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Duarte Variant Galactosemia

Synonym: Duarte Galactosemia

Judith L Fridovich-Keil, PhD,[1] Michael J Gambello, MD, PhD,[2] Rani H Singh, PhD, RD,[2] and J Daniel Sharer, PhD[3]

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Summary

Clinical characteristics

Infants with Duarte variant galactosemia who receive breast milk or a high galactose-containing formula (dairy milk-based formula) are typically asymptomatic and show the same prevalence of acute issues seen in the general newborn population. For decades it has been unclear whether Duarte variant galactosemia results in long-term developmental problems either with or without dietary intervention. However, a recent study of 350 children ages six to 12 years reported no detectable differences in developmental outcomes tested between children with Duarte variant galactosemia and controls, or among children with Duarte variant galactosemia as a function of galactose exposure in infancy. Premature ovarian insufficiency, which is common in classic galactosemia, also has not been reported for girls or women with Duarte variant galactosemia.

Diagnosis/testing

Duarte variant galactosemia is diagnosed by a combination of biochemical and genetic testing. Specifically, erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity is typically about 25% of control activity, and *GALT* genotyping reveals the presence of one heterozygous pathogenic *GALT* variant together with either a heterozygous or homozygous Duarte (D_2) *GALT* variant.

Management

Treatment of manifestations: Currently, there is no uniform standard of care regarding restriction of dietary galactose for infants with Duarte variant galactosemia. Thus, some health care providers, or parents, may choose to restrict dietary galactose in the first year of life, while others may not. When dietary galactose is restricted in infancy, centers often perform a galactose challenge around age one year followed by measurement of the erythrocyte galactose-1-phosphate level. If the level is within the normal range (<1.0 mg/dL), dietary restriction

Author Affiliations: 1 Department of Human Genetics Emory University School of Medicine Atlanta, Georgia; Email: jfridov@emory.edu. 2 Division of Medical Genetics Department of Human Genetics Emory University School of Medicine Atlanta, Georgia; Email: mgambel@emory.edu; Email: rsingh@emory.edu. 3 UAB Biochemical Genetics and Metabolic Disease Laboratory Department of Genetics University of Alabama at Birmingham Birmingham, Alabama; Email: dsharer@uab.edu.

of galactose is generally discontinued. When dietary galactose is not restricted in infancy, some health care providers may still choose to check the erythrocyte galactose-1-phosphate level at age one year to confirm that the level is approaching the normal range.

Surveillance: For infants on dietary restriction of galactose: if the erythrocyte galactose-1-phosphate level is >1.0 mg/dL following a galactose challenge at age one year, galactose restriction may be resumed. In this case, the galactose challenge and measurement of erythrocyte galactose-1-phosphate level may be repeated every four to six months until the erythrocyte galactose-1-phosphate level stabilizes at <1.0 mg/dL.

Agents/circumstances to avoid: Opinion varies as to whether avoidance of all dairy products (including breast milk and dairy milk-based formula) until age one year is warranted.

Evaluation of relatives at risk: If families with one child with Duarte variant galactosemia wish to evaluate their other children for Duarte variant galactosemia, molecular genetic testing for the *GALT* variants identified in the family can be performed.

Genetic counseling

Duarte variant galactosemia is inherited in an autosomal recessive manner. When one parent is heterozygous for the *GALT* D_2 allele and the other parent is heterozygous for a *GALT* pathogenic variant, each child has a 25% chance of having Duarte variant galactosemia, a 25% chance of being an asymptomatic carrier of the D_2 allele, a 25% chance of being an asymptomatic carrier of the *GALT* pathogenic variant, and a 25% chance of being unaffected and also not a carrier of either *GALT* variant. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk requires prior identification of the *GALT* variants in the family and determination of the parental origin of each allele.

Diagnosis

Duarte variant galactosemia is defined by a combination of the following:

- One *GALT* pathogenic variant (G allele) present in the heterozygous state plus the *GALT* Duarte (D_2) variant allele present in either the heterozygous state (*in trans* to the G allele) or in the homozygous state (both *in cis* and *in trans* to the G allele)
- Erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity that is typically about 25% of control activity

Suggestive Findings

Duarte variant galactosemia, caused by a partial deficiency in erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme, **should be suspected** in infants with a positive newborn screening (NBS) result for galactosemia but few if any clinical findings when on a high-galactose diet (e.g., breast milk or a dairy milk-based formula).

Positive NBS result

- NBS for classic galactosemia and its variants (including Duarte variant galactosemia) is primarily based on quantification of erythrocyte GALT enzyme activity on dried blood spots.

  Note: While all states in the US now include screening for classic galactosemia in their NBS panel, some states have set their newborn screening GALT enzyme activity cutoff level to ensure the detection of classic and clinical variant galactosemia while minimizing false positives and the detection of infants with Duarte variant galactosemia [Pyhtila et al 2015]. In those states, a NBS result for galactosemia that is not flagged as "abnormal" may not be informative for Duarte variant galactosemia.

- GALT enzyme activity below the cutoff defined by the screening program is considered positive and requires follow-up diagnostic testing (see Establishing the Diagnosis).

  Note: GALT is a labile enzyme; exposure of the sample to heat and/or humidity in storage or transit (as sometimes occurs in hot climates especially during the summer months) can result in artifactual loss of activity and higher false positive rates.

Follow-up testing. Quantitative testing of erythrocyte GALT enzyme activity is the first recommended follow-up approach for a positive NBS result for galactosemia. Testing of erythrocyte galactose-1-phosphate and/or urinary galactitol may also be useful as a baseline or if the infant is on a high-galactose diet (e.g., breast milk or a dairy milk-based formula).

- **Erythrocyte GALT enzyme activity** that is typically about 25% of control activity is consistent with a diagnosis of Duarte variant galactosemia (reviewed in Carney et al [2009], Walter & Fridovich-Keil [2014], Pyhtila et al [2015]).
- **The erythrocyte galactose-1-phosphate (Gal-1P) concentration** may range from high (>30 mg/dL) to normal (<1.0 mg/dL) depending on the infant's recent dietary exposure to breast milk or galactose-containing formula.

  Note: Dairy milk products contain lactose, which is metabolized to glucose and galactose by normal digestion. Therefore, any product that contains dairy milk and/or lactose also contains galactose.

  - Erythrocyte galactose-1-phosphate concentrations may exceed 30 mg/dL within the first few weeks of life; however, even in infants with Duarte variant galactosemia who are not treated with a galactose-restricted diet the concentration tends to normalize (<1.0 mg/dL) within the first year [Ficicioglu et al 2008, Ficicioglu et al 2010, Pyhtila et al 2015].
  - Erythrocyte galactose-1-phosphate concentration in infants placed on a galactose-restricted diet normalizes rapidly, decreasing to an almost undetectable level within one month [Ficicioglu et al 2008].
- **Urinary galactitol** may be elevated, but not to the same extent seen in classic galactosemia [Ficicioglu et al 2010].
  - The mean urinary galactitol level in a cohort of young children with Duarte variant galactosemia on unrestricted (regular) diet at age one year was 46±14 mmol/mol creatinine [Ficicioglu et al 2008], and in a cohort of children with Duarte variant galactosemia on unrestricted galactose (regular) diet at ages one to six years was 31.6 mmol/mol creatinine.
  - Mean urinary galactitol in controls (<1 year of age) was reported to range from 2-78 mmol/mol creatinine, and mean urinary galactitol in infants (<1 year) with classic galactosemia was 466±166 mmol/mol [Palmieri et al 1999].

Click here (pdf) for information on testing of historical interest.

Establishing the Diagnosis

The diagnosis of Duarte variant galactosemia **is established** in a proband by a combination of: (1) erythrocyte GALT enzyme activity that is typically about 25% of control activity; and (2) molecular genetic test results that identify the presence of one heterozygous pathogenic *GALT* variant together with either a heterozygous or homozygous Duarte (D_2) *GALT* variant (Table 1).

Duarte variant (D_2) allele. Five sequence changes in *cis* configuration are found on the Duarte variant (D_2) allele.

Of primary importance is a 4-bp deletion in the *GALT* promoter region (c.-119_-116delGTCA) that is considered to cause diminished transcription (reviewed in Carney et al [2009]). The four remaining variants unique to the D_2 allele are described in Molecular Genetics, **Benign variants** and Table 3.

Pathogenic allele. A *GALT* pathogenic variant is one that results in absent or barely detectable GALT enzyme activity when it occurs in the homozygous state or the compound heterozygous state with another pathogenic variant; the resulting phenotypes are classic (<1% GALT activity) or clinical variant galactosemia (1%-10% GALT activity) (see Classic Galactosemia and Clinical Variant Galactosemia). Note: Pathogenic *GALT* variants are sometimes referred to collectively as G alleles.

Single-gene testing. Sequence analysis of *GALT* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected by sequence analysis.

- **Sequence analysis** can detect the D_2 *GALT* allele as well as most *GALT* pathogenic variants. However, a nearly whole-gene deletion of *GALT* that has been reported predominantly among affected individuals of Ashkenazi Jewish ancestry (see Classic Galactosemia and Clinical Variant Galactosemia) may not be detected by traditional sequencing technologies.
- If the D_2 variant is identified in a sample in which GALT enzyme activity is about 25%, but no *GALT* pathogenic variant is identified by sequence analysis, **deletion/duplication analysis** should be considered. This is especially true if variants characteristic of the D_2 allele appear homozygous; the other allele of *GALT* may be deleted.

Interpretation of molecular genetic test results. See Molecular Genetics for details.

Table 1. Molecular Genetic Testing Used in Duarte Variant Galactosemia

Gene [1]	Method	Proportion of Probands in Whom the Method Detects:	
		The Duarte (D_2) variant	A pathogenic variant [2]
GALT	Sequence analysis [3]	100%	>95%
	Deletion/duplication analysis [4]	0 [5]	Estimated <1% [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. 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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may 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.
5. Deletion/duplication analysis will not identify the D_2 allele.
6. Exon and multiexon *GALT* deletions have been reported; while rare overall, such deletions may be common in specific populations. See Table A, **Locus-Specific Databases**.

Clinical Characteristics

Clinical Description

The neonatal period. Infants with Duarte variant galactosemia who are on breast milk or a high galactose-containing formula (here referred to as "dairy milk-based formula") are typically asymptomatic. However, anecdotal reports suggest that some infants with Duarte variant galactosemia, like some infants who do not have any form of galactosemia, may experience jaundice or other acute symptoms that resolve over time following removal of breast milk or dairy milk-based formula from the diet [Author, personal observation].

Note: Resolution of acute symptoms over time following removal of breast milk or dairy milk-based formula from the diet does **not** confirm that the problem was related to galactose.

Neurodevelopment. A recent study by Carlock et al [2019] reported 73 outcomes representing five general domains of development (cognitive, physical, motor, socio-emotional, and speech/language) in 350 children, 206 with Duarte variant galactosemia and 144 controls. Cases and controls were derived from the same set of families and ascertained from 13 different states in the United States, so they were well-matched by geography, race, socioeconomic status, and other covariates.

- No significant difference in prevalence of complications was seen between affected individuals and controls for any of the outcomes tested.
- No significant difference was seen comparing developmental outcomes of children with Duarte variant galactosemia who consumed breast milk or dairy milk-based formula versus low-galactose formula in the first year of life.
- Combined, these results strongly support the assertion that Duarte variant galactosemia does not cause developmental complications in children with or without dietary restriction of galactose.

Note: The developmental outcomes of school-age children with Duarte variant galactosemia has been a point of controversy for some time, in part because a study by Powell et al [2009] reported that children age three to ten years with Duarte variant galactosemia in metropolitan Atlanta were more likely than age-matched controls from the general population to receive speech-language intervention in public school. However, a reconsideration of these data in 2019 revealed a number of important confounding factors that may explain the results observed [Fridovich-Keil et al 2019].

Ovarian function in females. A study of anti-müllerian hormone in young girls with enzymatically and/or molecularly confirmed Duarte variant galactosemia demonstrated no evidence of premature ovarian insufficiency [Badik et al 2011]. Further, family studies of newly diagnosed infants with classic or Duarte variant galactosemia sometimes reveal that the mother herself has Duarte variant galactosemia, confirming that women with Duarte variant galactosemia can be fertile and carry a pregnancy successfully to term [Author, personal observation].

Genotype-Phenotype Correlations

No significant genotype-phenotype relationships for Duarte variant galactosemia with regard to different pathogenic *GALT* alleles *in trans* with the D_2 allele have been reported.

Nomenclature

Duarte variant galactosemia may also be called Duarte galactosemia, DG, or biochemical variant galactosemia.

Sometimes, Duarte variant galactosemia is simply called variant galactosemia; however, this term is better reserved for individuals now said to have "clinical variant galactosemia," who do not have a *GALT* D_2 allele but rather have biallelic *GALT* pathogenic variants of which at least one is hypomorphic, resulting in a low level of residual GALT enzyme activity. Of note, galactokinase deficiency and epimerase deficiency are also sometimes called "variant" galactosemia. Thus, unless the term Duarte, D, DG, or D_2 is explicit, the reader should not assume that the term variant galactosemia implies Duarte variant galactosemia.

Prevalence

The prevalence of Duarte variant galactosemia is difficult to confirm due to incomplete ascertainment. Duarte variant galactosemia is detected in as many as 1:3,500 screened births in some states and essentially zero in others, largely reflecting differences in NBS protocols [Pyhtila et al 2015] (see Diagnosis, **Erythrocyte GALT enzyme activity**).

The true prevalence of Duarte variant galactosemia in the US newborn population is estimated to be approximately tenfold the prevalence of classic galactosemia [Fernhoff 2010, Pyhtila et al 2015].

Among newborns diagnosed with Duarte variant galactosemia some patterns implicating differential prevalence by race are evident [Pyhtila et al 2015]. For example, Duarte variant galactosemia is more common among infants of European ancestry and less prevalent among infants of African, African American, or Asian ancestry. These differences parallel recognized differences among these populations in the prevalence of the D_2 variant and/or other known *GALT* pathogenic variants [Pyhtila et al 2015].

Genetically Related (Allelic) Disorders

Classic galactosemia and clinical variant galactosemia are also associated with mutation of *GALT*. The genotypes that give rise to these phenotypes have two *GALT* pathogenic variants that result in either absent or only trace GALT enzyme activity.

The Los Angeles (LA) variant (D_1) has the identical p.Asn314Asp *GALT* missense variant as the Duarte (D_2) variant but does not have the promoter deletion c.-119_-116delGTCA. Instead, it is in *cis* configuration with the missense variant p.Leu218=. This variant does not cause galactosemia and is associated with normal to increased erythrocyte GALT enzyme activity (see Classic Galactosemia and Clinical Variant Galactosemia).

Differential Diagnosis

Most infants with Duarte variant galactosemia are diagnosed because of a positive NBS result for galactosemia. The differential diagnosis of a positive NBS for galactosemia is:

- Classic galactosemia and clinical variant galactosemia
- Duarte variant galactosemia
- GALE (epimerase) deficiency galactosemia
- GALK (galactokinase) deficiency (OMIM 230200)
- GALM deficiency galactosemia (OMIM 618881)
- Compromised galactose utilization not caused by a Leloir enzyme deficiency (e.g., Fanconi-Bickel syndrome [OMIM 227810] or portosystemic shunt [Bernard et al 2012]).
- A false positive result that includes:
  - Heterozygotes (carriers) for a *GALT* pathogenic variant;
  - Other combinations of partially impaired *GALT* alleles (e.g., D_2 variant homozygotes);
  - Individuals with completely normal *GALT* alleles and enzyme activity whose samples were technically compromised by exposure to heat and/or humidity in storage or transit.

Erythrocyte GALT enzyme activity. Measuring erythrocyte GALT enzyme activity is often the first step in differential diagnosis of a positive NBS result for galactosemia.

Table 2. Disorders to Consider Given a Newborn Screening Result Suggestive of Galactosemia

Erythrocyte GALT Enzyme Activity [1]	Diagnosis
Very low to undetectable	Classic galactosemia
1%-10%	Clinical variant galactosemia
~15%-33%	Duarte variant galactosemia [2]
~50%	Carrier of 1 pathogenic *GALT* allele or homozygous for the D_2 variant
~75%	Carrier of 1 D_2 variant

Table 2. continued from previous page.

Erythrocyte GALT Enzyme Activity [1]	Diagnosis
Indistinguishable	GALE (epimerase) deficiency or GALK (galactokinase) deficiency [3] or GALM (galactose mutarotase) deficiency [4]

1. Compared with the erythrocyte GALT enzyme activity of controls
2. See Classic Galactosemia and Clinical Variant Galactosemia.
3. Carney et al [2009], Pyhtila et al [2015]
4. Iwasawa et al [2019], Wada et al [2019]

Erythrocyte galactose-1-phosphate levels in infants with Duarte variant galactosemia exposed to galactose may be elevated. Although these erythrocyte galactose-1-phosphate levels overlap those seen in classic galactosemia, they typically do not exceed 30 mg/dL [Ficicioglu et al 2008, Pyhtila et al 2015]. In contrast, in classic galactosemia levels >50 mg/dL are not uncommon, and in some samples erythrocyte galactose-1-phosphate exceeds 100 mg/dL [Walter & Fridovich-Keil 2014, Pyhtila et al 2015].

Management

Evaluations Following Initial Diagnosis

An infant who is symptomatic should be seen by a metabolic specialist for evaluation for other possible conditions.

To assist the family with understanding the genetic implications of a diagnosis of Duarte variant galactosemia for the child and family, a genetic counseling consultation is recommended.

Treatment of Manifestations

Current data suggest that infants and children with Duarte variant galactosemia are not at increased risk for acute or long-term developmental [Carlock et al 2019] or ovarian [Badik et al 2011] complications regardless of dietary exposure to galactose in infancy. In light of these data, some healthcare providers may conclude that dietary intervention in Duarte variant galactosemia is neither required nor desirable [McCandless 2019]; however, other providers may disagree.

If the decision is made to restrict dietary galactose, health care providers may recommend one or more of the following [Fernhoff 2010, Pyhtila et al 2015]:

- Immediate dietary galactose restriction for infants with erythrocyte galactose-1-phosphate >10 mg/dL
- Full dietary restriction of galactose by feeding low-galactose formula, through age one year, at which time a galactose challenge is performed
- A compromise approach in which parents wishing to breastfeed alternate breast milk with a low-galactose formula

The galactose challenge. If dietary galactose is restricted, conducting a galactose challenge by age 12 months should be considered. For example:

- Obtain a baseline erythrocyte galactose-1-phosphate level at diagnosis and again around age six months (i.e., after the introduction of solid foods).
- At age 12 months, gradually liberalize the dietary intake of galactose, and obtain an erythrocyte galactose-1-phosphate level one month later.
- If the erythrocyte galactose-1-phosphate level is within the normal range (<1.0 mg/dL) despite dairy milk ingestion, dietary restriction of galactose is not resumed.

Surveillance

Most individuals diagnosed with Duarte variant galactosemia as infants who are followed by a genetics or metabolic specialist are discharged from follow up after a successful galactose challenge at age one year (see Treatment of Manifestations).

Among children with Duarte variant galactosemia who have been restricted for dietary galactose as infants, if the erythrocyte galactose-1-phosphate level is >1.0 mg/dL following a galactose challenge at age one year, galactose restriction may be resumed, and the galactose challenge and measurement of erythrocyte galactose-1-phosphate level repeated every four to six months until the level stabilizes at <1.0 mg/dL.

Agents/Circumstances to Avoid

Some health care providers recommend avoiding all high galactose foods (e.g., dairy milk products) until age one year; other health care providers argue that this precaution is neither warranted nor desirable [McCandless 2019].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: As there are no negative health consequences documented for this condition, there may not be any clinical trials.

Genetic Counseling

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

Mode of Inheritance

Duarte variant galactosemia is inherited in an autosomal recessive manner.

Individuals with Duarte variant galactosemia have at least one Duarte (D_2) variant *GALT* allele and one *GALT* pathogenic variant (G allele) in *trans* configuration (on homologous chromosomes).

Risk to Family Members

Parents of a proband

- Molecular genetic testing is needed to clarify the genetic status of parents.
- Typically, one parent of a child with Duarte variant galactosemia carries the Duarte (D_2) variant *GALT* allele and the other parent carries a *GALT* pathogenic variant (G allele).
- Rarely, a parent may have Duarte variant galactosemia or another genotype that includes the D_2 variant (e.g., homozygosity for the Duarte variant). Recurrence risks may vary for these couples.

- Heterozygotes (carriers) of a single *GALT* pathogenic variant in *trans* configuration with a normal *GALT* allele, or people who carry either one or two D_2 alleles, are clinically asymptomatic and do not have Duarte variant galactosemia.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent is heterozygous for the D_2 allele and the other parent is heterozygous for a *GALT* pathogenic variant each sib has at conception:
  - A 25% chance of having Duarte variant galactosemia;
  - A 25% chance of being an asymptomatic carrier of the D_2 allele;
  - A 25% chance of being an asymptomatic carrier of a *GALT* pathogenic variant (G allele);
  - A 25% chance of being unaffected and not a carrier of either variant.
- In some families, it is possible for the sibs of a proband with Duarte variant galactosemia to have classic or clinical variant galactosemia depending on the genetic status of the proband's parents. For example, if one parent has Duarte variant galactosemia and the other parent is a carrier for a pathogenic *GALT* variant, each sib at conception has:
  - A 25% chance of having Duarte variant galactosemia;
  - A 25% chance of having classic galactosemia or clinical variant galactosemia;
  - A 25% chance of being an asymptomatic carrier of the D_2 allele;
  - A 25% chance of being an asymptomatic carrier of a *GALT* pathogenic variant (G allele).
- Risks to sibs are different for other parental genotypes. Referral for genetic counseling is indicated for such families.
- Heterozygotes (carriers) of (1) a single *GALT* pathogenic variant in *trans* configuration with a normal *GALT* allele or (2) either one or two D_2 *GALT* alleles are clinically asymptomatic and do not have Duarte variant galactosemia.

Offspring of a proband

- The offspring of an individual with Duarte variant galactosemia are typically heterozygotes (carriers) of a *GALT* variant allele (i.e., either a *GALT* pathogenic variant or the D_2 allele).
- Accurate determination of the risk to offspring is only possible after molecular genetic testing of the proband's reproductive partner.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier; typically, one side of the family will be at increased risk of carrying a D_2 *GALT* allele while the other side of the family will be at increased risk of carrying a *GALT* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GALT* variants in the family and determination of the parental origin of each allele.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of available prenatal testing options is before pregnancy.
- Although current research indicates that individuals with Duarte variant galactosemia are typically asymptomatic [Badik et al 2011, Carlock et al 2019], they are heterozygotes (carriers) for a pathogenic *GALT* allele. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who have Duarte variant galactosemia, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GALT* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **Duarte Galactosemia**
  www.duartegalactosemia.org
- **Medical Home Portal**
  Galactosemia
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

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

Table A. Duarte 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 Duarte Variant Galactosemia (View All in OMIM)

230400	GALACTOSEMIA I; GALAC1
606999	GALACTOSE-1-PHOSPHATE URIDYLYLTRANSFERASE; GALT

Molecular Pathogenesis

The mechanism of pathogenesis of the *GALT* D_2 allele was a point of some confusion in the past (reviewed in Carney et al [2009]), likely reflecting the complex nature of the allele and the fact that the linked 4-bp promoter deletion (c.-119_-116delGTCA) was not initially recognized. The consensus is now that this 4-bp promoter deletion is actually the causal variant, leading to slight impairment of expression of what is a fully functional GALT protein.

The mechanism of pathogenesis of different *GALT* pathogenic variants as a cause of classic / clinical variant galactosemia is described in Classic Galactosemia and Clinical Variant Galactosemia.

Gene structure. See Classic Galactosemia and Clinical Variant Galactosemia for information about *GALT*. See also Table A, **Gene**.

Benign variants

- **Duarte variant (D_2) allele.** Some consider the D_2 variant allele itself to be benign. Five sequence changes in *cis* configuration are found on the D_2 allele.
  - Four are noncoding nucleotide variants that are unique to the D_2 allele (see Table 3).
  - Of primary importance is a 4-bp deletion in the *GALT* promoter region (c.-119_-116delGTCA) that slightly impairs gene expression (reviewed in Carney et al [2009]).
  - The three remaining variants unique to D_2 are c.378-27G>C, c.508-24G>A, and c.507+62G>A.
  - The fifth sequence change is the missense variant c.940A>G (p.Asn314Asp, also called N314D); while always on the D_2 allele, c.940A>G also occurs on other functionally normal *GALT* alleles (reviewed in Carney et al [2009]).
- **Los Angeles (or D_1) variant allele** results in no diminution of GALT enzyme activity and is considered benign. Note: The Los Angeles (LA) *GALT* variant (D_1) has the identical c.940A>G missense variant as the D_2 variant but does not have the c.-119_-116delGTCA promoter deletion. Instead, it is in *cis* configuration with the silent variant c.652C>T (p.Leu218=, also called L218L). See Classic Galactosemia and Clinical Variant Galactosemia. The D_1 variant allele does not cause galactosemia and is associated with normal or slightly increased erythrocyte GALT enzyme activity (reviewed in Carney et al [2009]).

Table 3. *GALT* Variants Associated with the D_2 Allele Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.-119_-116delGTCA	NA [2]	NM_000155.2 NP_000146.2
c.940A>G	p.Asn314Asp	
c.378-27G>C (IVS4-27G>C)	NA	
c.508-24G>A (IVS5-24G>A)	NA	
c.507+62G>A (IVS5-62G>A)	NA	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Reduces promoter function (reviewed in Carney et al [2009])

Interpretation of molecular genetic test results. Although rare, some individuals with Duarte variant galactosemia are homozygous for c.940A>G (p.Asn314Asp, also called N314D) and heterozygous for a pathogenic *GALT* variant, indicating that the pathogenic variant coexists in these individuals in a *cis* configuration with either a D_2 or D_1 allele.

Also, rarely, some individuals with classic galactosemia (who by definition have biallelic *GALT* pathogenic variants) may also have either a D_2 or D_1 allele in *cis* configuration with one or both pathogenic *GALT* variants.

Therefore, demonstrating the presence of the D_2 variant – or any of the individual *GALT* sequence changes associated with a D_2 allele (e.g., c.940A>G; p.Asn314Asp, or N314D) – does not confirm a diagnosis of Duarte variant galactosemia or rule out a diagnosis of classic galactosemia. The presence of *GALT* variants must always be interpreted in conjunction with GALT enzyme activity levels.

Of note, the parents of a child with an identified D_2 *GALT* variant allele and a *GALT* pathogenic variant allele can undergo molecular genetic testing themselves to determine whether each parent carries one variant, or whether both *GALT* variants are found in one parent while the other parent carries neither variant.

- If each parent carries one variant found in the child, the D_2 and pathogenic *GALT* variants identified in the child are in *trans* configuration (on separate chromosomes) consistent with a diagnosis of Duarte variant galactosemia in the child.
- If one parent carries both the D_2 and pathogenic *GALT* variants identified in the child while the other parent carries neither, the D_2 and pathogenic *GALT* variants in the child are most likely in *cis* configuration (coexisting on the same chromosome) consistent with a diagnosis of unaffected galactosemia carrier rather than Duarte variant galactosemia in the child. In this scenario, the child would also be expected to show a GALT enzyme activity level close to 50% of control.

Pathogenic variants. See Classic Galactosemia and Clinical Variant Galactosemia for information on other *GALT* alleles.

Normal gene product. The normal human GALT protein contains 379 amino acids and functions as a homodimer with two active sites [Wedekind et al 1995, Holden et al 2003].

A *GALT* allele with only the c.940A>G (p.Asn314Asp) variant is thought to produce a fully functional protein (reviewed in Carney et al [2009]).

Abnormal gene product. Abnormal gene products associated with different pathogenic alleles of *GALT* are described in Classic Galactosemia and Clinical Variant Galactosemia.

Chapter Notes

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Revision History

- 25 June 2020 (AA) Revision: added GALM deficiency and associated references
- 23 May 2019 (ma) Comprehensive update posted live
- 4 December 2014 (me) Review posted live
- 20 May 2014 (jfk) Original submission

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