days of life, the severe acute neonatal complications are usually prevented. Long-term outcomes among treated individuals with clinical variant galactosemia may also be milder.

- **Duarte variant galactosemia (biochemical variant galactosemia).** Infants with Duarte variant galactosemia who receive breast milk or a high galactose-containing formula (dairy milk-based formula) are typically asymptomatic and show no greater prevalence of developmental complications than is seen in the general population. Erythrocyte GALT enzyme activity is typically about 25% of control activity. Infants with Duarte variant galactosemia may or may not be detected by newborn screening depending on the GALT enzyme activity cutoff defined by the screening program, but should demonstrate partial deficiency of GALT, potentially with some elevation of galactose metabolites if the baby has consumed breast milk or a dairy milk-based formula).

Galactokinase (GALK) deficiency (OMIM 230200) should be considered in otherwise healthy individuals with cataracts, increased plasma concentration of galactose, and increased urinary excretion of galactitol. Affected individuals have normal GALT enzyme activity and most do not accumulate gal-1P [Hennermann et al 2011] (surprisingly, some individuals with GALK deficiency apparently do accumulate gal-1P) [Rubio-Gozalbo et al 2021]. Affected individuals reported in each of two studies – one including 18 affected individuals identified in Germany [Hennermann et al 2011] and the other describing an independent cohort of 56 affected individuals from 11 countries [Rubio-Gozalbo et al 2021] – displayed a range of acute and long-term outcomes, some of which overlap with complications seen in classic galactosemia. Detection of reduced GALK enzyme activity in hemolysates is diagnostic. Biallelic pathogenic variants in *GALK1* are causative; inheritance is autosomal recessive. The prevalence of GALK deficiency in most populations is unknown; however, a study from Germany reported a prevalence of about 1:40,000, which is similar to the prevalence of classic galactosemia in the same population [Hennermann et al 2011]. In other populations the prevalence may be far lower.

Note: Studies in a mouse model confirmed that the cataracts seen in GALK-deficiency, and presumably also in other forms of galactosemia, are caused by accumulation of the galactose metabolite, galactitol, in the lens. Galactitol is an impermeant alcohol which results in increased intracellular osmolality and swelling with loss of plasma membrane redox potential and consequent cell death.

GALM deficiency galactosemia (OMIM 618881) should be considered in individuals who have increased plasma concentration of galactose and may have cataracts, but are otherwise healthy [Timson 2019, Wada et al 2019]. These individuals have a negative Beutler test (ruling out GALT deficiency) and normal GALK and GALE enzyme activities. In affected individuals described to date, galactose-1-phosphate (gal-1P) levels on newborn screening ranged from 0.3 mg/dL to 10.8 mg/dL. Unlike GALE deficiency, the ratio between blood gal-1P and galactose was reported to be normal in GALM galactosemia [Wada et al 2019]. Biallelic pathogenic variants in *GALM* are causative; identification of biallelic pathogenic variants in *GALM* on molecular genetic testing is diagnostic (a diagnostic biochemical assay is not available at this time). In one study, the incidence of GALM deficiency was estimated to be almost 1:10,000 in African populations, almost 1:80,000 in the Japanese population, and much lower in many other populations [Iwasawa et al 2019].

Other. A number of other conditions, including the following, can also lead to elevated galactose or galactose metabolites in the blood or urine of an infant consuming milk:

- Liver dysfunction / liver failure
- Portosystemic venous shunting
- Hepatic arteriovenous malformations

- Fanconi-Bickel syndrome (OMIM 227810), caused by biallelic pathogenic variants in *SLC2A2*. Individuals with this condition have hepatorenal glycogen accumulation, impaired utilization of glucose and galactose, and proximal tubular nephropathy.
- Congenital disorder of glycosylation type 1T (PGM1-CDG, see Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview), caused by biallelic pathogenic variants in *PGM1* [Tegtmeyer et al 2014]. Individuals with this condition can manifest mildly increased galactose-1-phosphate levels in RBC. They may have cleft palate/bifid uvula at birth and abnormal liver enzymes. They can develop liver disease, intermittent hypoglycemia, dilated cardiomyopathy, and exercise intolerance with increased serum creatine kinase.

Management

When epimerase deficiency galactosemia is suspected during the diagnostic evaluation (for example, if total galactose is elevated on newborn screening results), initiation of a galactose/lactose-restricted diet should begin immediately (see Treatment of Manifestations).

To the authors' knowledge, no clinical practice guidelines for epimerase deficiency galactosemia have been published.

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Epimerase Deficiency Galactosemia

System/Concern	Evaluation	Comment
Constitutional	Measurement of height, weight, & head circumference	
Neurologic	Neurologic eval	To incl assessment of tone
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures & clubfoot • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Feeding/Nutrition	Nutrition / feeding team eval	To incl eval of nutritional status & feeding skills
Hepatic	Liver function tests [1]	
Renal	Urinalysis [2]	• Incl for non-glucose reducing substances • Consider renal imaging, such as renal ultrasound, if renal abnormalities are suspected.
Eyes	Ophthalmologic eval	To assess for cataracts
Hearing	Audiologic eval	Assess for sensorineural hearing loss.
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of epimerase deficiency galactosemia in order 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.

OT = occupational therapy; MOI= mode of inheritance; PT = physical therapy
1. To include serum AST, ALT, albumin, total protein, total and conjugated bilirubin, prothrombin time, and partial thromboplastin time
2. One affected person who died in the neonatal period was reported to have large kidneys with intratubular renal calcifications [Dias Costa et al 2017].
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Generalized epimerase deficiency galactosemia. The acute and potentially lethal symptoms of generalized epimerase deficiency galactosemia are prevented or corrected by a galactose/lactose-restricted diet (see Table 4).

Intermediate epimerase deficiency galactosemia. Individuals with intermediate epimerase deficiency galactosemia are typically treated with dietary galactose/lactose restriction, at least in infancy (see Table 4). They may be at an (as-yet unknown) increased risk for long-term complications including learning impairment and/or cataracts. Continued breastfeeding or exposure to a milk-based formula containing high levels of galactose/lactose may therefore be inadvisable for these infants; however, insufficient data exist to make firm recommendations.

Table 4. Treatment of Manifestations in Individuals with Generalized or Intermediate Epimerase Deficiency Galactosemia

Principle/ Manifestation/ Concern	Treatment	Considerations/Other
Galactose/lactose-restricted diet [1]	In infants: switch from breast milk or a milk-based formula to a formula w/trace levels of galactose or lactose (e.g., soy formula).	• Elemental formula (which is prescribed for infants w/classic galactosemia) should NOT be used. [2] • The galactose intake needed for optimal outcome remains unknown.
	In older children: Dietary restriction involves continued restriction of **dairy** products.	While dietary restriction of high-galactose dairy products is recommended, a diet that restricts non-dairy sources of galactose (legumes, some fruits & vegetables, organ meat) is NOT recommended. [3]
Developmental delay	See Developmental Delay / Intellectual Disability Management Issues.	
Contractures & clubfoot	Standard treatment per orthopedist	
Poor weight gain / Failure to thrive	Feeding therapy	
Cataracts	Mature cataracts that do not resolve w/dietary restriction of galactose/lactose may require surgical removal.	
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district

Table 4. continued from previous page.

Principle/ Manifestation/ Concern	Treatment	Considerations/Other
Family/ Community	Ensure appropriate social work involvement to connect families w/local resources & support.	Consider involvement in adaptive sports or Special Olympics.

1. Restriction of dietary galactose/lactose appears to correct or prevent the common acute signs and symptoms of the disorder: hepatic dysfunction, renal dysfunction, and mild cataracts. However, it may not correct tissue damage that occurred due to prolonged galactose exposure (e.g., hepatic cirrhosis or mature cataracts) (see Prevention of Primary Manifestations).
2. Elemental formula should not be prescribed for infants with generalized epimerase deficiency galactosemia because the GALE enzyme is required for the endogenous biosynthesis of UDP-galactose; that is, persons with epimerase deficiency galactosemia may require trace environmental sources of galactose.
3. Historically, some healthcare providers recommended that individuals with classic galactosemia also abstain from non-dairy foods that contain more than trace levels of galactose/lactose; however, most non-dairy foods have been deemed acceptable for individuals with classic galactosemia [Van Calcar et al 2014].

Peripheral epimerase deficiency galactosemia. Individuals with peripheral epimerase deficiency galactosemia do not require any dietary restriction.

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.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - 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.

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

Communication issues. Affected individuals with speech and language delay typically require speech therapy until the complication has been resolved.

Prevention of Primary Manifestations

The challenge in treating an asymptomatic newborn with epimerase deficiency galactosemia is that it may take months to obtain the results of tests used to distinguish peripheral epimerase deficiency galactosemia from intermediate epimerase deficiency galactosemia (see Establishing the Diagnosis, Additional Testing); furthermore, such tests may not be available. The most conservative approach, therefore, is to advise dietary restriction of galactose/lactose for all infants with epimerase deficiency galactosemia, relaxing the restriction as warranted once a more accurate diagnosis has been confirmed.

In generalized epimerase deficiency galactosemia restriction of dietary galactose/lactose appears to correct or prevent the common acute signs and symptoms of the disorder: hepatic dysfunction, renal dysfunction, and mild cataracts. Presumably, as in classic galactosemia, dietary treatment would not correct profound tissue damage resulting from prolonged galactose exposure (e.g., hepatic cirrhosis or mature cataracts) or structural defects that likely originated in utero (e.g., cardiomyopathy).

In generalized epimerase deficiency galactosemia dietary restriction of galactose/lactose also prevents early feeding issues, vomiting, poor weight gain, hepatic dysfunction, and cataracts.

Surveillance

Table 5. Recommended Surveillance for Individuals with Generalized or Intermediate Epimerase Deficiency Galactosemia

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	At each visit
Biochemical	Assessment of hemolysate gal-1P or urinary galactitol [1, 2]	At each visit or as indicated by any ongoing concerns or relevant dietary changes
Development	Monitor developmental progress & educational needs.	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Eyes	Ophthalmology eval	As clinically indicated (assuming the affected person is on a galactose-restricted diet)
Hearing	Audiology eval	At least annually in infancy & childhood or as clinically indicated
Family/ Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy
1. Especially if the diet is to be normalized
2. Acceptable levels of gal-1P in GALE deficiency are not known but are estimated from experience with classic galactosemia to be <3.5 mg/100 mL in red blood cells.

Agents/Circumstances to Avoid

Persons with generalized epimerase deficiency galactosemia should be on a galactose/lactose-restricted diet, certainly as infants and perhaps for life.

Persons with intermediate epimerase deficiency galactosemia may be placed on a galactose/lactose-restricted diet, either transiently or long term. Assessment of hemolysate gal-1P and/or urinary galactitol following a galactose challenge (e.g., 2 weeks on a normal diet) may help determine if an individual should remain on a galactose/lactose-restricted diet for longer periods of time.

Evaluation of Relatives at Risk

If prenatal testing has not been performed (see Genetic Counseling), each at-risk newborn sib should be treated with dietary restriction of galactose from birth until results of diagnostic testing are available. Diagnostic evaluations can include the following:

- Molecular genetic testing if the pathogenic variants in the family are known
- Measurement of GALE enzyme activity in red blood cells if the pathogenic variants in the family are not known

Note: If there are concerns about the reliability of the prenatal testing, soy-based formula may be given while the diagnostic testing is being performed.

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

Epimerase deficiency galactosemia is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically heterozygotes (i.e., carriers of a *GALE* pathogenic variant).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *GALE* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, 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. Uniparental isodisomy could not explain a proband who is compound heterozygous for two different pathogenic variants in *GALE*.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing symptoms of generalized epimerase deficiency galactosemia.

Sibs of a proband

- If both parents are known to be heterozygous for a *GALE* pathogenic variant, each full 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.
- Data [Walter et al 1999] suggest that the subtype of epimerase deficiency galactosemia identified in a given family should "run true," meaning that if one sib has generalized epimerase deficiency galactosemia, other affected sibs in that family are also likely to have generalized epimerase deficiency galactosemia; if one sib has peripheral epimerase deficiency galactosemia, other sibs in that family are likely to have the same form.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing symptoms of generalized epimerase deficiency galactosemia.

Offspring of a proband. Unless an affected individual's reproductive partner also has epimerase deficiency galactosemia or is a carrier, offspring will be heterozygous for a pathogenic variant in *GALE* but will not be affected unless a second *GALE* pathogenic variant is acquired by an alternative genetic mechanism (e.g., a *de novo* pathogenic variant or uniparental isodisomy).

Other family members. Assuming no other family history of galactosemia, each full sib of the proband's parents is at a 50% risk of being a carrier of the familial *GALE* pathogenic variant.

Carrier Detection

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

Note: Although biochemical testing to detect carriers is also a possibility, the ranges for control and carrier GALE enzyme activity overlap, thus making molecular genetic testing the preferred method for carrier detection.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 affected, are carriers, or are at increased risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

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

Note: Theoretically, prenatal testing could be accomplished by enzymatic studies of amniocytes or CVS tissue; however, due to lack of a GALE reference range for the relevant sample type and appropriate controls, this testing is not typically offered on a clinical basis.

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.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  Galactosaemia

- **Medical Home Portal**
  Galactosemia

- **The Galactosemia Foundation**
  350 Northern Boulevard
  Suite 324 - 1079
  Albany NY 12204-1000
  Phone: 866-900-7421
  Email: outreach@galactosemia.org
  www.galactosemia.org

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

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. Epimerase Deficiency Galactosemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GALE	1p36.11	UDP-glucose 4-epimerase	GALE database	GALE	GALE

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 Epimerase Deficiency Galactosemia (View All in OMIM)

230350	GALACTOSEMIA III; GALAC3
606953	UDP-GALACTOSE-4-EPIMERASE; GALE

Molecular Pathogenesis

Galactose is metabolized in humans and other species by the three-enzyme Leloir pathway comprising the enzymes galactokinase (GALK, EC 2.7.1.6), galactose 1-P uridylyltransferase (GALT, EC 2.7.7.12), and UDP-galactose 4'-epimerase (GALE, EC 5.1.3.2). A fourth enzyme, galactose mutarotase (GALM, EC 5.1.3.3), catalyzes the epimerization of β-D-galactose, released from lactose, to α-D-galactose, which is a substrate for GALK. As illustrated in Figure 1, GALE catalyzes an essential step in this pathway converting UDP-galactose to UDP-glucose. GALE is a reversible enzyme that also catalyzes the synthesis of UDP-galactose from UDP-glucose when other sources of UDP-galactose are limiting. Functioning outside of the Leloir pathway, GALE also interconverts UDP-N-acetyl galactosamine and UDP-N-acetylglucosamine. All four of these UDP-sugars are essential substrates for the biosynthesis of glycoproteins and glycolipids in humans.

As in classic galactosemia, the cataracts associated with epimerase deficiency galactosemia are believed to be caused by galactitol accumulation in the ocular lens; it is possible, but not proven, that other acute findings may be caused by tissue accumulation of gal-1P (galactose-1-phosphate) or other metabolites.

Persons with epimerase deficiency galactosemia who are exposed to galactose demonstrate abnormal accumulation of UDP-galactose (UDP-gal). However, because GALE is required in humans for the endogenous biosynthesis of UDP-gal and also UDP-N-acetylgalactosamine (UDP-galNAc), at least part of the pathophysiology of epimerase deficiency galactosemia may result from inadequate production of these compounds, especially in utero, ostensibly leading to deficient or aberrant production of glycoproteins and glycolipids including cerebrosides.

Mechanism of disease causation. Loss of function

No individuals with complete loss of GALE enzyme activity in non-peripheral cells have been reported [Kalckar 1965]. In addition, fruit fly [Sanders et al 2010, Daenzer et al 2012] and *C elegans* [Brokate-Llanos et al 2014] models for GALE impairment suggest that complete loss of GALE enzyme activity may be lethal.

The c.280G>A (p.Val94Met) pathogenic variant, which is associated with a severe presentation, leaves approximately 5% residual enzyme activity with regard to UDP-gal metabolism and close to 25% residual enzyme activity with regard to UDP-galNAc metabolism [Wohlers et al 1999, Wohlers & Fridovich-Keil 2000].

Table 6. Notable *GALE* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000403.4 NP_000394.2	c.151C>T	p.Arg51Trp	Segregated w/thrombocytopenia in a consanguineous family [Seo et al 2019]; see Genetically Related Disorders.
	c.280G>A	p.Val94Met	Identified in homozygous state in persons w/severe, generalized form of epimerase deficiency galactosemia [Wohlers et al 1999, Dias Costa et al 2017]
	c.505C>T	p.Arg169Trp	Account for 67% of alleles reported in a cohort of asymptomatic Koreans w/ peripheral epimerase deficiency galactosemia [Park et al 2005]
	c.715C>T	p.Arg239Trp	
	c.905G>A	p.Gly302Asp	
	c.770A>G	p.Lys257Arg	Assoc w/asymptomatic peripheral epimerase deficiency galactosemia in African Americans [Alano et al 1997, Openo et al 2006]
	c.956G>A	p.Gly319Glu	

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

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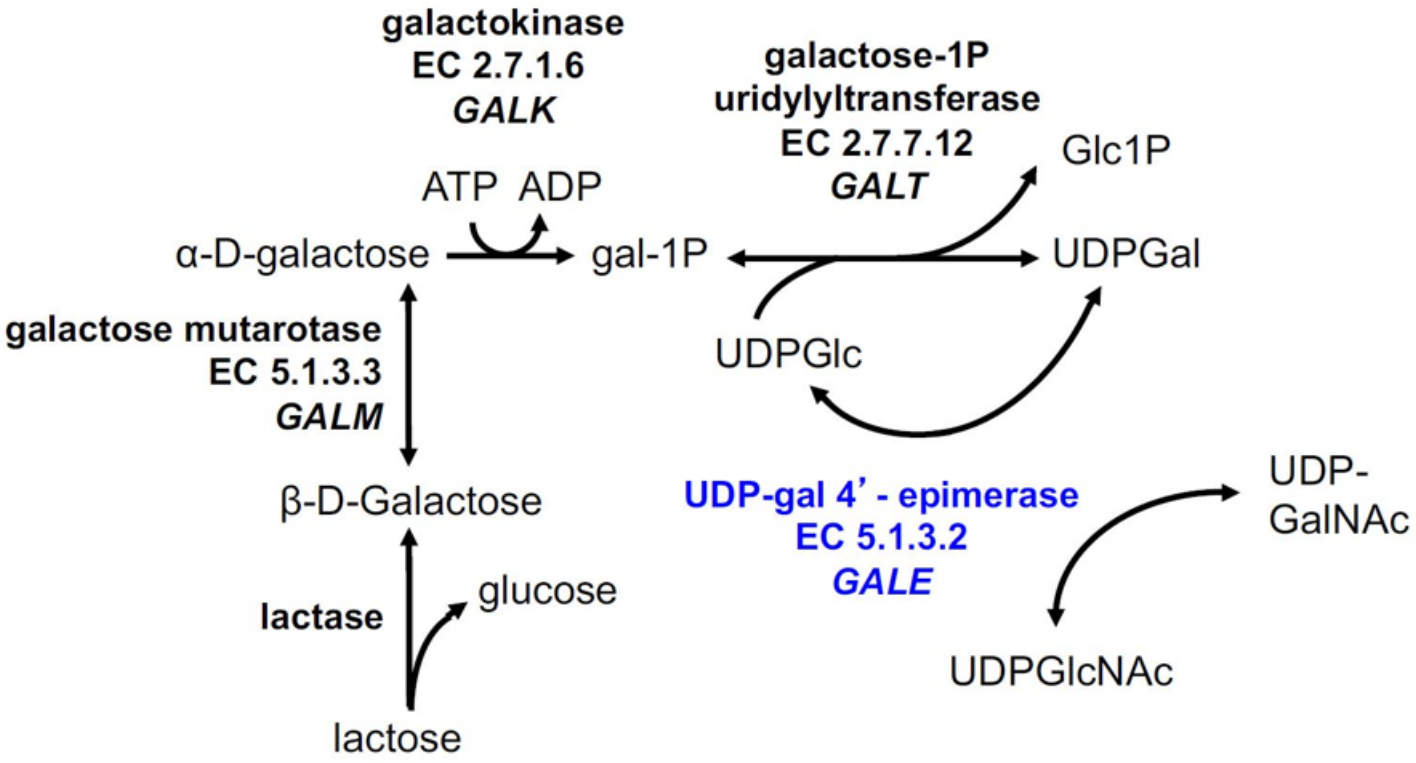

Figure 1. Leloir pathway

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