Classic Galactosemia and Clinical Variant Galactosemia

Synonyms: GALT Deficiency, Galactose-1-Phosphate Uridylyltranserase Deficiency

Gerard T Berry, MD, FFACMG
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts
gerard.berry@childrens.harvard.edu

Summary

Clinical characteristics. The term galactosemia refers to disorders of galactose metabolism that include classic galactosemia, clinical variant galactosemia, and biochemical variant galactosemia. This *GeneReview* focuses on:

- Classic galactosemia, which 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. Almost all females with classic galactosemia manifest premature ovarian insufficiency (POI).

- Clinical variant galactosemia, which can result in life-threatening complications including feeding problems, failure to thrive, hepatocellular damage including cirrhosis and bleeding in untreated infants. This is exemplified by the disease that occurs 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 and breath testing is normal. If a lactose-restricted diet is provided during the first ten days of life, the severe acute neonatal complications are usually prevented. African Americans with clinical variant galactosemia and adequate early treatment do not appear to be at risk for long-term complications including POI.

Diagnosis/testing. The diagnosis of classic galactosemia and clinical variant galactosemia is established by detection of elevated erythrocyte galactose-1-phosphate concentration, reduced erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity, and/or biallelic pathogenic variants in *GALT*.

In classic galactosemia, erythrocyte galactose-1-phosphate is usually higher than 10 mg/dL and erythrocyte GALT enzyme activity is absent or barely detectable. In clinical variant galactosemia, erythrocyte GALT enzyme activity (which may be absent or barely detectable, as in African Americans) is much higher in brain and intestinal tissue (e.g., 10% of control values). Other individuals with clinical variant galactosemia may have erythrocyte GALT enzyme activity close to or above 1% of control values but probably never above 10%-15%.

Virtually 100% of infants with classic galactosemia or clinical variant galactosemia can be detected in newborn screening programs that include testing for galactosemia in their panel. However, infants with clinical variant galactosemia may be missed if the program only measures blood total galactose level and not erythrocyte GALT enzyme activity.

Management. *Prevention of primary manifestations*: Standard of care in any newborn who is "screen-positive" for galactosemia is immediate dietary intervention while diagnostic testing is underway. If erythrocyte galactose-1-phosphate concentration is >10 mg/dL and erythrocyte GALT enzyme activity is ≤10% of control activity (i.e., the child has classic galactosemia or clinical variant galactosemia), restriction of galactose intake is continued and all

milk products are replaced with lactose-free formulas (e.g., Isomil® or Prosobee®) containing non-galactose carbohydrates; management of the diet becomes less important after infancy and early childhood.

Treatment of manifestations: In rare instances, cataract surgery may be needed in the first year of life. Childhood apraxia of speech and dysarthria require expert speech therapy. Developmental assessment at age one year by a psychologist and/or developmental pediatrician is recommended in order to formulate a treatment plan with the speech therapist and treating physician. For school age children, an individual education plan and/or professional help with learning skills and special classrooms as needed. Hormone replacement therapy as needed for delayed pubertal development and/or primary or secondary amenorrhea.

Prevention of secondary complications: Recommended calcium, vitamin D, and vitamin K intake to help prevent decreased bone mineralization.

Surveillance: Routine monitoring for: the accumulation of toxic analytes (e.g., erythrocyte galactose-1-phosphate and urinary galactitol); cataracts; speech and development; POI; and osteoporosis.

Agents/circumstances to avoid: Breast milk, proprietary infant formulas containing lactose, cow's milk, dairy products, and casein or whey-containing foods; medications with lactose and galactose.

Pregnancy management: Women with classic galactosemia should maintain a lactose restricted diet during pregnancy.

Evaluation of relatives at risk: To allow for earliest possible diagnosis and treatment of at-risk sibs:

- Perform prenatal diagnosis when the *GALT* pathogenic variants in the family are known; or

- If prenatal testing has not been performed, test the newborn for either the family-specific *GALT* pathogenic variants or erythrocyte GALT enzyme activity.

Genetic counseling. Classic galactosemia and clinical variant galactosemia are inherited in an autosomal recessive manner. Couples who have had one affected child have a 25% chance of having an affected child in each subsequent pregnancy. Molecular genetic carrier testing for at-risk sibs and prenatal diagnosis for pregnancies at increased risk are an option if the *GALT* pathogenic variants in the family are known. If the *GALT* pathogenic variants in a family are not known, prenatal testing can rely on assay of GALT enzyme activity in cultured amniotic fluid cells.

Diagnosis

Classic galactosemia and clinical variant galactosemia are the topics covered in this *GeneReview*. Individuals with these forms of galactosemia will or may exhibit clinical disease. An international clinical guideline for the diagnosis, management, treatment and follow-up of classic galactosemia has been published [Welling et al 2017].

The biochemical variant form of galactosemia is exemplified by the Duarte Variant Galactosemia and is thought by many to not be a real disease (see also Genetically Related Disorders) [Berry 2012].

Suggestive Findings

Classic galactosemia and clinical variant galactosemia **should be suspected** in individuals with the following newborn screening results, clinical features, family history and supportive laboratory findings:

Newborn screening

- Positive newborn screen for galactosemia (National Newborn Screening Status Report [pdf])

- Newborn screening utilizes a small amount of blood obtained from a heel prick to quantify:

  - Total content of erythrocyte galactose-1-phosphate and blood galactose concentration; and/or

  - Erythrocyte GALT enzyme activity.

- State Newborn Screening (NBS) programs vary as to which of these tests is performed – or, if both are

performed, in what sequence.

Clinical features

- Untreated Infant:
    - Feeding problems
    - Failure to thrive
    - Liver failure
    - Bleeding
    - *E. coli* sepsis
- Untreated older person:
    - Developmental delay
    - Speech problems
    - Abnormalities of motor function, including extrapyramidal findings with ataxia
    - Cataracts
    - Liver failure/cirrhosis
    - Premature ovarian failure in females

Family history of an affected sibling. Note: Lack of a family history of galactosemia does not preclude the diagnosis.

Supportive laboratory findings

- In classic galactosemia:
    - Erythrocyte galactose-1-phosphate may be as high as 120 mg/dL, but usually is >10 mg/dL in the newborn period. When the affected individual is on a lactose-free diet, the level is ≥1.0 mg/dL. Normal level of erythrocyte galactose-1-phosphate is <1 mg/dL.
    - Plasma free galactose is usually >10 mg/dL, but may be as high as 90-360 mg/dL (5-20 mmol/L).
    - Galactose-1-phosphate uridylyltranserase (GALT) enzyme activity that is absent or barely detectable.
- In clinical variant galactosemia:
    - Erythrocyte galactose-1-phosphate is usually >10 mg/dL. When the affected individual is on a lactose-free diet, the level is usually <1.0 mg/dL. Normal level of erythrocyte galactose-1-phosphate is <1 mg/dL.
    - Plasma free galactose is usually >10 mg/dL, but may be as high as 90-360 mg/dL (5-20 mmol/L).
    - Erythrocyte GALT enzyme activity that is 1%-10% of normal

      In certain populations (e.g., African Americans with hypomorphic alleles including p.Ser135Leu/Ser135Leu), erythrocyte GALT enzyme activity may be absent or barely detectable.

Establishing the Diagnosis

The diagnosis of classic galactosemia and clinical variant galacosemia **is established** in a proband by detection of elevated erythrocyte galactose-1-phosphate concentration, reduced erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity, and/or biallelic pathogenic variants in *GALT* (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**:

- **Sequence analysis** of *GALT* is performed first and followed by **gene-targeted deletion/duplication analysis** if only one or no pathogenic variant is found.

- **Targeted analysis** for common pathogenic variants can be performed first in individuals of European or African ancestry (see Table 1). This approach is most efficient when testing large numbers of samples (e.g., carrier screening or newborn screening).

Table 1.

Molecular Genetic Testing Used in Classic Galactosemia and Clinical Variant Galactosemia

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
GALT	Targeted analysis [3, 4]	~90% [5, 6]
	Sequence analysis [7]	>95% [8]
	Gene-targeted deletion/duplication analysis [9]	See footnotes 4, 10

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. Common pathogenic variants associated with classic galactosemia include p.Gln188Arg, p.Lys285Asn, p.Leu195Pro, p.Tyr209Cys, p.Phe171Ser, and c.253-2A>G (common in Hispanics) [Elsas & Lai 1998], as well as the p.Ser135Leu pathogenic variant associated with clinical variant galactosemia and the D_2 Duarte (c.[940A>G;c.-119_116delGTCA]) pathogenic variant, which is almost always associated with biochemical variant galactosemia (see Genetically Related Disorders).
4. The 5.2-kb deletion is common in the Ashkenazim (see Molecular Genetics, **Pathogenic variants**).
5. Pathogenic variants included in targeted variant panels may vary by laboratory; detection rates will vary accordingly.
6. In individuals with biochemically confirmed classic galactosemia and clinical variant galactosemia [Elsas & Lai 1998]
7. 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.
8. Tyfield et al [1999]
9. 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.
10. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

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) 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. This categorization allows for proper counseling of the parents of an infant with galactosemia, especially regarding the so-called diet-independent complications.

Classic Galactosemia

Within days of ingesting breast milk or lactose-containing formulas, infants with classic galactosemia develop life-threatening complications including feeding problems, failure to thrive, hypoglycemia, hepatocellular damage, bleeding diathesis, and jaundice (see Table 2). If classic galactosemia is not treated, sepsis with *Escherichia coli*, shock, and death may occur [Levy et al 1977]. Infants who survive the neonatal period and continue to ingest lactose may develop severe brain damage [Otaduy et al 2006].

Table 2.

Frequency of Specific Findings in Symptomatic Neonates with Classic Galactosemia

Finding	Percent of Affected Neonates w/Finding	Additional Details
Hepatocellular damage	89%	Jaundice (74%) Hepatomegaly (43%) Abnormal liver function tests (10%) Coagulation disorders (9%) Ascites (4%)
Food intolerance	76%	Vomiting (47%) Diarrhea (12%) Poor feeding (23%)
Failure to thrive	29%	
Lethargy	16%	
Seizures	1%	
Sepsis	10%	*Escherichia coli* (26 cases) *Klebsiella* (3) *Enterobacter* (2) *Staphylococcus* (1) *Beta-streptococcus* (1) *Streptococcus faecalis* (1)

From a survey reporting findings in 270 symptomatic neonates [Waggoner et al 1990]

If a lactose-free diet is provided during the first three to ten days of life, the signs resolve quickly and prognosis for prevention of liver failure, *Escherichia coli* sepsis, and neonatal death is good. Failure to implement effective newborn screening may have catastrophic consequences such as liver failure [Malone et al 2011].

If the diagnosis of classic galactosemia is not established, the infant who is partially treated with intravenous antibiotics and self-restricted lactose intake demonstrates relapsing and episodic jaundice and bleeding from altered hemostasis concomitant with the introduction of lactose. If treatment is delayed, complications such as poor growth retardation and progressive liver disease are likely. Rare affected individuals may develop vitreous hemorrhages that may produce blindness [Levy et al 1996, Takci et al 2012].

Even with early and adequate therapy, the long-term outcome in older children and adults with classic galactosemia can include cataracts, speech defects, poor growth, poor intellectual function, neurologic deficits (predominantly extrapyramidal findings with ataxia), and premature ovarian insufficiency (POI) [Schweitzer-Krantz 2003].

Classic galactosemia is associated with extreme variability in chronic complications and/or long-term outcome. Even individuals who have not been sick in the newborn period and who were begun on a lactose-free diet from birth (e.g., those with a prior affected sib in the family) may manifest language delay, speech defects, learning disabilities, cognitive impairment, and, in females, premature ovarian insufficiency. These problems may manifest as early as age one to two years, and in almost all instances, no findings that would have predicted eventual brain and ovarian dysfunction were present in early infancy. A minority of individuals may exhibit documented neurologic

abnormalities including tremor (postural or intentional), cerebellar ataxia, and dystonia. No findings early in the disease course are good predictors of these long-term complications. Overall, the quality of life is reduced in adults with classic galactosemia, and more so when compared to individuals with phenylketonuria (PKU) [Gubbels et al 2011, ten Hoedt et al 2011, Hoffmann et al 2012].

Outcome and the "disease burden" can be predicted based on the level of erythrocyte GALT enzyme activity, *GALT* genotype, age at which successful therapeutic control was achieved, and compliance with lactose restrictions. Formal outcome analysis for POI and for verbal dyspraxia found the $^{13}CO_2$ breath test (available on a research basis only) to be the most sensitive and specific prognostic parameter [Guerrero et al 2000, Webb et al 2003, Barbouth et al 2006].

The following details on long-term outcome were reported by Waggoner et al [1990] as the result of a retrospective, cross-sectional survey of 270 individuals with classic galactosemia. To summarize, the data on long-term outcome indicate that complications involving the nervous system and ovary do not correlate with any of the well-known biochemical variables (e.g., erythrocyte galactose-1-phosphate levels); furthermore, manifestations of one or more of these complications vary even among individuals with the same genotype associated with classic galactosemia (see Table 3) [Doyle et al 2010, Schadewaldt et al 2010, Hoffmann et al 2011, Krabbi et al 2011, Coss et al 2012, Waisbren et al 2012].

Intellectual development. Of 177 individuals age six years or older with no obvious medical causes for developmental delay other than galactosemia, 45% were described as developmentally delayed. The mean IQ scores of the individuals as a group declined slightly (4-7 points) with increasing age. Studies of Dutch individuals at various ages using a quality of life questionnaire indicated subnormal cognitive outcomes [Bosch et al 2004b].

Speech problems were reported in 56% (136/243) of individuals age three years or older.

More than 90% of individuals with speech problems were described as having delayed vocabulary and articulation problems. The speech problems resolved in only 24%. A more formal analysis found speech problems in 44% of individuals; 38% had a specific diagnosis including childhood apraxia of speech [Robertson & Singh 2000, Webb et al 2003]. Speech defects are heterogeneous, involving both central defects and motor abnormalities, and evolve with time [Potter et al 2013].

The developmental quotients and IQ scores observed in individuals with speech disorders as a group were significantly lower than those of individuals with normal speech; however, some individuals with speech problems tested in the average range.

Motor function. Among individuals older than age five years, 18% had fine-motor tremors and problems with coordination, gait, and balance. Severe ataxia was observed in two teenagers. Adults manifested tremors, dysarthria, cerebellar ataxia and dystonia [Waisbren et al 2012, Rubio-Agusti et al 2013].

Gonadal function. Of 47 girls and women, 81% had signs of premature ovarian insufficiency (POI). The mean age at menarche was 14 years with a range from ten to 18 years. Eight out of 34 women older than age 17 years (including 2 with "streak gonads") had primary amenorrhea. Most women developed oligomenorrhea and secondary amenorrhea within a few years of menarche. Only five out of 17 women older than age 22 years had normal menstruation. Two, who gave birth at ages 18 and 26 years, had never experienced normal menstrual periods.

Guerrero et al [2000] determined that the development of POI in females with galactosemia is more likely if the following are true:

- The individual is homozygous for p.Gln188Arg;

- The mean erythrocyte galactose-1-phosphate concentration is greater than 3.5 mg/dL during therapy; and

- The recovery of 13CO2 from whole-body 13C galactose oxidation is reduced below 5% of administered 13C galactose.

Normal serum concentrations of testosterone and/or follicle-stimulating hormone (FSH) and luteinizing hormone

(LH) were reported for males. However, the literature has few reports of males with classic galactosemia who have fathered a child [Panis et al 2006a, Waisbren et al 2012, Gubbels et al 2013]. There have been no data to support structural abnormalities in the male reproductive tract that would lead to infertility; preliminary data suggest an increased prevalence of cryptorchidism and low semen volume [Gubbels et al 2013].

Growth. In many individuals, growth was severely delayed during childhood and early adolescence; when puberty was delayed and growth continued through the late teens, final adult heights were within the normal range. Decreased height over mean parental height was related to low insulin-like growth factor-I (IGF-I) [Panis et al 2007].

Cataracts were reported in 30% of 314 individuals. Nearly half the cataracts were described as "mild," "transient," or "neonatal" and resolved with dietary treatment; only eight were treated surgically. Dietary treatment had begun at a mean age of 77 days for those with cataracts compared to 20 days for those without cataracts. However, one of the eight individuals who required cataract surgery was an infant who had been treated from birth.

Relationship between treatment and outcome. No significant associations were found between treatment and outcome except for a greater incidence of developmental delay among individuals who were not treated until after age two months. However, IQ scores were not highly correlated with the age at which treatment began. The effect of early treatment on outcome was also studied in 27 sibships, three of which had three affected sibs. The older sibs were diagnosed and treated after clinical symptoms occurred or newborn screening results had been reported, whereas the younger sibs were treated within two days of birth. Although the younger sibs were treated early and only one developed neonatal symptoms, the differences in IQ scores among the sibs were not statistically significant, and the speech and ovarian function of the younger sibs were no better than those of their older sibs.

Restriction of milk in the mother's diet during pregnancy was reported for 21 of the 38 infants who were treated from birth. The long-term outcome of these 21 was no better than that of the 17 individuals whose intake of mother's milk was not restricted during the pregnancy.

No significant differences could be observed in the rate of complications between the individuals with residual enzyme activity and those with no measurable enzyme activity, except that individuals with some enzyme activity tended to be taller for age.

Individuals with/without neurologic complications. No differences were observed in treatment or biochemical factors between the 56 individuals with normal intellect, speech, and motor function and the 25 individuals with developmental delay and speech and motor problems.

Relationships of complications. Developmental delay and low IQ scores were associated with speech problems, motor problems, and delayed growth, but not with abnormal ovarian function.

Gender differences. Females had lower mean IQ scores than males after age ten years (p <0.05) and had lower mean heights for age at five to 12 years (p <0.05), but did not differ in frequency of speech or motor problems or in the treatment variables, including age treatment began, neonatal illness, or galactose-1-phosphate erythrocyte concentration. However, the association of problems with intellectual development, speech, and motor function could also indicate a specific neurologic abnormality in some cases of galactosemia [Schadewaldt et al 2010].

Clinical Variant Galactosemia

Individuals with variant forms of galactosemia may have some aspects of classic galactosemia, including early cataracts, liver disease, mild intellectual disability with ataxia, and growth retardation [Fridovich-Keil et al 2011]. Clinical variant galactosemia can result in life-threatening complications in untreated infants including feeding problems, failure to thrive, hepatocellular damage (including cirrhosis), and bleeding.

Clinical variant galactosemia is exemplified by the disease that occurs in African Americans and native Africans in South Africa with a p.Ser135Leu/Ser135Leu genotype. Neonates with clinical variant galactosemia may be missed with newborn screening (NBS) because the hypergalactosemia is not as marked as in classic galactosemia and breath testing is normal [Crushell et al 2009].

If a lactose-restricted diet is provided during the first ten days of life, the severe acute neonatal complications are usually prevented.

To the best of current knowledge, African Americans with clinical variant galactosemia and adequate early treatment do not develop long-term complications including POI.

Pathophysiology

The GALT enzyme catalyzes the conversion of galactose-1-phosphate and UDPglucose to UDPgalactose and Glu-1-P in a two-step process termed a ping-pong or bi-bi molecular reaction (Figure 1):

1. UDPglucose binds to the active site and glucose-1-phosphate is released, leaving UMP covalently linked to the enzyme.

2. Galactose-1-phosphate then lands at the active site, engages the bound UMP, and following cleavage of the phosphonium bond, UDP galactose is released.

When GALT enzyme activity is deficient, galactose-1-phosphate, galactose, and galactitol accumulate (Figure 2). Galactose is converted to galactitol in cells and produces osmotic effects including swelling of lens fibers that may result in cataracts. The same process has been hypothesized to produce swelling of brain cells and subsequently, pseudotumor cerebri.

Since individuals with classic galactosemia who are prospectively treated may manifest all of the so-called chronic diet-independent complications, and since the amniotic fluid of affected fetuses contains high levels of galactitol and cord blood of affected newborns contains elevated levels of erythrocyte galactose-1-phosphate, one must consider whether the long-term complications of GALT enzyme deficiency are due to prenatal toxicity [Komrower 1982]. One hypothesis is that the prenatal CNS insult is secondary to myo-inositol deficiency [Berry 2011].

Genotype-Phenotype Correlations

Significant genotype-phenotype correlations have been noted [Shield et al 2000, Tyfield 2000]. Although the *GALT* genotype informs prognosis [Guerrero et al 2000, Webb et al 2003], some confusion about genotype-phenotype correlations appears to have resulted from the variability of the manifestations and severity of the chronic complications of classic galactosemia.

Use of the galactosemia classification system in Table 3 helps dispel confusion. The most common pathogenic variants that result in the three galactosemia phenotypes – classic, clinical variant, and biochemical variant – are shown in Table 3. (See Diagnosis and Genetically Related Disorders for definitions.)

Table 3.

GALT Genotypes and Biochemical/Clinical Phenotypes

Classic Galactosemia (Alias [1])	Clinical Variant Galactosemia (Alias [1])	Biochemical Variant Galactosemia (Alias [1])
p.[Gln188Arg]+[p.Gln188Arg] (Q188R/Q188R)	p.[Ser135Leu]+[Ser135Leu] (S135L/S135L) [2]	c.[940A>G; c.-16_119delGTCA] (4bp 5' del + N314D/Q188R) [3]
p.[Lys285Asn]+[Lys285Asn] (K285N/K285N)		
p.[Leu195Pro]+[Leu195Pro] (L195P/L195P)		
(Δ5.2 kb del/ Δ5.2 kb del) [4]		

1. Variant designation that does not conform to current naming conventions

2. The original identification of the p.Ser135Leu pathogenic variant was exclusively in African Americans; however, it is present on occasion in infants without known African American heritage.

3. Known as "Duarte variant galactosemia" or the "Duarte D$_2$ variant"

4. See Table 5, footnote 4.

p.Gln188Arg. Approximately 70% of the alleles in persons with GALT deficiency from the white population of northern European background have a substitution of an arginine for a glutamine at amino acid position 188 (p.Gln188Arg).

In the homozygous state, the pathogenic variant interferes with the catalytic reaction. It is associated with increased risks for premature ovarian insufficiency (POI) and childhood apraxia of speech [Robertson & Singh 2000].

In one cross-sectional retrospective study correlating genotype with outcome in individuals with classic galactosemia, a greater proportion of individuals with a poor outcome were homozygous for the p.Gln188Arg pathogenic variant, and a greater proportion with a good outcome were not homozygous for the p.Gln188Arg pathogenic variant. However, one adult female and one adult male homozygous for the p.Gln188Arg pathogenic variant who had begun normal lactose intake at age three years exhibited no worsening of the underlying classic galactosemia phenotype [Lee et al 2003, Panis et al 2006a].

p.Ser135Leu. The p.Ser135Leu allele, in which a leucine is substituted for serine at amino acid 135, is prevalent in Africa.

If therapy is initiated in the neonatal period, African Americans with galactosemia who have this allele in the homozygous state have a good prognosis. Generally, these individuals are not prone to *E. coli* sepsis in the neonatal period or chronic complications (i.e., speech disorder, POI, and intellectual disability) when treated from infancy [Lai et al 1996].

Data are limited on outcome in persons who are compound heterozygous (p.[Ser135Leu];[Gln188Arg]); however, they appear to have fewer complications than individuals with the genotype p.[Gln188Arg]+[p.Gln188Arg], associated with classic galactosemia.

p.Asn314Asp. The Duarte (D$_2$) variant is the allele in which an aspartate is substituted for asparagine at residue 314 (p.Asn314Asp) and a second variant in *cis* configuration – a 4-bp deletion in the promoter region (c.-119_116delGTCA) – results in reduced erythrocyte GALT enzyme activity. The D$_2$ allele designation is c. [940A>G; c.-119_116delGTCA].

In the homozygous state D$_2$ erythrocyte GALT enzyme activity is reduced by 50%.

Compound heterozygotes with D$_2$ and a pathogenic variant associated with classic galactosemia have a good prognosis [Langley et al 1997, Lai et al 1998].

However, compound heterozygosity for D$_2$ (Duarte) and D$_1$ (LA variant) is known to occur. The D$_1$ allele has a p.Leu218Leu in *cis* configuration with the p.Asn314Asp pathogenic variant p.[Leu218Leu;Asn314Asp], which confers "superactivity" (i.e., heterozygotes have ~117% erythrocyte GALT activity while homozygotes display ~134% activity).

Other. Substitution of an asparagine for a lysine at position 285 (p.Lys285Asn) is prevalent in southern Germany, Austria, and Croatia; it is associated with a poor prognosis for neurologic and cognitive function in either the homozygous state or compound heterozygous state with p.Gln188Arg and is considered classic galactosemia.

Other compound heterozygotes (e.g., p.[Gln188Arg]+[p.Arg333Gly]) have a good long-term outcome [Ng et al 2003].

- A clear genotype-phenotype correlation is seen when classic galactosemia with genotypes such as p. [Gln188Arg]+[p. Gln188Arg] is compared with clinical variant galactosemia caused by the p.[Ser135Leu]+ [p.Ser135Leu] genotype. For example, almost all females with the p.[Gln188Arg]+[p.Gln188Arg] genotype

manifest POI, whereas POI is almost unheard of in African American women with the p.[Ser135Leu]+[p.Ser135Leu] genotype. A critical unanswered question is how much residual GALT enzyme activity in target tissues there must be to eliminate chronic diet-independent complications. To illustrate, cryptic residual GALT enzyme activity may be a potential modifier of scholastic outcome in school-age children [Ryan et al 2013].

- While on a lactose-restricted diet, persons with classic galactosemia display erythrocyte galactose-1-phosphate levels between 1 to 5 mg/dL and urine galactitol levels between 100 to 400 μmol/mmol creatinine, whereas persons with a p.[Ser135Leu]+[p.Ser135Leu] genotype usually have an erythrocyte galactose-1-phosphate level below 1 mg/dL, and urine galactitol that is below 100 μmol/mmol creatinine and often in the normal range [Saudubray et al 2012, Walter & Fridovich-Keil 2014].

- Persons with biochemical variant galactosemia – for example, compound heterozygotes for c.563A>G (p.Gln188Arg) and D_2 c.[940A>G; c.-119_116delGTCA] genotype – differ from those with either classic galactosemia or clinical variant galactosemia: they generally exhibit no signs and symptoms of disease, only biochemical perturbations.

Note: Many of the more than 300 *GALT* pathogenic variants have been identified following newborn screening with little or no long-term follow-up data. In these instances, the term classic galactosemia should be applied with caution or not at all. It would be inappropriate to counsel new parents that their infant will develop one or more of the chronic complications seen in galactosemia without supportive data.

Nomenclature

The genetic hypergalactosemias

- Galactokinase deficiency secondary to pathogenic variants in *GALK*

- Epimerase deficiency galactosemia secondary to pathogenic variants in *GALE*

- Galactose-1-phosphate uridylyltransferase deficiency secondary to pathogenic variants in *GALT*
  - Classic galactosemia
    - Severe GALT enzyme deficiency with absent or barely detectable activity in erythrocytes and liver
    - Also known as G/G and carriers as G/N
  - Clinical variant galactosemia
    - 1%-10% residual GALT enzyme activity in erythrocytes and/or liver
  - Biochemical variant galactosemia
    - 15%-33% residual GALT enzyme activity in erythrocytes
    - Includes the D_2 Duarte biochemical variant state also known as G/D

Prevalence

Based on the results of newborn screening programs, the prevalence of classic galactosemia is 1:48,000 [National Newborn Screening and Genetics Resource Center 2014]. However, when erythrocyte GALT enzyme activity <5% of control activity and erythrocyte galactose-1-phosphate concentration >2 mg/dL are used as diagnostic criteria, some newborn screening programs record a prevalence of 1:10,000 [Bosch et al 2005].

The frequency of classic galactosemia in Ireland is 1:16,476 [Coss et al 2013].

While it is not possible to provide prevalence data for clinical variant galactosemia, the estimated prevalence of the p.Ser135Leu/Ser135Leu genotype is 1:20,000 [Henderson et al 2002].

Genetically Related (Allelic) Disorders

Duarte variant galactosemia, an example of biochemical variant galactosemia, is associated with specific pathogenic variants in *GALT*.

The Duarte variant (D$_2$) has in *cis* configuration (i.e., in the same allele) the pathogenic missense variant p.Asn314Asp and a GTCA deletion in the promoter region (c.-119-116delGTCA) that impairs a positive regulatory domain. It is designated c.[940A>G; c.-119_116delGTCA] (see Table 3).

Note: The Los Angeles (LA) variant (D$_1$) has the identical p.Asn314Asp pathogenic missense variant as the Duarte variant but does not have the GTCA promoter deletion. Instead, it is in *cis* configuration with the missense variant p.Leu218Leu. This variant does not cause galactosemia and is associated with increased erythrocyte GALT enzyme activity [Langley et al 1997, Elsas et al 2002].

In biochemical variant galactosemia:

- Erythrocyte galactose-1-phosphate is usually >1 mg/dL, but may be as high as 35 mg/dL. When the individual is on a lactose-free diet, the level is <1 mg/dL.

- Residual erythrocyte GALT enzyme activity is usually >15% and, on average, is 25% of control values.

Expert opinion and anecdotal information suggest that Duarte variant galactosemia, the most prevalent form of biochemical variant galactosemia, does not result in clinical disease. There has been no prospective long-term evidence-based medicine study to prove that, for example, persons with the D$_2$ c.[940A>G; c.-119_116delGTCA] genotype exhibit no disease with or without dietary intervention. This remains controversial, as a higher prevalence of speech abnormalities and/or developmental problems were noted in two out of three relatively small cohorts, suggesting that central nervous system dysfunction may be present in a subset of people with Duarte variant galactosemia [Ficicioglu et al 2008, Powell et al 2009, Lynch et al 2015].

Agreement has not been reached as to whether individuals with Duarte variant galactosemia with residual erythrocyte GALT enzyme activity in the range of 13%-33% of control activity should be restricted from galactose intake during infancy and early childhood. Continued galactose-1-phosphate accumulation may be seen with lactose ingestion but is usually without sequelae.

Differential Diagnosis

The differential diagnosis for neonatal hepatotoxicity includes: infectious diseases; obstructive biliary disease including Alagille syndrome, severe ATP8B1 deficiency (progressive familial intrahepatic cholestasis) and citrin deficiency; hereditary fructose intolerance; tyrosinemia type 1; and other metabolic diseases including Neimann-Pick disease type C.

Note: Establishing the diagnosis of sepsis does not exclude the possibility of galactosemia, as sepsis, particularly *E. coli* sepsis, occurs commonly in infants with classic galactosemia.

Galactokinase (GALK) deficiency (OMIM 230200) should be considered in individuals who have cataracts, increased plasma concentration of galactose, and increased urinary excretion of galactitol, but are otherwise healthy. These individuals have normal erythrocyte GALT enzyme activity and do not accumulate erythrocyte galactose-1-phosphate. The cataracts are caused by accumulation of galactose in lens fibers and its reduction to galactitol, an impermeant alcohol that results in increased intracellular osmolality and water imbibition. Other individuals with GALK deficiency develop CNS disease. Detection of reduced GALK enzyme activity is diagnostic. Biallelic pathogenic variants in *GALK1* are causative [Kolosha et al 2000, Hunter et al 2001]. The prevalence of GALK deficiency is unknown, but is probably less than 1:100,000.

Epimerase deficiency galactosemia (UDP-galactose 4'-epimerase [GALE] deficiency) should be considered in individuals who have liver disease, failure to thrive, and elevated erythrocyte galactose-1-phosphate concentrations but normal erythrocyte GALT enzyme activity. To date, only eight individuals with the severe form of GALE

deficiency have been reported. In contrast, most individuals with GALE deficiency have a benign peripheral form and do not manifest disease: they are healthy newborns with a positive newborn screen, increased erythrocyte galactose-1-phosphate, and normal erythrocyte GALT enzyme activity. Detection of reduced GALE enzyme activity is diagnostic. Biallelic pathogenic variants in *GALE* are causative. GALE deficiency has an estimated prevalence of 1:23,000 in Japan and an unknown prevalence in other populations.

Management

Evaluations Following Initial Diagnosis in the Newborn Period

To establish the extent of disease and needs in a newborn diagnosed with classic galactosemia or clinical variant galactosemia, the following evaluations are recommended [Walter et al 1999]:

- Consultation with a specialist in biochemical genetic disorders

- Measurement of erythrocyte galactose-1-phosphate concentration and urinary galactitol as a baseline for monitoring the effect of treatment (see Prevention of Primary Manifestations).

- Neurologic examination and brain MRI as needed

- Ophthalmologic examination, including slit lamp examination for cataracts

- If applicable, evaluation for hepatocellular disease, especially in affected individuals with late-treated disease who may be at risk for cirrhosis

Treatment of Manifestations and Complications

An international clinical guideline addressing management has been published [Welling et al 2017] (full text).

See Prevention of Primary Manifestations for information on dietary intervention. Lactose restriction reverses liver disease in newborns who already have hepatocellular disease.

Ophthalmologic treatment. Cataract surgery may need to be performed in the first year of life, especially in the rare individuals where failure to perform NBS has resulted in delayed diagnosis.

Speech treatment. Affected individuals with childhood apraxia of speech and dysarthria require therapy by a speech expert until the complication has been brought under control. This may require years of intensive therapy.

Developmental treatment should include developmental examination by a psychologist and/or developmental pediatrician at age one year, followed by the psychologist and/or developmental pediatrician working closely with the speech therapist and treating physician to map out a treatment plan and evaluation scheme tailored to each child. An individual education plan and/or professional help with learning skills and special classrooms may be needed depending on the timing of the clinical manifestations and the nature of the complications, which may be quite variable, even for children with the same genotype.

Premature ovarian insufficiency (POI) treatment. While biochemical/endocrine tests may indicate POI during early infancy, females do not usually exhibit signs of POI until there is delayed pubertal development or primary or secondary amenorrhea. Therefore, during pubertal development or adolescence females should be referred to a pediatric endocrinologist for consultation. When appropriate, the affected female should be seen by an obstetrician-gynecologist specializing in adolescent services and/or infertility.

Estrogen and progesterone may need to be given in a minority of instances to promote pubertal development or (more likely) when secondary amenorrhea occurs.

There is controversy as to whether females should be given estrogen and progesterone early in adolescence to retard "oocyte wastage" and whether more aggressive treatment plans (similar to those used in oncology) should be employed. In this regard, the autonomy of the affected female must be respected and, in the case of a pre-adolescent individual, her capacity for making an informed decision taken into consideration. Hospital ethics boards should be

involved in any decision making and each case treated individually [van Erven et al 2013].

The consideration of ovarian biopsy with oocyte preservation for future use in females with classic galactosemia and POI is controversial. If this type of procedure (which is becoming more common for females undergoing cancer chemotherapy) is being considered, consultation with the hospital ethics committee is recommended.

Fertility is possible for certain persons with classic galactosemia. Therefore, adults should be afforded this opportunity and helped to secure consultation with an obstetrician-gynecologist who specializes in infertility and who will promote conception.

Infertility. Because of the ovarian dysfunction, stimulation with FSH may be useful in producing ovulation in some women.

One female with premature ovarian insufficiency (POI) conceived following FSH therapy, and subsequently delivered a normal child [Menezo et al 2004]. Others have found that POI in classic galactosemia may be caused by reduced number or maturation of ovarian follicles and in some instances may be potentially treatable by exogenous pharmacologic stimulation with gonadotropic hormones [Rubio-Gozalbo et al 2010].

Prevention of Primary Manifestations

Dietary intervention. Immediate dietary intervention is indicated in infants whose erythrocyte GALT enzyme activity is ≤10% of control activity and whose erythrocyte galactose-1-phosphate concentration is >10 mg/dL.

Because 90% of the newborn's carbohydrate source is lactose and human milk contains 6%-8% lactose, cow's milk 3%-4% lactose, and most proprietary infant formulas 7% lactose, all of these milk products must be replaced immediately by a formula that is free of lactose (e.g., Isomil® or Prosobee®). Such soy formulas contain sucrose, fructose, and galactose-containing oligosaccharides that cannot be hydrolyzed in the small intestine.

Elemental formulas that contain small amounts of galactose such as Alimentum®, Nutramigen®, and Pregestimil® made with casein hydrolysates have been employed in the past without obvious side effects. A formula (Neocate®) that contains neither free nor bound galactose has been used without any side effects [Zlatunich & Packman 2005].

Dietary restrictions on all lactose-containing foods including cow's milk and other dairy products should continue throughout life; however, managing the diet becomes less important after infancy and early childhood, when milk and dairy products are no longer the primary source of energy. It is debated how stringent the diet should be after infancy [Berry et al 2004, Bosch et al 2004a, Schadewaldt et al 2004], as endogenous galactose production is an order of magnitude higher than that ingested from foods other than milk. Until more prospective evidence-based medicine studies have been performed with a large number of subjects, parents should be educated about the lifelong need for dietary restriction of cow's milk and dairy products.

Prevention of Secondary Complications

Because bone mineral density in children and adults with classic galactosemia and clinical variant galactosemia may be diminished, supplements of vitamin D in excess of 1000 IU/day and vitamin K have been advocated [Panis et al 2006b, Batey et al 2013].

For calcium and vitamin D intake for individuals with classic and clinical variant galactosemia, see the recommended dietary allowances and adequate intakes (pdf) from the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. Click here for additional dietary reference intake tables.

If routine follow-up visits with a dietitian knowledgeable about metabolic disorders have verified that calcium and vitamin D intake are adequate for age and if plasma 25-hydroxyvitamin D is within the normal range but bone mineral density is decreased, consultation with a pediatric and/or adult endocrinologist may be warranted.

Surveillance

See also the management guidelines published by Welling et al [2017] (full text).

Biochemical Testing

Individuals with classic galactosemia and clinical variant galactosemia should be monitored routinely [Walter et al 1999] for the accumulation of analytes:

- Measure erythrocyte galactose-1-phosphate level at each clinic visit and as needed (e.g., during the introduction of a new food). Concentrations <5 mg/dL are considered within the therapeutic range.

  Note: Erythrocyte galactose-1-phosphate is a good way to evaluate for acute ingestion of galactose.

- Urinary galactitol (a product of an alternate pathway for galactose metabolism) levels may be performed but are not necessary for long-term monitoring.

  - Note that erythrocyte galactose-1-phosphate and urine galactitol may provide comparable information regarding compliance with a lactose restricted diet.

  - Urinary galactitol analysis is especially valuable in affected individuals who have been given red blood cell transfusions; values >78 mmol/mol creatinine are abnormal.

  - Urinary galactitol is often not affected by acute dietary ingestion of galactose.

If sudden increases in either erythrocyte galactose-1-phosphate or urinary galactitol are detected, dietary sources of excess galactose should be sought or evaluation undertaken for other causes.

Schedule for Individuals with Classic or Clinical Variant Galactosemia

Biochemical genetics clinic visits

- Every three months for the first year of life or as needed depending on the nature of potential acute complications

- Every six months during the second year of life

- Yearly thereafter

Metabolic dietician clinic visits. As above, plus interim visits and phone consultations as necessary

Ophthalmologic evaluations. The timing of follow-up examinations depends on the presence or absence of neonatal cataracts. If absent, an examination may be performed at age one year, age five years, and during adolescence. Note: It is very unusual for a person with classic galactosemia to present after early infancy with cataracts, as cataract development probably requires significant intake of cow's milk and dairy products.

Speech evaluations

- Evaluation by a speech expert at age 18 months (recommended for all affected children)

- If the initial evaluation does not reveal a diagnosis of a speech or language disorder, reevaluation every three to 12 months during infancy and early childhood depending on the assessments performed by the developmental specialists and physicians

Developmental evaluations. Affected individuals should undergo a developmental examination by a psychologist and/or developmental pediatrician at age one year and thereafter every one to three years depending on the extent of delay in one or more spheres of development.

Evaluations for premature ovarian insufficiency (POI). Measurement of plasma 17-beta-estradiol and FSH in females is recommended if they reach age 12 years with insufficient secondary sex characteristics or age 14 years with no regular menses [Welling et al 2017].

Evaluations for osteopenia

- Measure plasma calcium, phosphorous, and 25-hydroxyvitamin D on a yearly basis and as needed.

- Because decreased bone mineral density is prevalent in individuals with classic galactosemia, a DEXA scan is recommended for surveillance at age six years, during puberty, through adolescence, and then every five years during adult life.

- Routine metabolic dietetic visits should verify that calcium and vitamin D intake is adequate for age and that plasma 25-hydroxyvitamin D is within the normal range. Even so, bone mineral density may be decreased in certain affected individuals for reasons that are not understood. Under these circumstances, consultation with a pediatric and/or adult endocrinologist may be warranted.

Agents/Circumstances to Avoid

The following should be avoided:

- Breast milk, proprietary infant formulas containing lactose, cow's milk, dairy products, and casein or whey-containing foods

- Lactose- or galactose-containing drug preparations

- Medicines that contain lactose (tablets, capsules, sweetened elixirs), especially during infancy

Evaluation of Relatives at Risk

When the pathogenic variants causing classic galactosemia or clinical variant galactosemia in the family are known, prenatal diagnosis of fetuses at risk may be performed via amniocentesis or CVS to allow for institution of treatment at birth.

If prenatal testing has not been performed, each at-risk newborn sib should be treated from birth and screened for classic galactosemia or clinical variant galactosemia using the erythrocyte GALT enzyme assay and/or genetic testing (if the familial pathogenic variants in the family are known) to allow for earliest possible diagnosis. 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.

Pregnancy Management

Both women with classic galactosemia and with clinical variant galactosemia should be on a lactose restricted diet during pregnancy.

There is no evidence that the outcome of children with classic galactosemia or clinical variant galactosemia is improved when their mothers (who are obligate carriers) were on a lactose-restricted diet during pregnancy. Therefore, unaffected pregnant women who are heterozygous for a pathogenic variant in *GALT* (carrier females) do **NOT** require a lactose-restricted diet during pregnancy.

Therapies Under Investigation

Research suggests that despite exogenous galactose restriction, endogenous galactose production may approach 1.0-2.0 g/day [Berry et al 2004, Schadewaldt et al 2004]. If this is true, "self-intoxication" with galactose may be more of a problem than restriction of galactose from exogenous sources in the management of older children and adults who no longer depend on milk as their primary source of energy.

Approaches to lowering endogenous production of galactose-1-phosphate are under investigation using small inhibitors of the GALK enzyme [Tang et al 2010]. While in vitro studies of GALT enzyme-deficient human fibroblasts demonstrated proof of concept, it is yet to be performed in an animal model. The *GALT* knockout mice generated by Leslie et al [1992] do not express the human phenotype of galactosemia and except for polyuria due to

hypergalactosemia and hypergalactosuria are largely without disease. As mice have lost *ARHI* (*DIRAS3*) during evolution [Lai et al 2008, Rubio-Gozalbo et al 2010, Tang et al 2010], a GALT enzyme-deficient mouse model that expresses an *ARHI* (*DIRAS3*) signal is needed to test the hypothesis that *ARHI* gene expression plays a role in phenotypic expression of disease and determine whether inhibition of galactose-1-phosphate production limits or abrogates the "human phenotype."

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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

Classic galactosemia and clinical variant galactosemia are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *GALT* pathogenic variant).

- Heterozygotes (carriers) are asymptomatic and do not develop galactosemia.

Sibs of a proband

- At conception, each sib of a proband with classic galactosemia or clinical variant galactosemia has a 25% chance of being affected, a 50% chance of being a carrier (heterozygote) of a pathogenic allele, and a 25% chance of being unaffected and not a carrier.

- Heterozygotes (carriers) are asymptomatic and do not develop galactosemia.

Offspring of a proband

- The offspring of an individual with classic galactosemia or clinical variant galactosemia are obligate heterozygotes (carriers) for a pathogenic variant in *GALT*.

- If one parent has classic galactosemia or clinical variant galactosemia and the other parent is a carrier, each child has a 50% chance of being a heterozygote and a 50% chance of having classic galactosemia or clinical variant galactosemia.

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

Carrier (Heterozygote) Detection

Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Molecular genetic testing. Carrier testing for at-risk family members is possible if the *GALT* pathogenic variants have been identified in the family.

Biochemical genetic testing

- Carrier testing is done by measuring erythrocyte GALT enzyme activity, which is approximately 50% of control

values in carriers of classic galactosemia or clinical variant galactosemia when the pathogenic variant is p.Ser135Leu.

- This will be different with other clinical variant galactosemia-causing pathogenic variants, which in the homozygous state result in 1%-10% residual erythrocyte GALT enzyme activity.

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, are carriers, or are at 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 both *GALT* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis (PGD) for classic galactosemia or clinical variant galactosemia are possible.

Prenatal testing (or preimplantation genetic diagnosis) using molecular genetic testing is preferred over enzyme analysis.

Biochemical testing. Analysis of GALT enzyme activity and molecular diagnosis rely on cells obtained by chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or amniocentesis usually performed at approximately 15 to 18 weeks' gestation.

Note: (1) When a fetus has classic galactosemia or clinical variant galactosemia, amniotic fluid concentration of galactitol is elevated in the late third trimester and has been used in the past for prenatal testing. (2) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider this to be the choice of the parents, discussion of these issues is appropriate.

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.

- **Galactosemia Support Group (GSG)**
  31 Cotysmore Road
  Sutton Coldfield West Midlands B75 6BJ
  United Kingdom
  Phone: +44 0121 378 5143

Email: sue@galactosaemia.org

- **My46 Trait Profile**
  Classic galactosemia

- **National Library of Medicine Genetics Home Reference**
  Galactosemia

- **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

- **Apraxia Kids**
  1501 Reedsdale Street
  Suite 202
  Pittsburgh PA 15233
  Phone: 412-785-7072
  www.apraxia-kids.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.

Classic Galactosemia and Clinical Variant Galactosemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GALT	9p13.3	Galactose-1-phosphate uridylyltransferase	GALT database	GALT	GALT

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 Classic Galactosemia and Clinical Variant Galactosemia (View All in OMIM)

230400	GALACTOSEMIA
606999	GALACTOSE-1-PHOSPHATE URIDYLYLTRANSFERASE; GALT

Gene structure. The gene is approximately 4 kb in length and has 11 exons and ten introns. The promoter is GC rich as in a "housekeeping gene." For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 300 *GALT* pathogenic variants are known [Elsas & Lai 1998, Tyfield et al 1999, Bosch et al 2005, Calderon et al 2007].

Pathogenic variants that are most prevalent in the United States are shown in Table 4. The frequency of the five most common *GALT* pathogenic variants in diverse ethnic groups was reported by Suzuki et al [2001].

A *GALT* 5.2-kb deletion is common in persons of Ashkenazi Jewish background [Coffee et al 2006]. The 5.2-kb deletion allele is a complex deletion that involves a 3163-nucleotide deletion of the GALT promoter and a 5' gene region along with a 2295-bp deletion of the 3' gene; only segments of exon 8 and intron 8 are retained [Coffee et al 2006]. The 5.2-kb complex deletion is detectable by MLPA.

Table 4.

Prevalence of *GALT* Mutated Alleles in 284 Individuals from the US with Classic Galactosemia

Pathogenic Variant	Number of Alleles	Percent of Total
p.Gln188Arg	280	49%
p.Ser135Leu	40	7%
p.Lys285Asn	20	4%
p.Leu195Pro	11	2%
p.Tyr209Cys	5	1%
5.2-kb deletion [1]	7	1%
p.Asn314Asp	141	25%
Other	64	11%
TOTAL	**568**	**100%**

Adapted from Elsas & Lai [1998]

1. See Table 5, footnote 4.

Table 5.

GALT Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.404C>T	p.Ser135Leu	
c.512T>C	p.Phe171Ser	

c.563A>G	p.Gln188Arg	
c.584T>C	p.Leu195Pro	
c.607G>A	p.Glu203Lys	
c.626A>G	p.Tyr209Cys	NM_000155.2
c.855G>T	p.Lys285Asn	NP_000146.2
c.[940A>G; c.-119_116delGTCA] [2]	p.Asn314Asp; effect on promoter variant	
c.997C>G	p.Arg333Gly	
c.253-2A>G (IVS2-2A>G) [3]	--	
(Δ5.2kb) or (5.2kbdel) [4, 5]	--	

Note on variant classification: Variants listed in the table have been provided by the author. *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. Variant designation that does not conform to current naming conventions
2. The Duarte D_2 variant allele with two variants in *cis* configuration
3. Seen in individuals of Hispanic heritage
4. A complex deletion that involves a 3163-bp deletion of the *GALT* promoter and a 5' gene region along with a 2295-bp deletion at the 3' end of the gene; only segments of exon 8 and intron 8 are retained [Barbouth et al 2006, Coffee et al 2006]. Standard HGVS nomenclature of this deletion is equally complex and may be best described as c.[-1039_753del; 820+50_*789delinsGAATAGACCCCA].
5. Seen in persons of Ashkenazi Jewish ethnicity

Normal gene product. The GALT protein functions as a dimer and demonstrates unique bimolecular ping pong kinetics. The GALT enzyme first binds UDP-glucose, then releases glucose-1-phosphate. A stable GALT-UMP complex is required for the second displacement reaction, which involves binding of galactose-1-phosphate with release of UDPgalactose and the free GALT enzyme.

Abnormal gene product

- The pathogenic variant p.Gln188Arg largely prevents formation of a GALT-UMP intermediate [McCorvie et al 2016].

- The LA variant (D_1) involves increased rates of translation caused at least in part by a nucleotide change in the codon for leucine at residue 218 from common to rare (c.652C>T), thereby stabilizing the p.Asn314Asp pathogenic variant. A combination of "codon preference" and increased gene expression resulting from a *GALT* promoter benign variant has been proposed to account for increased activity in the LA variant [Langley et al 1997]. The LA variant (D_1) in codon 218 is p.Leu218= (c.652C>T).

- The Duarte D_2 variant is a deletion in the E-box, a carbohydrate response element that reduces *GALT* gene expression [Elsas et al 2001].

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Suggested Reading

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Chapter Notes

Author History

Gerard T Berry, MD, FFACMG (2014-present)
Louis J Elsas II, MD, FFACMG; University of Miami (1999-2014)

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Figures

The Primary Enzymes of the Galactose Pathway

α-D-galactose
+
ATP

GALK

Galactose 1-phosphate
+
ADP

Galactokinase

Galactose 1-phosphate
+
UPDglucose

GALT

UDP-galactose
+
D-glucose 1-phosphate

Galactose 1-phosphate
uridyltransferase

UDP-galactose

GALE

UDP-glucose

UDP-galactose 4'-epimerase
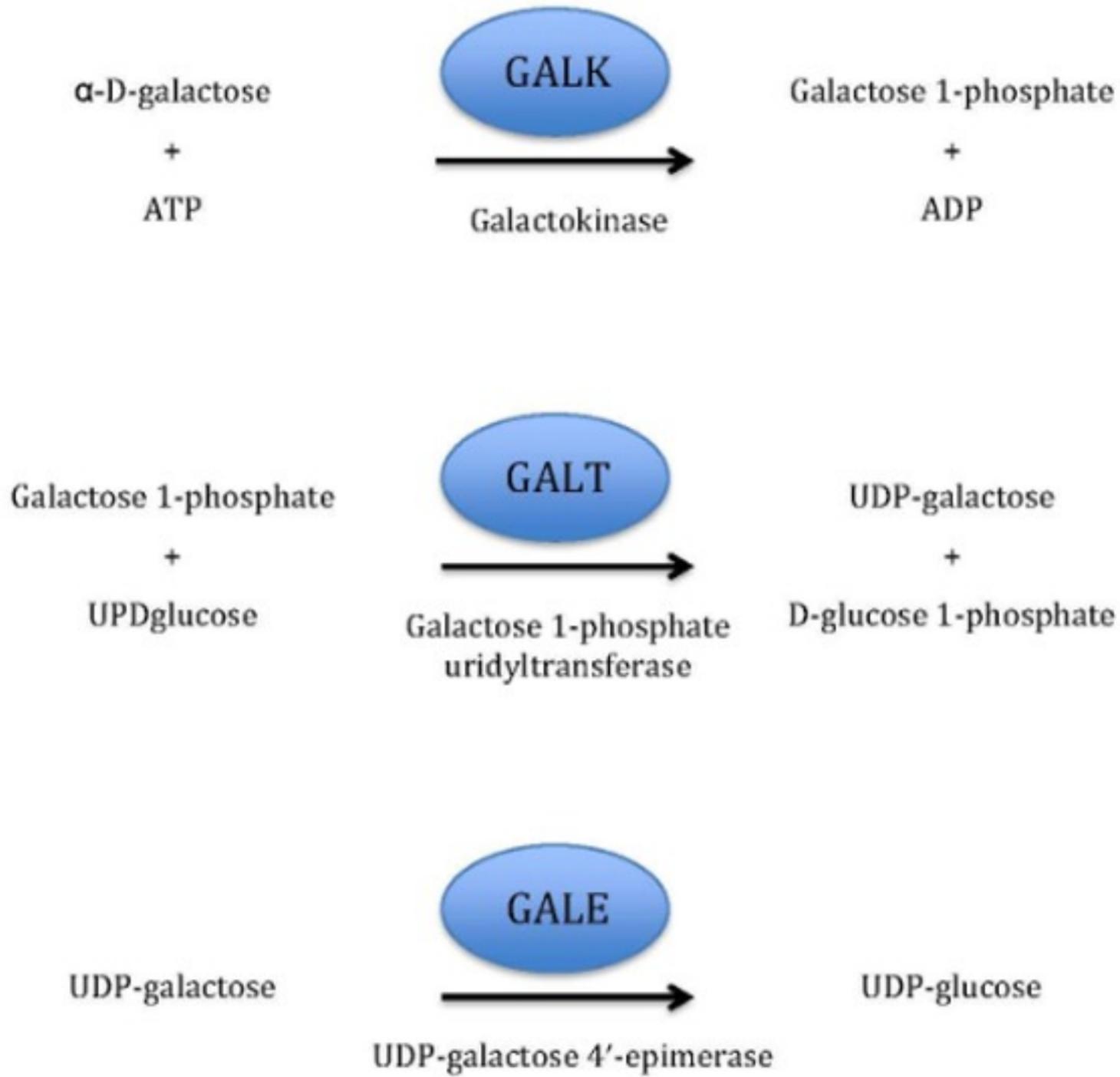
Figure 1.

Galactose metabolism, the Leloir pathway
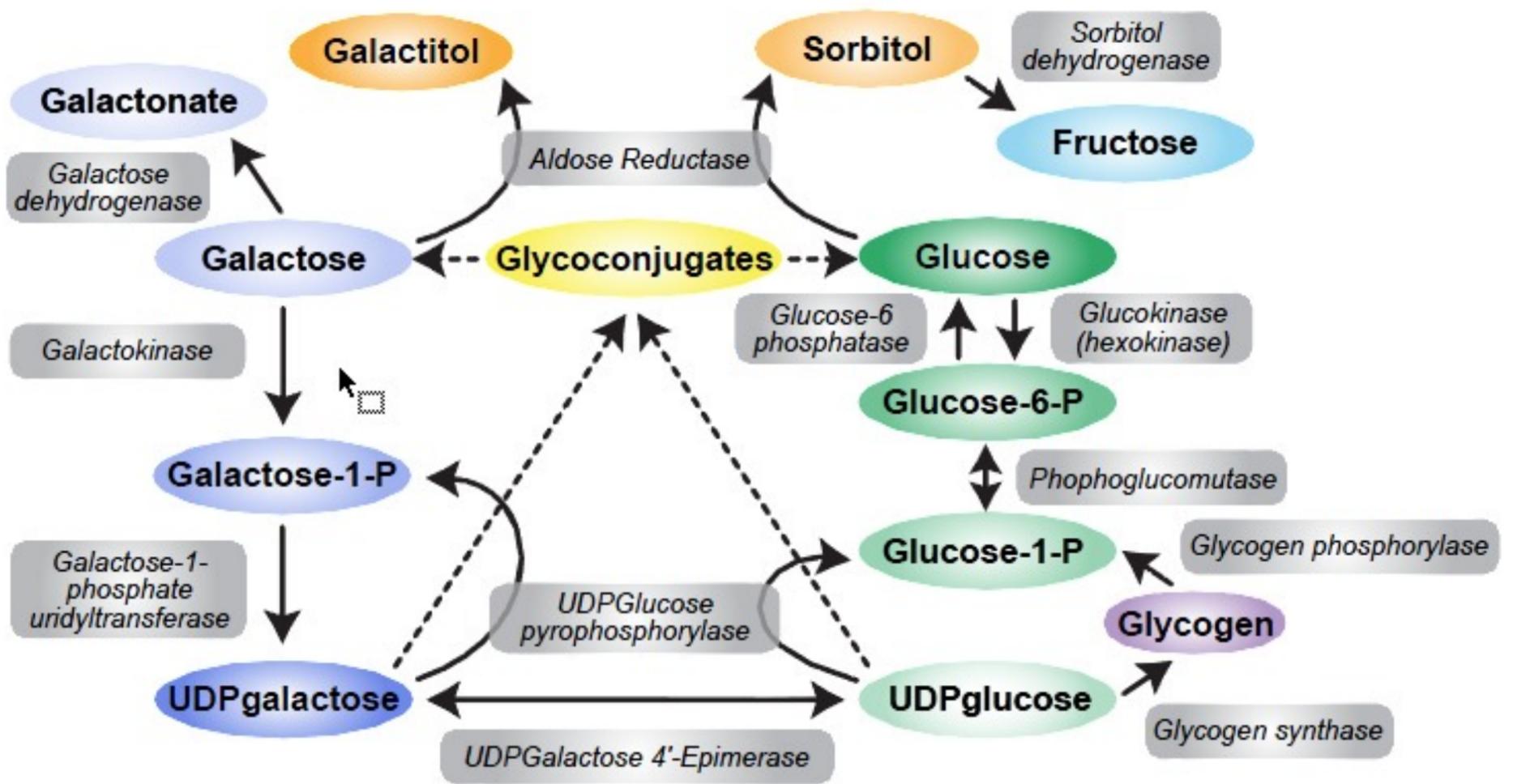
Figure 2.

Galactose metabolism, GALT deficiency