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Epimerase Deficiency Galactosemia

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

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Summary

Clinical characteristics. 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 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. 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 and/or the identification of biallelic pathogenic variants in *GALE* on molecular genetic testing. The degree of GALE enzyme activity impairment in RBC does not distinguish between the clinically severe generalized and the milder intermediate or peripheral forms of epimerase deficiency. Further testing in other cell types such as stimulated leukocytes or EBV-transformed lymphoblasts is required to make that distinction.

Management. *Treatment of manifestations:* The 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.

Prevention of primary manifestations: In generalized epimerase deficiency galactosemia, restriction of dietary galactose/lactose appears to correct or prevent the 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 children. 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.

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 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. At conception, 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 and prenatal testing for pregnancies at increased risk 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 (on a normal milk diet) with the following newborn screening results, clinical features, and supportive laboratory findings:

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 affected infant will have

a normal newborn screening result for galactosemia.

Clinical features

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

Supportive laboratory findings

- 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 enzyme activity

Establishing the Diagnosis

A diagnosis of epimerase deficiency galactosemia **is established** in a proband by one 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

  AND/OR

- <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]

  AND/OR

- The identification of biallelic pathogenic variants in *GALE* on molecular genetic testing (see Table 1)

Molecular testing approaches can include **single-gene testing** and use of a **multi-gene 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 multi-gene 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 varies by laboratory and over time. (2) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing based tests.

Table 1.

Molecular Genetic Testing Used in Epimerase Deficiency Galactosemia

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This 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 allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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 Fridovich-Keil & Walter [2008]); 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 that may be used include: 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. 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 [Fridovich-Keil & Walter 2008] 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 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

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. 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: fewer than ten persons with this form have been reported [Walter et al 1999, Sarkar et al 2010]. 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. Of note, a majority of the individuals reported were born to consanguineous parents, raising the concern that homozygosity for other autosomal recessive alleles, independent of *GALE*, may underlie some if not most of the long-term complications reported. Those few individuals with generalized epimerase deficiency who have been followed long-term demonstrate apparently normal puberty with no apparent evidence of premature ovarian insufficiency [Walter et al 1999].

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 by 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.

Pathophysiology

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). 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.

Genotype-Phenotype Correlations

Because insufficient numbers of individuals with molecularly confirmed epimerase deficiency galactosemia have been followed clinically to identify genotype/phenotype correlations, studies of transformed lymphoblasts or other "non-peripheral" cell types are the only way to distinguish biochemically between the different forms of epimerase deficiency galactosemia [Mitchell et al 1975, Openo et al 2006].

Nomenclature

Some authors refer to the different forms of galactosemia as type I, type II, and type III 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)

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 American infants of European ancestry [Alano et al 1997, Fridovich-Keil & Walter 2008].

Genetically Related (Allelic) Disorders

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

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 problems, 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 problems (termed childhood apraxia of speech and dysarthria), and abnormalities of motor function. The vast majority of women with classic galactosemia manifest premature ovarian insufficiency (POI).
- **Clinical variant galactosemia** can result in life-threatening complications in untreated infants including feeding problems, 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 the p.Ser135Leu *GALT* allele that occurs at high frequency in African Americans and native Africans in South Africa. Persons with clinical variant galactosemia may be missed with newborn screening (NBS) as the hypergalactosemia is not as marked as in classic galactosemia. 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).** Persons with Duarte variant galactosemia who are fed breast milk or a lactose-containing formula are typically (though not always) asymptomatic, at least as infants.

Galactokinase (GALK) deficiency (OMIM) 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 do NOT accumulate gal-1P. The cataracts 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. Detection of reduced GALK enzyme activity in hemolysates is diagnostic. Biallelic pathogenic variants in *GALK1* are causative [Kolosha et al 2000, Hunter et al 2001]; inheritance is autosomal recessive. The prevalence of GALK deficiency in most populations is unknown; however, a recent 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.

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

- Portosystemic venous shunting
- Hepatic arteriovenous malformations
- Fanconi-Bickel syndrome (OMIM) due to biallelic pathogenic variants in *SLC2A2*. Individuals with this condition have hepatorenal glycogen accumulation, impaired utilization of glucose and galatose, and proximal tubular nephropathy.
- Congenital disorder of glycosylation type 1T (OMIM) due to 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 can develop intermittent hypoglycemia, dilated cardiomyopathy, exercise intolerance with increased serum creatine kinase, and liver disease.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with epimerase deficiency galactosemia the following evaluations are recommended:

- Measurement of height, weight, and head circumference
- Nutrition and feeding assessments
- Neurologic examination
- Developmental assessment
- Liver function testing (serum AST, ALT, albumin, total protein, total and conjugated bilirubin, prothrombin time, and partial thromboplastin time)
- Ophthalmology consult to evaluate for cataracts
- Consultation with a clinical geneticist

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. This means switching infants from breast milk or a milk-based formula to a formula with only trace levels of galactose or lactose, such as soy formula. Of note, some infants with classic galactosemia are prescribed elemental formula, which has even lower galactose content than soy formula. 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**. However, the galactose intake needed for optimum outcome remains unknown.

For older children with generalized epimerase deficiency galactosemia, dietary restriction of galactose/lactose involves continued restriction of dairy products.

Note: Some, but not all, physicians recommend that individuals with classic galactosemia also abstain from non-dairy foods that contain more than trace levels of galactose/lactose (e.g., some fruits and vegetables, organ meats); this more rigorous dietary restriction may not be advisable for persons with generalized epimerase deficiency galactosemia.

In generalized epimerase deficiency galactosemia restriction of dietary galactose/lactose appears to correct or prevent the 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). Mature cataracts that do not resolve with dietary restriction of galactose/lactose may require surgical removal.

Peripheral Epimerase Deficiency Galactosemia

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

Intermediate Epimerase Deficiency Galactosemia

Individuals with intermediate epimerase deficiency galactosemia are typically treated with dietary galactose/lactose restriction, at least in infancy. They may be 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.

Prevention of Primary Manifestations

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

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.

Surveillance

The following are appropriate:

- Monitor hemolysate gal-1P or urinary galactitol, especially if the diet is to be normalized. 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.
- Follow growth.
- Monitor developmental milestones; propose supportive intervention as needed.

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 from birth until results of diagnostic testing are available. Diagnostic evaluations can include:

- 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 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing symptoms of generalized epimerase deficiency galactosemia.

Sibs of a proband

- At conception, 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 also not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing symptoms of generalized epimerase deficiency galactosemia.

- 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 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.

Offspring of a proband. All of the offspring conceived by an affected individual with an unaffected, non-carrier partner are obligate heterozygotes (carriers) for a pathogenic variant in *GALE*.

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 a pathogenic variant in *GALE*.

Carrier (Heterozygote) Detection

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

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.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing symptoms of generalized epimerase deficiency galactosemia.

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, clarification of carrier status, and discussion of the availability of prenatal 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 or at increased risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *GALE* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for epimerase deficiency galactosemia are possible options.

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.

- **Save Babies Through Screening Foundation, Inc.**
  P. O. Box 42197
  Cincinnati OH 45242
  Phone: 888-454-3383
  Email: email@savebabies.org
  www.savebabies.org

- **The Galactosemia Foundation**
  P.O. Box 2401
  Mandeville LA 70471
  Phone: 866-900-7421
  Email: president@galactosemia.org
  galactosemia.org

- **Association for Neuro-Metabolic Disorders (ANMD)**
  5223 Brookfield Lane
  Sylvania OH 43560-1809
  Phone: 419-885-1809; 419-885-1497
  Email: volk4olks@aol.com

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org

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	GALACTOSE EPIMERASE DEFICIENCY
606953	UDP-GALACTOSE-4-EPIMERASE; GALE

Gene structure. *GALE* is just over 4 kb in length and has 11 coding exons that together encode a protein of 348 amino acids. Multiple alternatively spliced transcripts encoding the same protein have been identified. Transcript NM_000403.3 represents the longest transcript with 1647 nucleotides and 12 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. For the purposes of this review, variants are considered pathogenic if they have been shown to reduce GALE expression, stability, or catalytic function in any cell type or assay system, whether or not they are known to cause clinical features. Most individuals identified with epimerase deficiency galactosemia are clinically asymptomatic, but do have *GALE* sequence variants that explain, or may explain, their biochemical findings.

One pathogenic variant, c.280G>A, has been identified in the homozygous state in persons with the severe, generalized form of epimerase deficiency galactosemia [Wohlers et al 1999]. This pathogenic variant 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].

Other pathogenic variants have been shown to cause moderate to severe reduction in GALE enzyme activity in vitro or in model systems (e.g., c.269G>A or c.548T>C [Quimby et al 1997, Wohlers et al 1999, Timson 2005]), but to date these alleles have been identified only in persons who are heterozygotes or compound heterozygotes.

The in vivo consequence of homozygosity for apparently severe pathogenic variants other than c.280G>A is unknown. Of note, no individuals reported with GALE enzyme deficiency have been completely null for GALE enzyme activity in non-peripheral cells: biochemical reasoning [Kalckar 1965] as well as 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 incompatible with life for humans and other metazoans.

The potential for interaction between two *GALE* alleles must also be considered. For example, a partial dominant-negative effect has been described in a yeast model system for the c.548T>C pathogenic variant, which demonstrates low GALE enzyme activity, and the c.101A>G pathogenic variant, which demonstrates slightly reduced GALE enzyme activity when expressed alone [Quimby et al 1997].

GALE variant alleles that are common in specific populations include the following:

- The c.505C>T, c.715C>T, and c.905G>A pathogenic variants together account for 67% of alleles reported in a cohort of asymptomatic Koreans with peripheral epimerase deficiency galactosemia [Park et al 2005].
- The c.770A>G and c.956G>A pathogenic variants are associated with asymptomatic peripheral epimerase deficiency galactosemia in African Americans [Alano et al 1997, Fridovich-Keil & Walter 2008].

Table 2.

Selected *GALE* Allelic Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Peripheral	c.505C>T	p.Arg169Trp	NM_000403.3 NP_000394.2
	c.715C>T	p.Arg239Trp	
	c.770A>G	p.Lys257Arg	
	c.905G>A	p.Gly302Asp	
	c.956G>A	p.Gly319Glu	
Suspected intermediate	c.101A>G	p.Asn34Ser [1]	
Reported or suspected generalized	c.269G>A	p.Gly90Glu	
	c.280G>A	p.Val94Met	
	c.548T>C	p.Leu183Pro [1]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Observed in *trans* in an individual with intermediate GALE deficiency; however, expression studies in a yeast model system demonstrated that p.Leu183Pro causes profound loss of GALE activity. The individual in whom this allele was identified may have had intermediate GALE deficiency because the other allele was mild (p.Asn34Ser). Evidence for a potential dominant-negative effect between p.Asn34Ser and p.Leu183Pro has also been reported.

Normal gene product. The UDP-galactose 4'-epimerase (known in UniProt as UDP-glucose 4-epimerase) protein encoded by *GALE* has 348 amino acids.

Abnormal gene product. Deficient GALE activity, either generalized or peripherial, causes epimerase deficiency galactosemia.

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Chapter Notes

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Figures

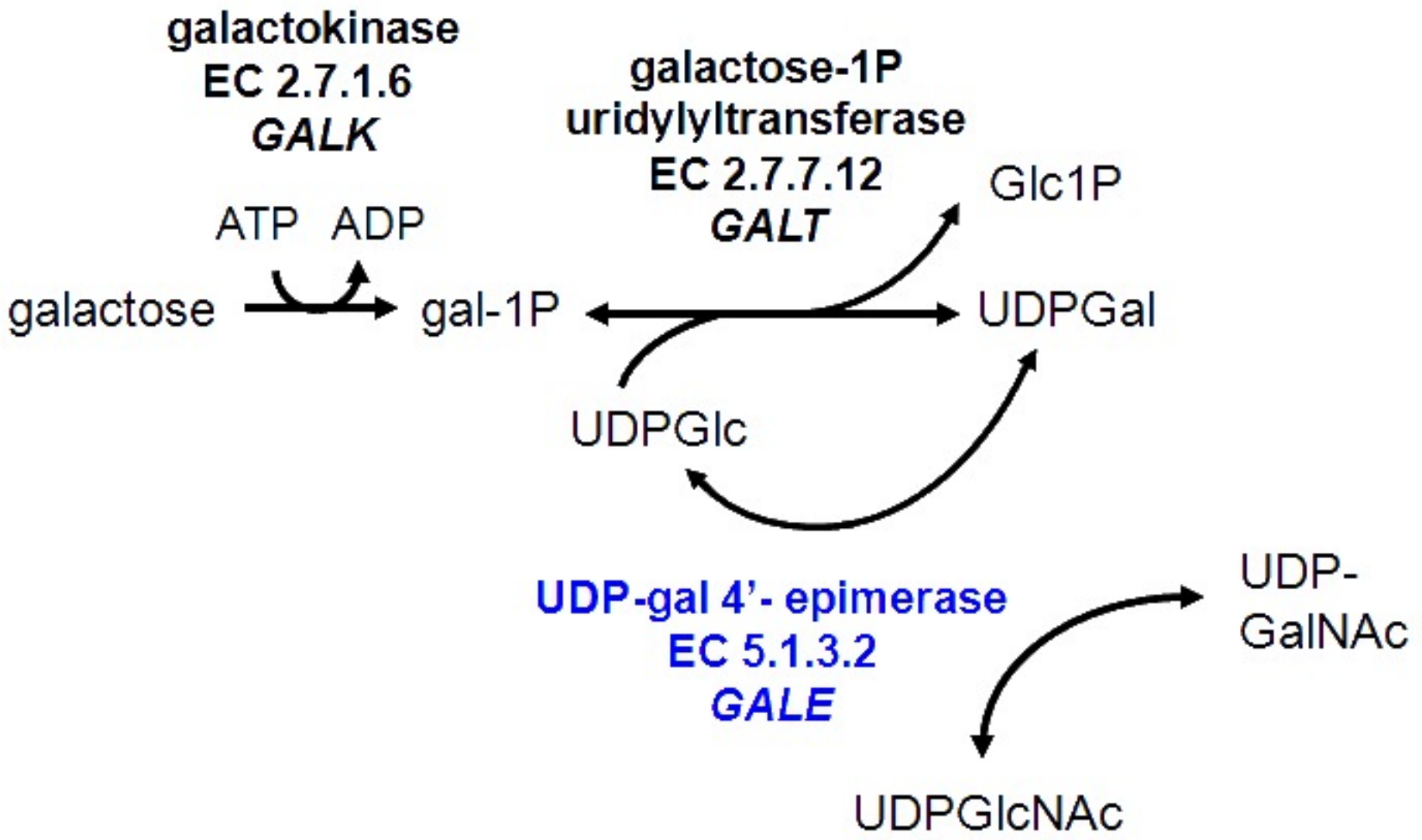

Figure 1

Leloir pathway

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