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Duarte Variant Galactosemia

Synonym: Duarte Galactosemia

Judith L Fridovich-Keil, PhD
Department of Human Genetics
Emory University School of Medicine
Atlanta, Georgia
jfridov@emory.edu

Michael J Gambello, MD, PhD
Division of Medical Genetics
Department of Human Genetics
Emory University School of Medicine
Atlanta, Georgia
mgambel@emory.edu

Rani H Singh, PhD, RD
Division of Medical Genetics
Department of Human Genetics
Emory University School of Medicine
Atlanta, Georgia
rsingh@emory.edu

J Daniel Sharer, PhD
Division of Medical Genetics
Department of Human Genetics
Emory University School of Medicine
Atlanta, Georgia
jon.d.sharer@emory.edu

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Summary

Clinical characteristics. Infants with Duarte variant galactosemia who are on breast milk or a lactose-containing formula are typically, but not always, asymptomatic. Abnormalities, such as jaundice, which may be seen in some infants, resolve rapidly when the baby is switched to a low-galactose formula. Many healthcare professionals believe that Duarte variant galactosemia does not result in clinical disease either with or without dietary intervention; however, there are also reports to the contrary and no adequately powered study either confirming or refuting this assumption has been reported. Because available data about the neurodevelopmental outcomes of children with Duarte variant galactosemia are conflicting, further studies are warranted to determine what long-term outcomes are and whether the dietary intake of galactose in the first year of life influences outcome. Premature ovarian insufficiency 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 14%-25% of control activity, and *GALT* genotyping reveals the presence of one pathogenic *GALT* variant in the heterozygous state together with a Duarte (D_2) *GALT* allelic variant in either the heterozygous or homozygous state.

Management. *Treatment of manifestations:* Currently no agreement exists as to whether infants with Duarte variant galactosemia benefit from dietary galactose restriction during infancy and early childhood. Thus, healthcare providers or parents may choose either to restrict dietary galactose in the first year of life or not. When dietary galactose is restricted in infancy, it is recommended that the child undergo 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 of galactose is generally discontinued. When dietary galactose is not restricted in infancy, some healthcare providers choose to check the erythrocyte galactose-1-phosphate level at age one year to assure 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 4-6 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 sources of milk and dairy products 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, 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, and a 25% chance of being unaffected and 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. Requests for prenatal testing for conditions such as Duarte variant galactosemia are not common.

Diagnosis

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

- One *GALT* pathogenic variant present in the heterozygous state plus the *GALT* Duarte (D_2) variant allele present in either the heterozygous or homozygous state
- Erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity that is typically 14%-25% of control activity

Suggestive Findings

Duarte variant galactosemia should be considered in infants with a positive newborn screening (NBS) result for galactosemia (especially those demonstrating elevated concentrations of galactose and galactose metabolites in blood following exposure to milk), but few if any clinical findings.

Follow up Testing

Quantitative testing of erythrocyte GALT enzyme activity is the first recommended approach for a positive NBS result for galactosemia. Testing of erythrocyte galactose-1-phosphate and/or urinary galactitol may also be useful.

- **Erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity** that is typically 14%-25% of control activity is consistent with a diagnosis of Duarte variant galactosemia [Langley et al 1997, Ficicioglu et al 2008, Carney et al 2009, Walter & Fridovich-Keil 2014, Pyhtila et al 2015].

  Note: (1) While all states in the US now include screening for classic galactosemia in the NBS panel, some states have adjusted the newborn screening GALT enzyme activity cut-off level to maximize 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. (2) GALT is a labile enzyme; exposure of the sample to heat and humidity in storage or transit (as sometimes occurs in hot climates especially during the summer months) can result in artifactual loss of activity.

- **Erythrocyte galactose-1-phosphate (Gal-1P) concentration** may range from high (>30 mg/dL) to completely normal (<1.0 mg/dL) depending on the infant's recent dietary exposure to breast milk or lactose-containing formula.

- 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 lactose-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 lactose-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. For example, the mean urinary galactitol level in a cohort of 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 [Ficicioglu et al 2010]; mean urinary galactitol in controls was reported as 29±23 mmol/mol creatinine [Ficicioglu et al 2010].

Click here (pdf) for information on testing of historic 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 14%-25% of control activity; and (2) molecular genetic test results that include a heterozygous pathogenic *GALT* variant and the Duarte (D_2) *GALT* allelic variant in either the heterozygous or homozygous state.

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

- Four of the sequence changes are noncoding nucleotide variants that are unique to the 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 [Kozák et al 1999, Elsas et al 2001, Trbusek et al 2001, Carney et al 2009]. The three remaining variants unique to the D_2 allele are c.378-27G>C, c.508-24G>A, and c.507+62G>A.
- While the fifth sequence change, the missense variant c.940A>G (p.Asn314Asp, also called N314D), is always present on the D_2 allele, it also occurs on other functionally normal *GALT* alleles that are called either D_1 or Los Angeles (LA) alleles. [Bergren & Donnell 1973, Podskarbi et al 1996, Langley et al 1997, Carney et al 2009]. For more information see Molecular Genetics.

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 or clinical variant galactosemia. Note: Sometimes these pathogenic *GALT* variants are referred to collectively as G alleles.

Approaches to molecular genetic testing can include the following:

- **Sequence analysis** can detect the D_2 *GALT* allele as well as most *GALT* pathogenic variants. If the D_2 variant is identified in a sample in which GALT enzyme activity is ≤25%, but no *GALT* pathogenic variant is identified, deletion/duplication analysis should be considered.
- **Targeted analysis for pathogenic variants** (i.e., use of defined panel [set] of *GALT* variants) would detect the D_2 allele assuming the sequence variants characteristic of the D_2 allele were included in the panel; however, targeted analysis for pathogenic variants may be less effective than sequence analysis in detecting a pathogenic *GALT* allele because of the high allelic heterogeneity in classic and clinical variant galactosemia and the limited number of pathogenic variants usually included in such a panel.

Table 1.

Summary of Molecular Genetic Testing Used in Duarte Variant Galactosemia

Gene [1]	Test Method	Proportion of Probands in Whom the Method Detects:	
		The Duarte (D_2) Variant	A Pathogenic Variant
GALT	Targeted analysis for pathogenic variants	100% for a panel that includes the D_2 allele [2]	Varies by panel
	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. See Molecular Genetics for information on allelic variants.
2. A panel detecting only N314D but not the non-coding 4bp deletion associated with the D_2 allele or L218L associated with the Los Angeles (D_1) allele may not be able to distinguish between the D_1 and D_2 alleles, thus making interpretation of test results difficult.
3. *GALT* sequence analysis detects the D_2 allele as well as other variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
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**.

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 *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 the D_2 allele, such as c.940A>G (p.Asn314Asp, or N314D), does not confirm the 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 galactosemia carrier rather than Duarte variant galactosemia in the child.

Clinical Characteristics

Infants with Duarte variant galactosemia who are on breast milk or a lactose-containing formula are typically

asymptomatic. However, anecdotal patient reports suggest that some infants with Duarte variant galactosemia may experience jaundice or other acute manifestations that resolve following removal of milk from the diet [Author, personal observation].

The etiology and prevalence of acute complications among neonates with Duarte variant galactosemia exposed to milk remains unknown.

Many healthcare professionals believe that Duarte variant galactosemia does not result in clinical disease either with or without dietary intervention; however, some reports contradict that assertion [Powell et al 2009; Lynch et al, in press] and no adequately powered study to confirm or refute it has been published.

Clinical Description

The natural history of Duarte variant galactosemia is poorly understood because (1) some infants with presumed Duarte variant galactosemia are born in states where they are not identified by newborn screening, and (2) those born in states where they are identified and diagnosed are typically clinically well as babies and toddlers and are therefore discharged from follow up.

Infants with Duarte variant galactosemia may remain apparently asymptomatic regardless of galactose exposure.

Neurodevelopment. A study of neurodevelopment in 28 toddlers and very young children with Duarte variant galactosemia (confirmed by GALT enzyme activity of ~12%-50% of controls and *GALT* molecular genetic test results consistent with Duarte variant galactosemia) suggested no significant developmental defects regardless of diet [Ficicioglu et al 2008].

In contrast, a study assessing developmental outcomes of older children with a diagnosis of Duarte variant galactosemia (also confirmed by GALT enzymatic activity and *GALT* molecular genetic test results) reported that by mid-elementary school these children were more than twice as likely as their peers to receive special educational services for speech and/or language [Powell et al 2009], implying the possibility of relatively increased risk of developmental difficulties in this population.

A pilot study involving direct developmental assessments of ten children with biochemically and molecularly determined Duarte variant galactosemia and five controls, all between ages six and11 years, also demonstrated some notable differences between children with Duarte variant galactosemia and controls in socio-emotional development, delayed recall, and auditory processing speed [Lynch et al, in press].

Thus, further studies are needed to define the long-term outcomes of older children with Duarte variant galactosemia and to determine if exposure to galactose in the first year of life modifies outcome [Fernhoff 2010].

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.

Genotype-Phenotype Correlations

By definition, all individuals with Duarte variant galactosemia have at least one D_2 *GALT* allele (see Molecular Genetics) and one pathogenic *GALT* allele in *trans* configuration; however, given the large number of known pathogenic *GALT* alleles, the pathogenic *GALT* allele is likely to differ between families with Duarte variant galactosemia. No significant genotype-phenotype relationships for Duarte variant galactosemia with regard to different pathogenic *GALT* alleles have been reported.

Nomenclature

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

In some instances Duarte variant galactosemia has been called 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 that result in a low level of residual GALT enzyme activity. Of note, kinase 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.

Pathogenic variants that completely or nearly abolish GALT enzyme activity are sometimes called G alleles. Individuals who have biallelic pathogenic variants have classic or clinical variant galactosemia.

Prevalence

The prevalence of Duarte variant galactosemia is difficult to confirm due to incomplete ascertainment. For example, while classic galactosemia is detected in close to 1:50,000 screened births in most states in the United States, 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 newborn screening protocols [Pyhtila et al 2015] (see Diagnosis, **Erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity**).

The true prevalence of Duarte variant galactosemia in the US newborn population is believed 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 American or Asian ancestry. These differences parallel recognized differences among these populations in the prevalence of the D_2 variant and other known *GALT* pathogenic variants [Pyhtila et al 2015].

Genetically Related (Allelic) Disorders

Classic galactosemia and clinical variant galactosemia are the two phenotypes, other than Duarte variant galactosemia, associated with mutation of *GALT*. The genotypes that give rise to these phenotypes have two *GALT* pathogenic variants that result in either absent or barely detectable GALT enzyme activity.

Differential Diagnosis

Most infants with Duarte variant galactosemia are diagnosed in the follow-up evaluation to a positive newborn screening result for galactosemia. The differential diagnosis of a positive newborn screen for galactosemia is:

- Classic galactosemia and clinical variant galactosemia
- Duarte variant galactosemia
- GALE (epimerase) deficiency
- GALK (galactokinase) deficiency
- A false positive result which 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 enzyme activity whose dried blood spot or markers of galactose metabolism were technically compromised for some reason.

Erythrocyte GALT enzyme activity. Measuring erythrocyte GALT enzyme activity is often the first step in

differential diagnosis of a positive newborn screening result for galactosemia. Erythrocytes from individuals with classic galactosemia demonstrate very low to undetectable GALT enzyme activity.

In contrast, GALT enzyme activity in erythrocytes from individuals:

- With Duarte variant galactosemia is close to 14%-25% that of controls [Ficicioglu et al 2008, Pyhtila et al 2015];
- Who are carriers of one pathogenic *GALT* allele or homozygous for the D_2 variant is close to 50% that of controls;
- Who are heterozygous for one D_2 variant (i.e., are carriers) is close to 75% that of controls;
- Who have GALE (epimerase) deficiency or GALK (galactokinase) deficiency is indistinguishable from that of controls [Langley et al 1997, Carney et al 2009, Pyhtila et al 2015].

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

To establish the extent of disease and needs in an infant diagnosed with Duarte variant galactosemia, a clinical genetics consultation is recommended.

Treatment of Manifestations

There is currently no uniform standard of care for patients with Duarte variant galactosemia. Agreement has not been reached as to whether individuals with Duarte variant galactosemia with residual erythrocyte GALT enzyme activity in the range of 14%-25% of controls should be restricted from galactose intake during infancy and early childhood. Until a sufficiently sensitive and statistically powerful study is conducted to determine whether galactose exposure negatively affects long-term developmental outcomes in children with Duarte variant galactosemia, the controversy concerning intervention and outcomes is likely to persist.

Because it is unclear if acute or long-term manifestations can result from Duarte variant galactosemia, and if so, whether dietary galactose restriction would prevent or resolve the issues that have been reported [Powell et al 2009, Lynch et al, in press], any developmental or psychosocial problems experienced by a child with Duarte variant galactosemia should be treated symptomatically and the possibility of other causes should be explored.

Approach for non-treatment. Healthcare providers who choose not to treat infants with Duarte variant galactosemia by dietary restriction of galactose in the first year of life generally consider Duarte variant galactosemia to be of no clinical significance. These healthcare providers argue against the interruption of breastfeeding when there is no clear evidence to justify it [Fernhoff 2010]. Of note, continued galactose-1-phosphate accumulation may be seen with lactose ingestion but is usually without overt sequelae.

If the infant has not been placed on a galactose-restricted diet, or if feedings are alternating between breast milk and low galactose formula, it is reasonable to check the erythrocyte galactose-1-phosphate level by age 12 months (or sooner if an earlier erythrocyte galactose-1-phosphate level was particularly high) to ensure that the level is approaching control range by age 12 months.

Approach for treatment. Healthcare providers who choose to treat infants with Duarte variant galactosemia by dietary restriction of galactose in the first year of life generally consider the intervention to be potentially preventive

rather than responsive to current disease manifestations. Options for dietary intervention [Fernhoff 2010, Pyhtila et al 2015] include:

- Full dietary restriction of galactose for all infants, through age one year, at which time a galactose challenge is performed;
- Following the recommendations for clinical variant galactosemia: immediate dietary galactose restriction for infants with erythrocyte galactose-1-phosphate >10 mg/dL;
- A compromise approach in which parents either alternate feeding breast milk with low galactose formula, or non-breastfeeding parents use low galactose formula rather than a milk-based formula.

The galactose challenge. If treatment is the chosen approach, conducting a galactose challenge at some point 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 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 can be stabilized at <1.0 mg/dL.

Agents/Circumstances to Avoid

It is unclear if there are any agents or circumstances that individuals with Duarte variant galactosemia should avoid.

Some healthcare providers recommend avoiding all sources of milk and dairy products until age one year as a precaution against possible galactose toxicity; other healthcare providers argue that this precaution is not warranted. See Treatment of Manifestations.

Evaluation of Relatives at Risk

Some families with one child with Duarte variant galactosemia wish to evaluate their other children for Duarte variant galactosemia; however, it has not been established that avoidance of all sources of milk and dairy products is warranted in any siblings who test positive for Duarte variant galactosemia.

If the *GALT* genotype of the proband is known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs: sibs can be tested for the presence of the D_2 allele and the specific *GALT* pathogenic variant identified in the proband.

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

Pregnancy Management

There are no known additional risks associated with pregnancy for a woman with Duarte variant galactosemia or for a

fetus with Duarte variant galactosemia.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

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 in *trans* configuration (on homologous chromosomes).

Risk to Family Members

Parents of a proband

- 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. Molecular genetic testing is needed to clarify the genetic status of parents (see Establishing the Diagnosis, **Interpretation of molecular genetic test results**).
- Rarely, a parent may have Duarte variant galactosemia or another genotype that includes the D_2 variant (e.g., homozygosity for the Duarte variant).
- 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.
- When 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;
  - 25% chance of being an asymptomatic carrier of the D_2 allele;
  - 25% chance of being an asymptomatic carrier of a *GALT* pathogenic variant;
  - 25% chance of being unaffected and not a carrier of either variant.
- 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.
- Risks to sibs are different for other parental genotypes. Referral for genetic counseling is indicated for such families.
  Note: 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 has a 25% chance of having classic or clinical variant galactosemia.

Offspring of a proband

- Each child of an individual with Duarte variant galactosemia is typically an obligate heterozygote (carrier) 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

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 available prenatal testing options is before pregnancy.
- 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.

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

If the *GALT* variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing.

Requests for prenatal testing for conditions such as Duarte variant galactosemia are not common. 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 decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the *GALT* variants have been identified.

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.

No specific resources for Duarte Variant Galactosemia have been identified by *GeneReviews* staff.

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
606999	GALACTOSE-1-PHOSPHATE URIDYLYLTRANSFERASE; GALT

Molecular Genetic Pathogenesis

The mechanism of pathogenesis of the *GALT* D_2 allele was a point of some confusion in the past [Elsas et al 1994, Fridovich-Keil et al 1995, Podskarbi et al 1996, Langley et al 1997, Lai et al 1998, Kozák et al 1999, Elsas et al 2001, 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 allelic 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.
    - Of primary importance is a 4-bp deletion in the *GALT* promoter region (c.-119_-116delGTCA) that slightly impairs gene expression [Kozák et al 1999, Elsas et al 2001, Trbusek et al 2001, 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 [Bergren & Donnell 1973, Podskarbi et al 1996, Langley et al 1997, 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.Leu218Leu, 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 [Langley et al 1997, Elsas et al 2001].

Table 2.

GALT Allelic 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 (reduces promoter function)	NM_000155.2 NP_000146.2
c.940A>G	p.Asn314Asp (N314D)	
c.378-27G>C (IVS4-27G>C)	NA	
c.508-24G>A (IVS5-24G>A)	NA	
c.507+62G>A (IVS5-62G>A)	NA	

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

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

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

Pathogenic allelic 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 [Andersen et al 1984, Fridovich-Keil et al 1995, 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.

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Chapter Notes

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