

## Galactosemia – an Overview

### Disease Summary

Galactosemia is an autosomal recessive disorder of galactose metabolism that, in its classic form, leads to liver damage, bleeding diathesis, and hyperammonemia within days or weeks of birth.<sup>1,2</sup> If left untreated, sepsis can result in neonatal death.<sup>1,2</sup> Mental retardation is common, even in treated patients.<sup>1</sup> Most cases of galactosemia, which has a prevalence of about 1 in 30,000, are detected through newborn screening of galactose-1-phosphate uridyltransferase (GALT) enzyme activity and/or galactose-1 phosphate concentration in red blood cells.<sup>1,2</sup> If GALT deficiency is detected, prompt removal of lactose and galactose from the diet can resolve acute neonatal symptoms and prevent death and mental retardation. Genetic testing of the gene encoding GALT can be used to confirm a newborn screening result and detect the specific mutations leading to galactosemia in a patient, with possible implications for disease prognosis.<sup>1,2</sup>

Even with timely treatment initiation, long-term consequences are common and can include speech defect (verbal dyspraxia), delay of mental development, motor dysfunction, poor growth, cataracts, and, in females, ovarian failure.<sup>1,2</sup> Prognosis may differ depending on the nature of the specific GALT mutation underlying the disease.<sup>1-3</sup> The variant p.Gln188Arg, which accounts for 70% of galactosemia in individuals of Northern European heritage, is associated with increased risk of speech defects, cognitive impairment, and premature ovarian

failure when homozygously present.<sup>1</sup> Similarly, the variant p.Lys285Asn, which is prevalent in Germany, Austria, and Croatia, is also associated with poor prognosis for cognitive and motor dysfunction if present homozygously or in compound heterozygosity with p.Gln188Arg.<sup>1</sup> In contrast, p.Ser135Leu, which is common in African Americans, generally indicates a good prognosis and absence of chronic problems.<sup>1</sup> Prognosis is also good for p.Asn314Asp, commonly known as the Duarte variant, since it leads to only partial reduction of GALT activity.<sup>1</sup> Importantly, p.Asn314Asp only reduces GALT activity if occurring together with the promoter variant c.-116\_-119delGTCA.<sup>1,2</sup> In absence of this promoter variant, p.Asn314Asp is known as LA variant and does not cause reduction of GALT activity.<sup>1,2</sup> Since the Duarte and the LA variant do not differ in their amino acid sequence, they cannot be distinguished by isoelectric focusing, a technique commonly used in the past to detect the Duarte variant.<sup>1</sup> In addition to the common GALT variants listed above, more than 100 “private” variants have also been identified.<sup>3</sup> Once the mutations causing galactosemia in a specific family have been identified, genetic testing for these mutations can help to diagnose affected siblings of patients prenatally or directly after birth and facilitate genetic counseling in other relatives.<sup>1</sup>

For additional information, see Tables 1-2 below and references 1-3.

**Table 1: Disease Facts about Galactosemia (based on references 1-3)**

Disease Fact	Galactosemia
MIM* number	230400
Estimated Prevalence	1:30,000
Average Age at Diagnosis	Infancy
<b>Typical Symptoms</b>	<p><b>Presenting Symptoms</b></p> <p>Hepatocellular damage (jaundice, hepatomegaly, coagulation disorders)            Food intolerance (vomiting, diarrhea, poor feeding)            Failure to thrive            Lethargy            Cataracts</p> <p><b>Symptoms associated with untreated galactosemia</b></p> <p>Seizures            Sepsis (E.coli, Klebsiella, Enterobacter, Staphylococcus, Streptococcus)            Mental retardation</p> <p><b>Symptoms associated with treated galactosemia</b></p> <p>Cognitive impairment            Verbal dyspraxia            Motor dysfunction (fine motor tremor, ataxia)            In females, ovarian failure            Delayed growth            Cataracts</p>
<b>Therapy</b>	Lactose/galactose restricted diet FSH therapy for infertility in female patients

\*MIM: Mendelian Inheritance in Man, see <http://www.ncbi.nlm.nih.gov/omim>

**Table 2: Molecular Genetics of Galactosemia (based on references 1-3)**

Gene (Protein)	Transmission	Mutation type	Penetrance	Comments
GALT (galactose-1-phosphate uridyl-transferase)	Autosomal recessive	Loss-of-function	High	Risk and type of chronic complications may vary depending on the specific mutations

## References

1. Elsas LJ Galactosemia. GeneReviews. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=galactosemia> Accessed 080110
2. Bosch AM (2006) Classical galactosemia revisited. J Inherit Metab Dis 29:516-25.
3. Tyfield L, Reichardt J, Fridovich-Keil J, Croke DT, Elsas LJ, et al (1999) Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. Human Mutation 13:417-30.