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FREQUENTLY ASKED QUESTIONS ABOUT **GALACTOSEMIA**

This is an interactive guide to understanding more about Classic Galactosemia.

APPLIED THERAPEUTICS

FREQUENTLY ASKED QUESTIONS ABOUT **GALACTOSEMIA**

- What is Galactosemia?
- What causes Galactosemia?
- What is Gal-1p, and why is it important?
- What is galactitol?

Sources: Berry G, et al. J Pediatr. 2001;138(2):260-2; Berry GT. Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al, eds. *GeneReviews®*. University of Washington: Seattle, WA: 993-2020; Berry GT, et al. *Lancet*. 1995;346(8982):1073-1074; Coelho A, et al. *J Inherit Metab Dis*. 2017;40(3):325-342; Martinelli, et al. *Neurology*. Jan 2016;86(3)e32-e33; Otaduy MCG, et al. *AJNR Am J Neuroradiol*. 2006;27(1):204-207; Rubio-Gozalbo ME, et al. *Orphanet J Rare Dis*. 2019;14(1):86; U.S. National Library of Medicine website; Welling L, et al. *J Inherit Metab Dis*. 2017;40(2):171-176.

APPLIED THERAPEUTICS

UNDERSTANDING **GALACTOSEMIA**

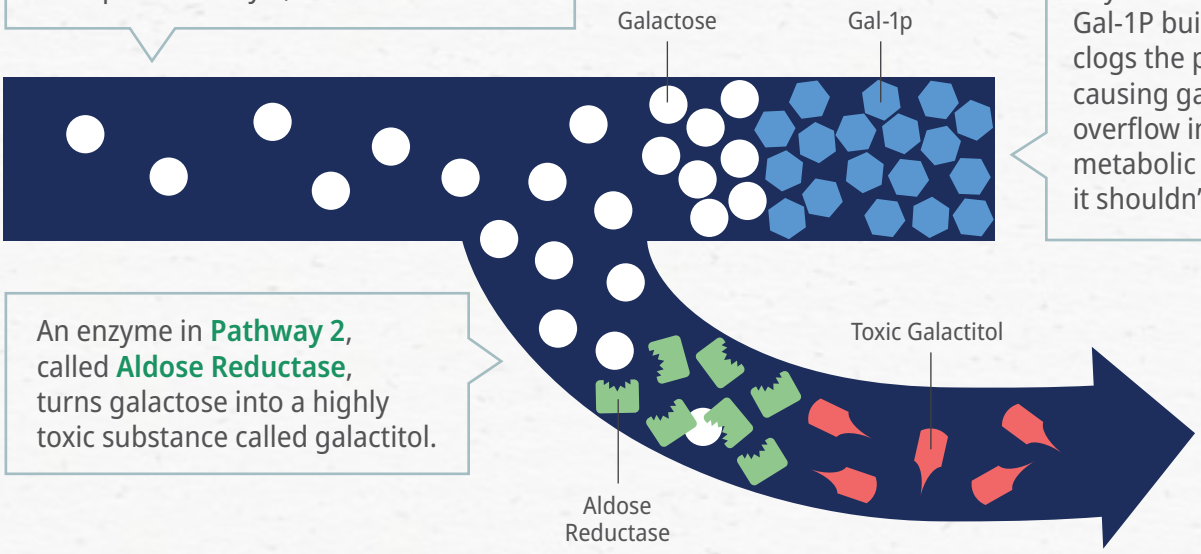
What is Galactosemia?

Classic Galactosemia (pronounced ga-lac-toe-SEE-me-ah) is a rare condition where the body has trouble processing a sugar called "galactose." Galactose is a type of sugar most commonly found in milk, dairy products, and certain other foods. Galactose is also made naturally in the body—this is called "endogenous" galactose. There are different types of Galactosemia, but the most common one that causes health problems is called "Classic Galactosemia."

Normally, the body turns galactose into glucose after it travels down a special pathway and interacts with an enzyme called GALK. GALK is what turns galactose into another compound called galactose-1-phosphate (Gal-1p). Then, Gal-1p continues down the path and is converted by another enzyme, GALT, into a substance called Glucose-1p, which eventually turns into glucose, providing your body with energy.

Pathway 1 is the normal pathway for processing galactose. In people with **Galactosemia**, galactose is changed into Gal-1p in Pathway 1, as it should be.

But because of the missing **GALT** enzyme, **Gal-1p** can't be processed any further. As a result, Gal-1P builds up and clogs the pathway, causing galactose to overflow into a different metabolic pathway, where it shouldn't go.



An enzyme in **Pathway 2**, called **Aldose Reductase**, turns galactose into a highly toxic substance called galactitol.

When people with Galactosemia make Gal-1p, it is mistakenly converted into toxic galactitol. An excess of toxic galactictol can be very harmful to children and adults living with Galactosemia.

Symptoms of Galactosemia are different for everyone. These include speech issues, cognitive and developmental delays, fertility issues in girls, cataracts, seizures, and tremor.

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What causes Galactosemia?

Classic Galactosemia is a rare condition that only 1 in every ~44,000 babies born in the US will develop. Galactosemia is a genetic condition, meaning that it is passed down through a child's parents. When a baby is conceived, it receives genes from each parent, creating thousands of pairs of genes that will determine things like the color of their eyes and hair. There is also a gene pair that enables the production of an enzyme that helps our bodies process galactose—this is the *GALT* gene.

Galactosemia occurs when each of the infant's parents carry one form of the gene that makes a working GALT enzyme and one nonworking gene that does not make the GALT enzyme. When a child inherits a nonworking form of the *GALT* gene from both parents to form a nonworking *GALT* gene pair, their GALT enzyme will not work as it should and causes Galactosemia. This kind of genetic inheritance is known as "autosomal recessive" inheritance.

After a child is diagnosed with Galactosemia, a blood test called an enzymatic and/or mutational analyses may be done to determine the type of Galactosemia that child has. If you have additional questions about how genes play a role in Galactosemia, ask your doctor.

UNDERSTANDING **GALACTOSEMIA**

What is Gal-1p, and why is it important?

Gal-1p stands for galactose-1-phosphate. Everybody makes Gal-1p. However, people with Galactosemia will experience an excess buildup of Gal-1p. This is because they are missing a key enzyme called GALT, which is needed to process Gal-1p.

Today, Gal-1p is important in the monitoring of Galactosemia. Children and adults with Galactosemia will have high levels of Gal-1p in their blood. After an infant has been diagnosed with Galactosemia, their doctor will do a blood test to see how much Gal-1p is in their blood. Once a child with Galactosemia has been on a galactose-reduced diet, their doctor will check their blood again periodically to see how the Gal-1p levels have changed. Although Gal-1p is monitored, there is no evidence that it directly causes health problems that people with Galactosemia may experience.

UNDERSTANDING **GALACTOSEMIA**

What is galactitol?

Galactitol is a toxic substance that forms when galactose is forced down an alternate metabolic pathway. Typically, galactose is eventually turned into glucose, which our bodies use for energy. In people with Classic Galactosemia, that is not the case. Because people with Galactosemia are missing a working *GALT* gene, galactose is instead processed by an enzyme called Aldose Reductase and is turned into galactitol.

Galactitol is harmful to the body. It has been shown that galactitol can build up in the blood, tissues, and organs, including the brain. Using magnetic resonance spectroscopy (MRS) technology, this build-up of galactitol in the brain can be seen.

There is evidence that toxic galactitol is responsible for a range of health problems that people with Galactosemia may experience. These can include the development of cataracts, speech issues, cognitive and developmental delays, fertility issues in girls, seizures, and tremor.