

Galactosemia

Dr Michel Tchan

Adult Genetic Metabolic Disorders Service

Westmead Hospital

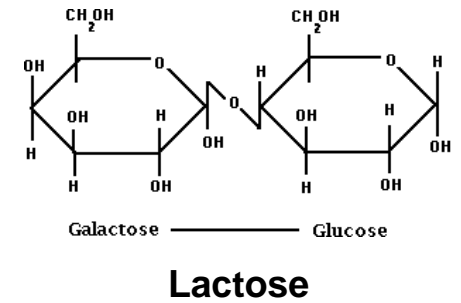
Galactosemia

- People with galactosemia are unable to metabolize the simple sugar galactose.

- infantile cataracts,
- jaundice,
- vomiting,
- poor feeding,
- infections
- Failure to thrive,
- hepatomegaly
- Speech disabilities,
- Sub-fertility
- (Intellectual disability)

**POTENTIALLY LETHAL IF
UNDIAGNOSED/UNTREATED**

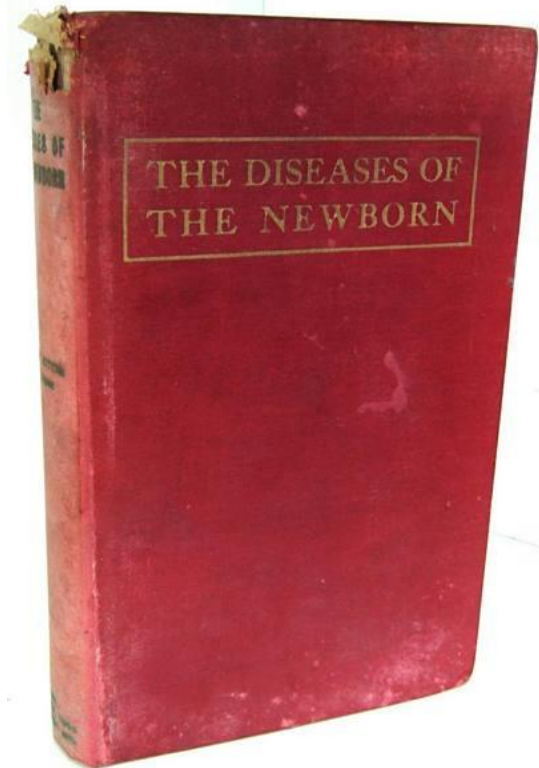
Galactose in Health



- Galactose is a vital energy source, particularly for babies
- Mostly found in dairy products as part of a sugar “lactose”
- Important for putting sugars onto proteins (glycosylation)
- We make some galactose internally, about 1000 – 2100 mg daily (adults, higher in children).

History

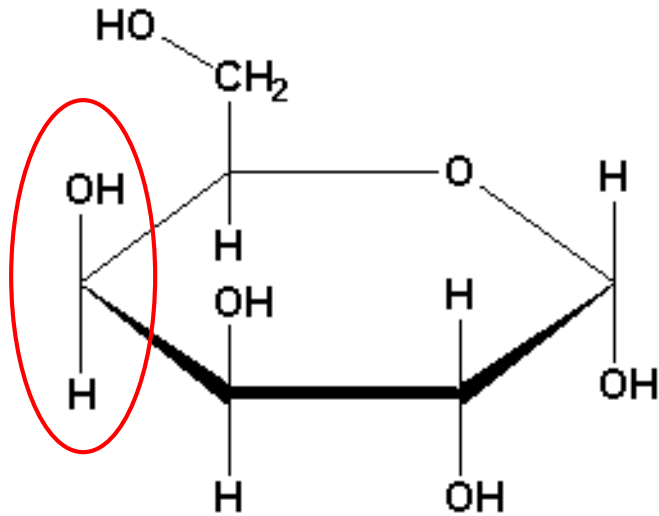
- Galactosemia was first discovered in **1908** by the physician Von Ruess.
- Publication entitled, "Sugar Excretion in Infancy," reported on a breast-fed infant with failure to thrive, enlargement of the liver and spleen, and "galactosuria".
- 1935 Treatment described by Mason and Turner



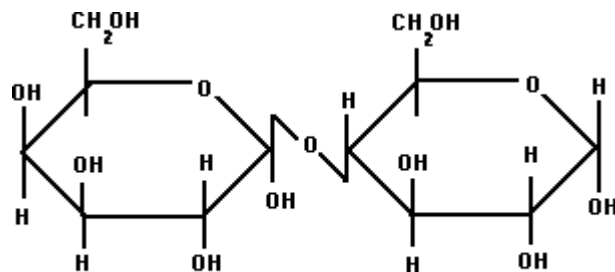
- Now diagnosed by newborn screening in Australia



Galactose



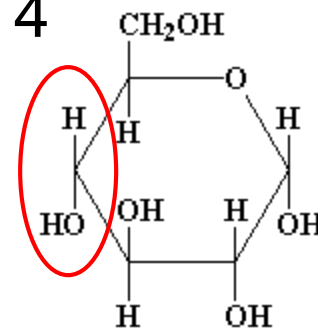
Galactose



Galactose — Glucose

Lactose

- Six carbon aldose carbohydrate
- Major dietary source is lactose from milk and milk products
- Epimer of glucose
 - Differs from glucose at carbon 4



glucose

“The Leloir pathway”

β-D-Galactose

α -D-Galactose

~~galactokinase~~

Glucose-1-phosphate

UTP → UDP-Glc + pyrophos.

~~Citrate Synthase~~

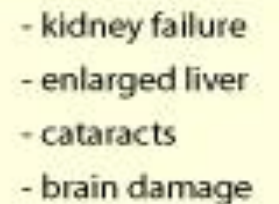
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- UDP-Galactose

~~UDP-Glc:Gal-1-P
uridylyltransferase~~

phosphoglucomutase

copyright M.V.V. King 1997

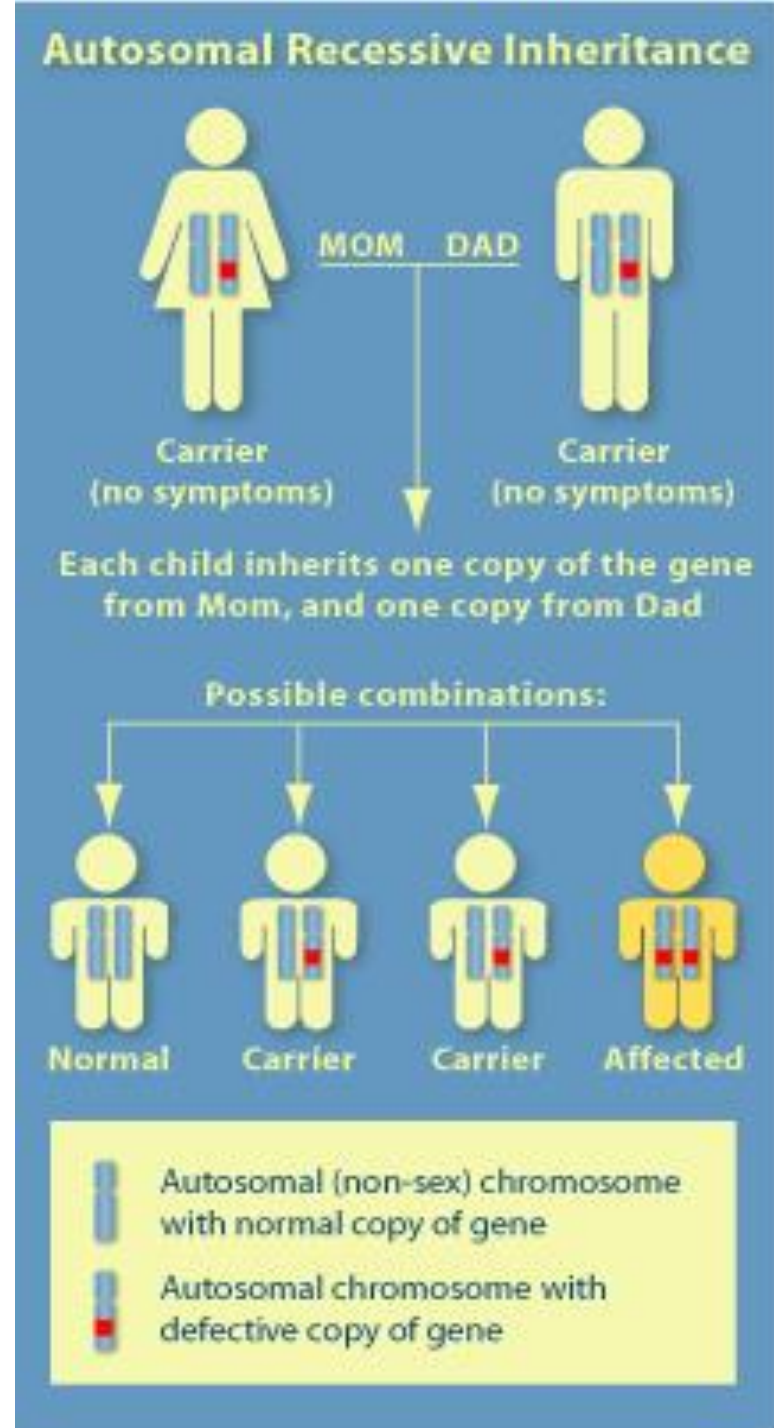


Galactosemia – a genetic disease

- Galactosemia is an inherited disorder.

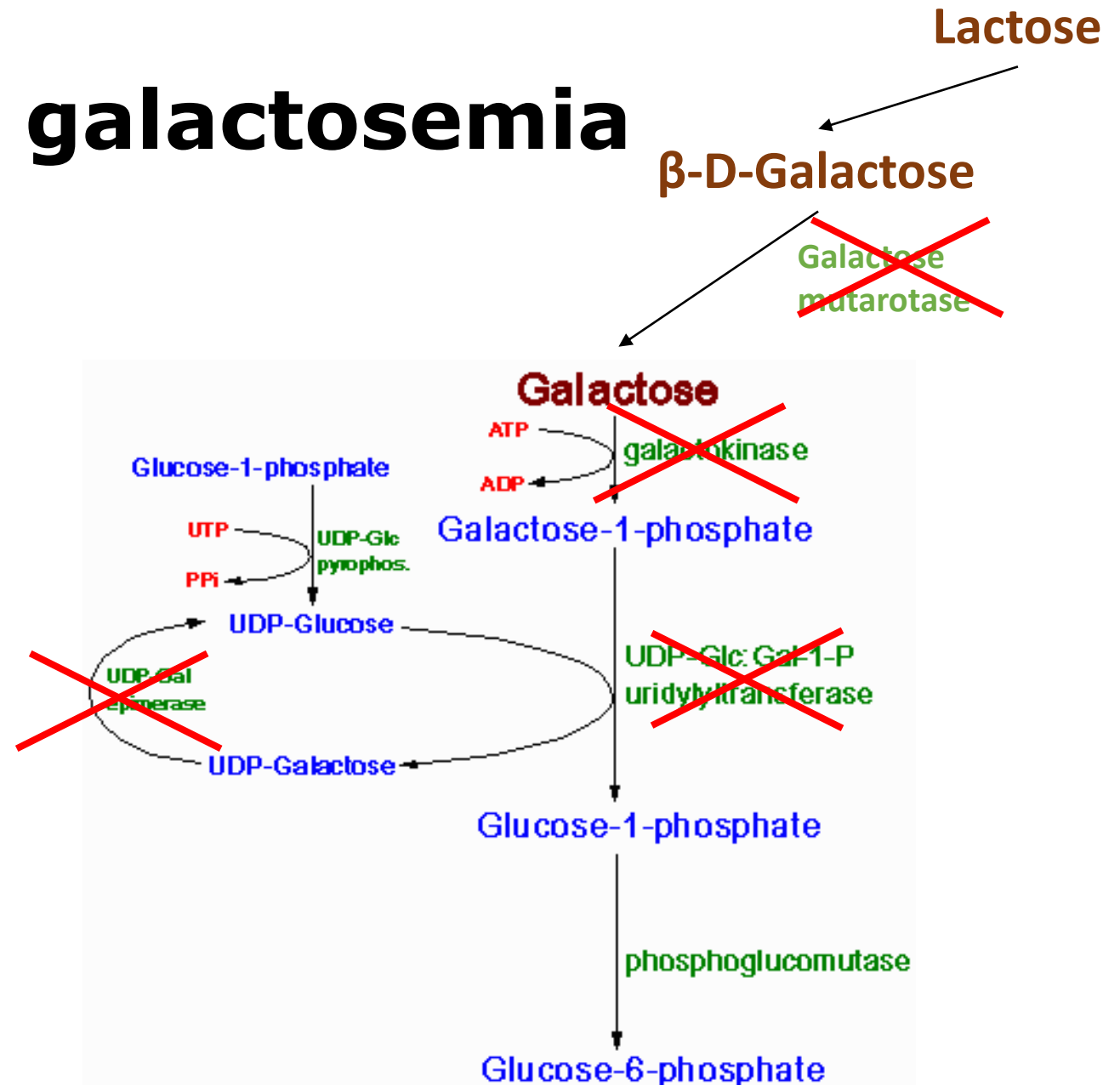
- Autosomal recessive pattern

- It occurs in approximately 1 out of every 60,000 births among Caucasians.
- About 6 or 7 babies a year
- The rate is different for other groups.



Four forms of galactosemia

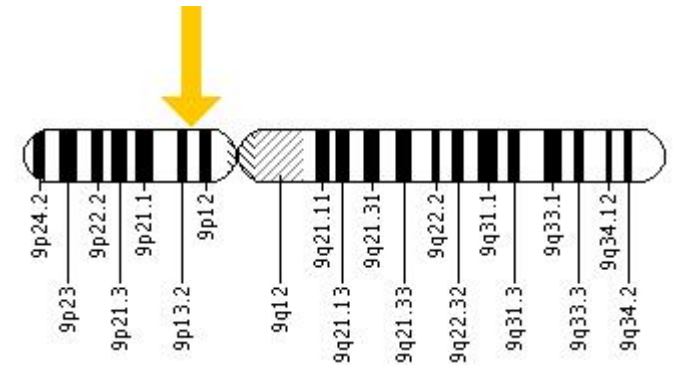
- Galactose-1 phosphate uridyl transferase deficiency (classic galactosemia, the *most common and most severe* form)- **(GALT) Type I**
- Deficiency of galactose kinase – **(GALK1) Type II**
- Deficiency of galactose-6-phosphate –epimerase **(GALE)-Type III**
- Deficiency of galactose mutarotase – **(GALM) Type IV**



Classic galactosemia – GALT _ type I

- **Galactose-1-phosphate uridylyltransferase defect** causes accumulation of **galactose**
- Galactose changes to **galactitol**. Galactitol accumulates in lens and causes **infantile cataracts**.
- **Jaundice, vomiting, poor feeding, infections**
- **Failure to thrive, hepatomegaly**
- **Speech disabilities,**
- **Female sub-fertility**
- **(Intellectual disability)**

- The official name of this gene is “galactose-1-phosphate uridylyltransferase.”
- GALT is the gene's official symbol.
- Cytogenetic Location: **9p13**



Missense mutations

within the GALT gene

S135L = Leu for Ser

- Almost exclusively in individuals of African decent

- 50% of African American mutations

K285N = Asn for Lys

- 2nd most common disease-causing mutation

→

5

6

←

→

9

10

←

Q188R = Arg for Gln

- Classic galactosemia

- 60-70% of mutated chromosomes

N314D = Asp for Asn

- Duarte and LA alleles

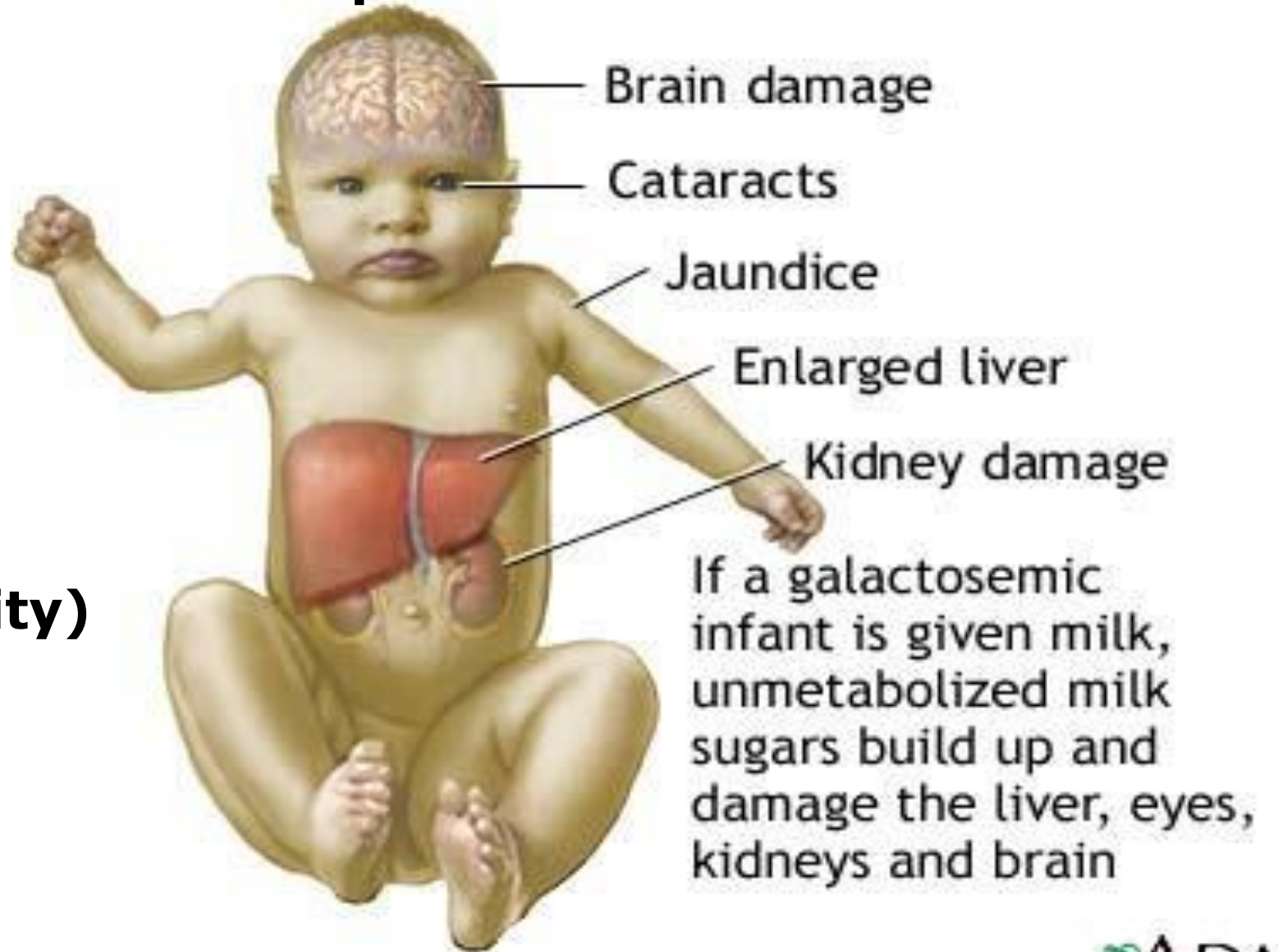
- 2 variations: D1 & D2

Q188R

- Most deleterious mutation on GALT gene
- Ireland and British (highest frequency)
- Homozygous individuals
show no activity (*in vitro*)

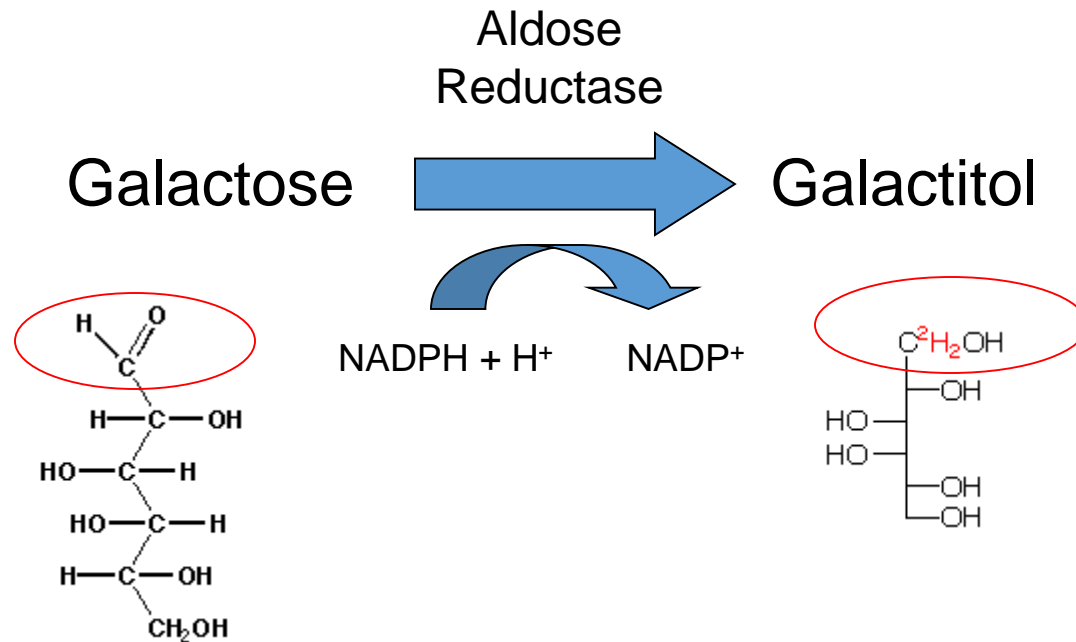
Galactosemia clinical picture

- **Infantile cataracts,**
- **jaundice,**
- **vomiting,**
- **poor feeding,**
- **infections**
- **Failure to thrive,**
- **hepatomegaly**
- **Speech disabilities,**
- **Female sub-fertility**
- **(Intellectual disability)**



Cause of Symptoms?

Complex! Poorly understood

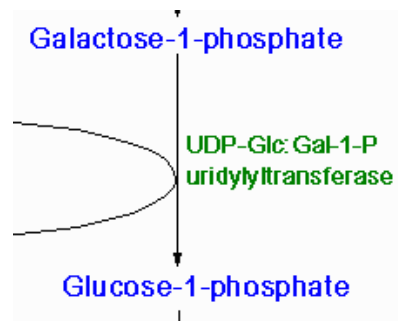


•Buildup of galactitol ?

- Intellectual disability
- Cataracts
- Ovarian damage

•Buildup of galactose-1-phosphate ?

- Liver and renal damage
- Intellectual problems



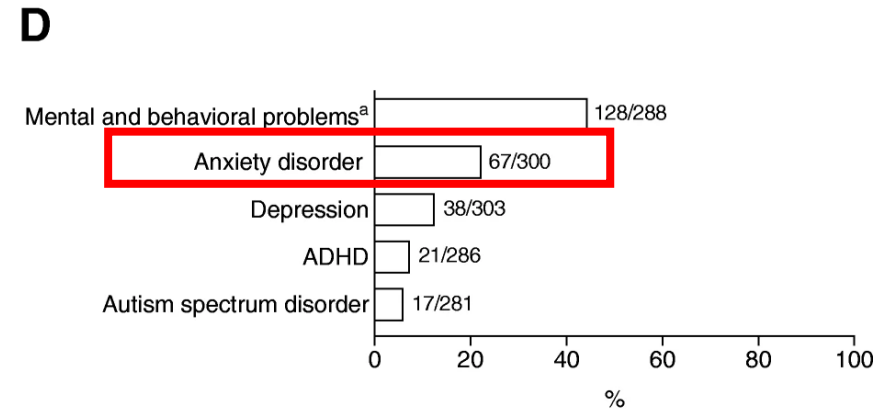
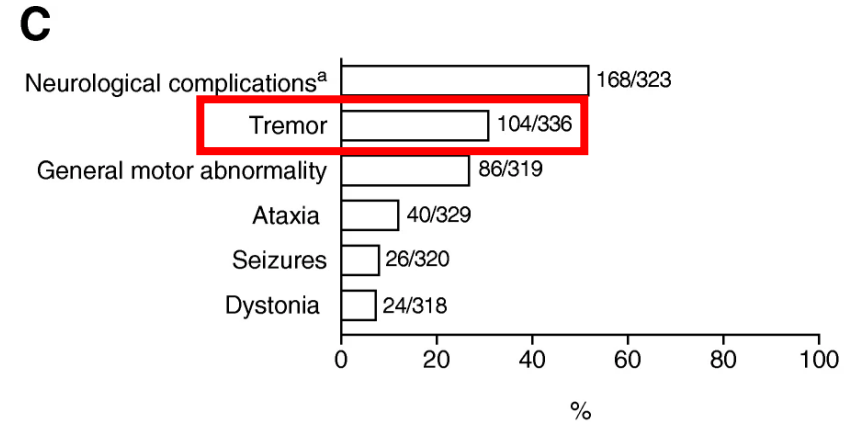
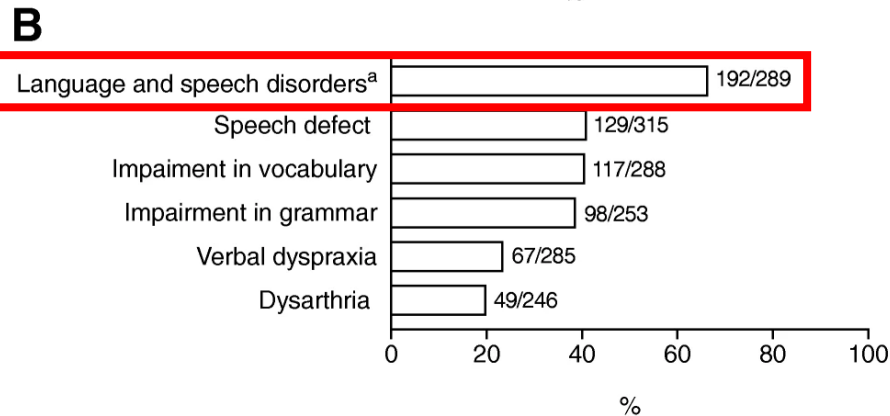
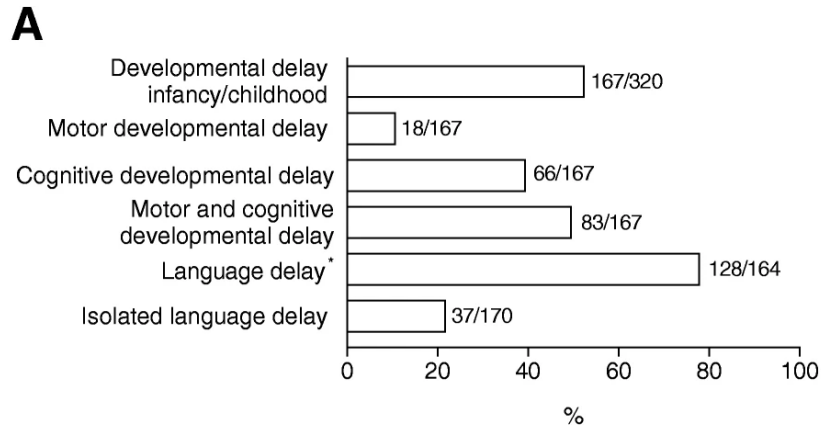
Type 1 – what do we know clinically?

- Recently published comprehensive study (Rubio-Gozalbo et al 2019)
 - GalNet
 - 509 patients worldwide
 - Aged 0 to 65 years
 - 93% Caucasian in this study
 - Q188R was 57.7% (233/404)
 - Diagnosed on NBS in 45.9% (215/468)

Neonatal illness

- reported in 79.8% (332/416)
 - elevated liver enzymes in 70.3% (211/300),
 - bleeding diathesis in 42.5% (128/301),
 - encephalopathy in 29.0% (71/245),
 - clinical signs of infection in 27.4% (96/351),
 - cataract in 25.8% (68/264) and
 - hypoglycemia in 25.1% (65/259).
- Early detection and treatment saves lives

Neurological, cognitive and behavioral complications



^a Defined as having at least one of the complications in that category, compared to having none of them.

* Language delay and motor and/or cognitive developmental delay.

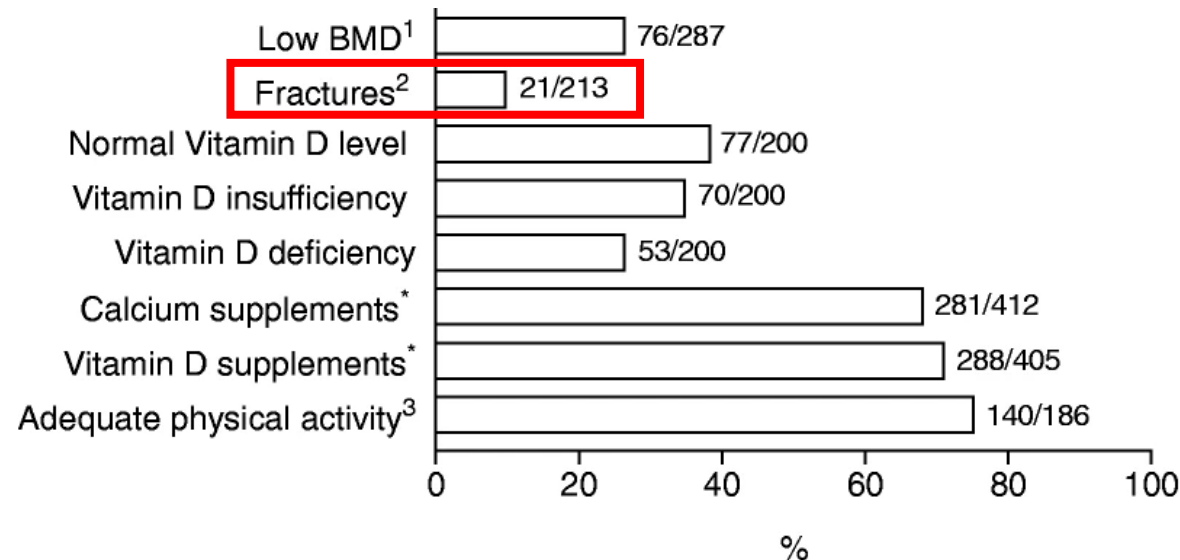
Frequency of neurological, cognitive and mental (psychiatric) complications. **a** Developmental delay infancy/childhood. **b** Language and speech disorders. **c** Neurological complications. **d** Mental (psychiatric) and behavioral problems. The n/valid n is shown per outcome

Sub-fertility

- Premature ovarian insufficiency (POI) was reported in 79.7% (118/148) of female patients.
- In females aged > 35 years, POI percentage increased to 85.1% (40/47)
- 16.8% (16/95) of female patients with POI tried to conceive and 25.0% (4/16) of these women successfully became pregnant without assisted reproduction.
- p.Gln188Arg mutation was associated with a higher odds ratio for POI
- 7.8% (5/64) males had fathered a child

Bone health

- Low bone density in 26.5% (76/287) of the patients, where 65.8% (50/76) were female
- The majority of patients received calcium and vitamin D supplements (68.2% (281/412) and 71.1% (288/405), respectively)



Cataract

- Cataract in the neonatal period in 25.8% (68/264).
- In 54.5% (24/44) the cataract disappeared after introduction of diet, whereas in 45.5% (20/44) of patients a residual cataract was documented.
- A minority of patients developed cataract after the neonatal period, 9.2% (22/238).
- There was another group of patients, 11.2% (10/89), in whom cataract was reported in adulthood (median 29.5 years, range 18 to 41 years)

Diet

- After the neonatal period, most of the patients followed a lactose-free diet, 94.2% (406/431).
- relaxed diet (lactose free without further restrictions), in 64.3% (245/381)
- strict diet (lactose free and restriction of non-dairy sources) in 35.7% (136/381)

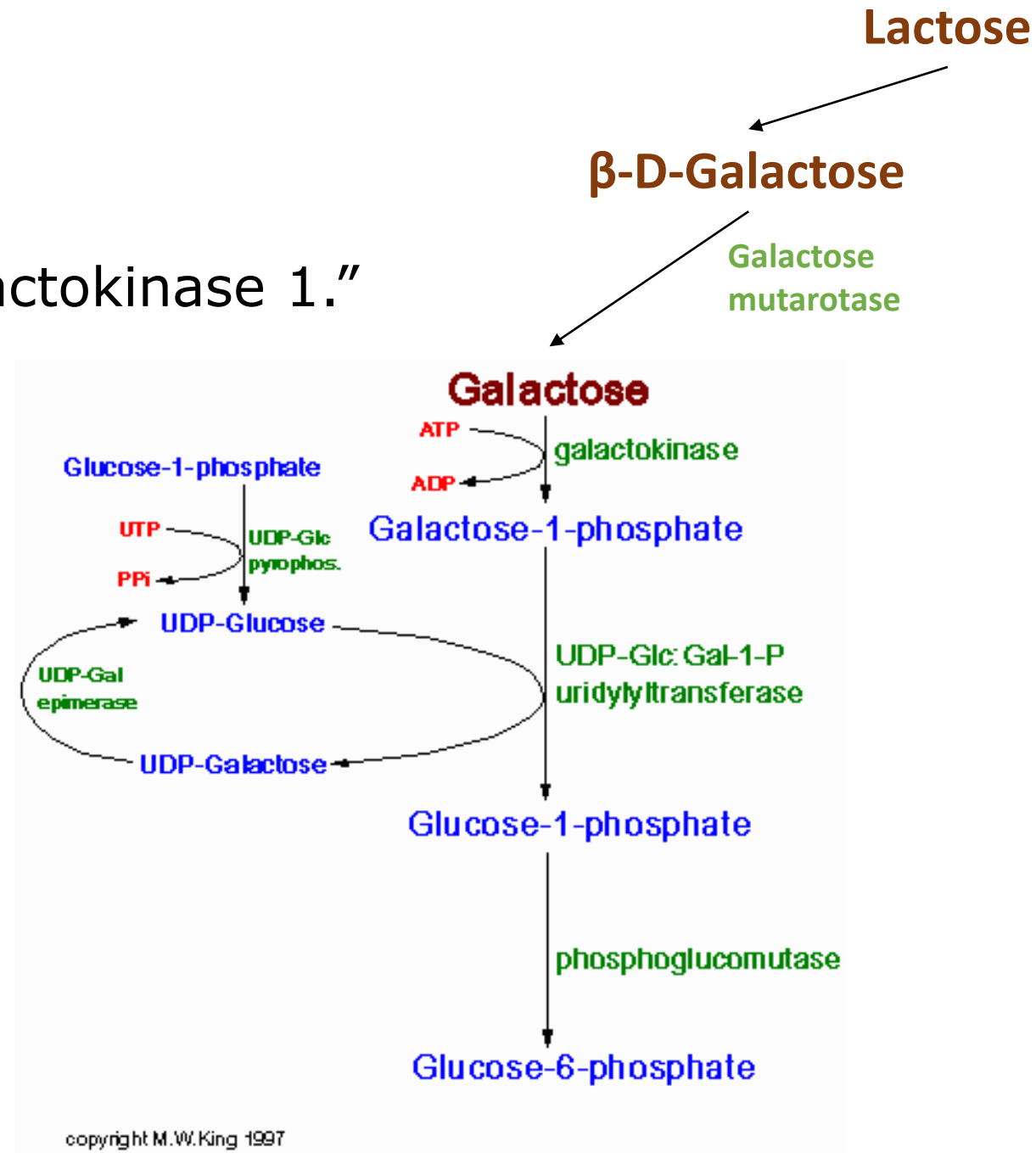
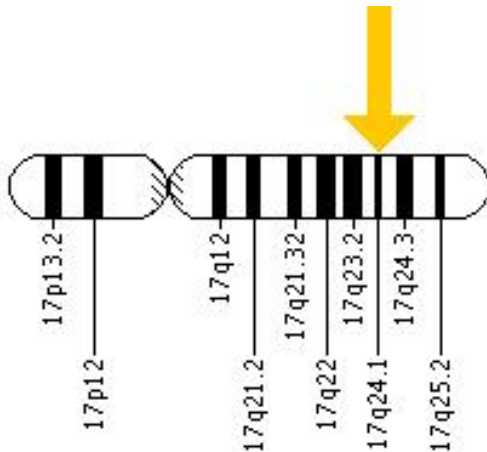
Genetic variations - GALT

- The **Duarte (D2) variant** is found in 1 in 20 persons.
- May be detected on NBS
- GALT enzyme (10-25% to 50% activity) and do not have any symptoms.
 - Do not develop illness in the newborn period
 - 350 children ages six to 12 years reported no detectable differences in developmental outcomes
 - No reports of female sub-fertility
- Carlock et al 2019

Galactokinase – deficiency or galactosemia Type II

- First identified in 1965,
 - cataracts and galactosuria that developed upon drinking milk.
- Neither liver disease nor signs of mental impairment were present.
- No accumulation of galactose-1-phosphate despite the accumulated galactose.

- The official name of this gene is "galactokinase 1."
- GALK1 is the gene's official symbol.
- Cytogenetic Location: 17q24



Clinical pictures of Galactosemia Type II

- Mild
- Cataract in the infant



Type II

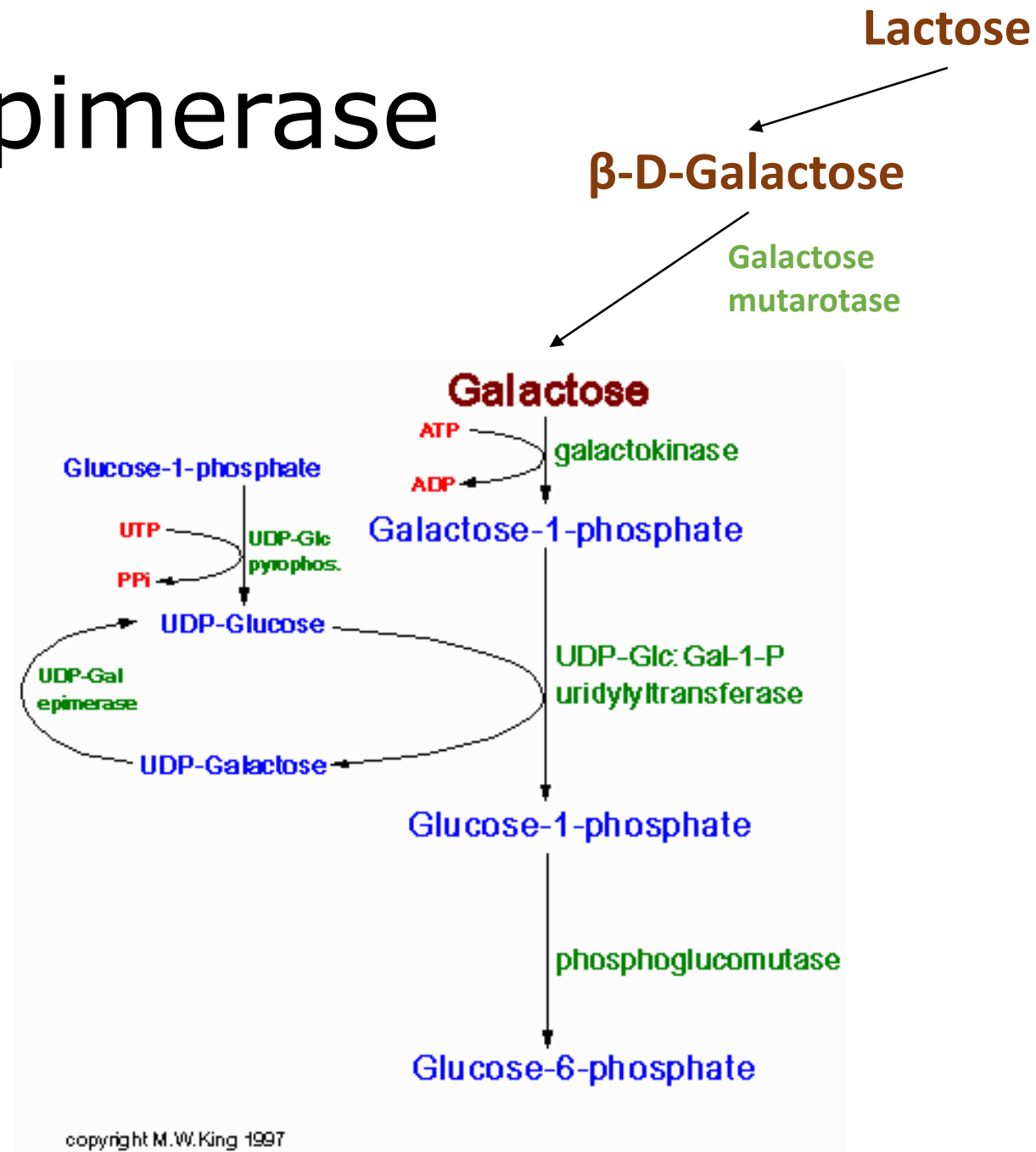
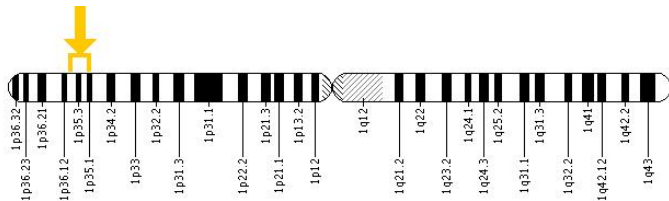
- Quite rare
 - <60 patients reported
- Cataract if not on diet
- Low galactose diet is recommended
- Rare reports of pseudotumour cerebri
 - Fluid buildup around the brain
- No other health concerns reported

Galactose epimerase (GALE) deficiency –galactosemia -Type III

- The official name of this enzyme is “UDP-galactose-4-epimerase.”
- More than 20 mutations in the GALE gene have been identified in people with a form of galactosemia known as type III or galactose epimerase deficiency.

UDP-galactose-4-epimerase deficiency

- Cytogenetic Location: 1p36-p35
- GALE is the gene's official symbol

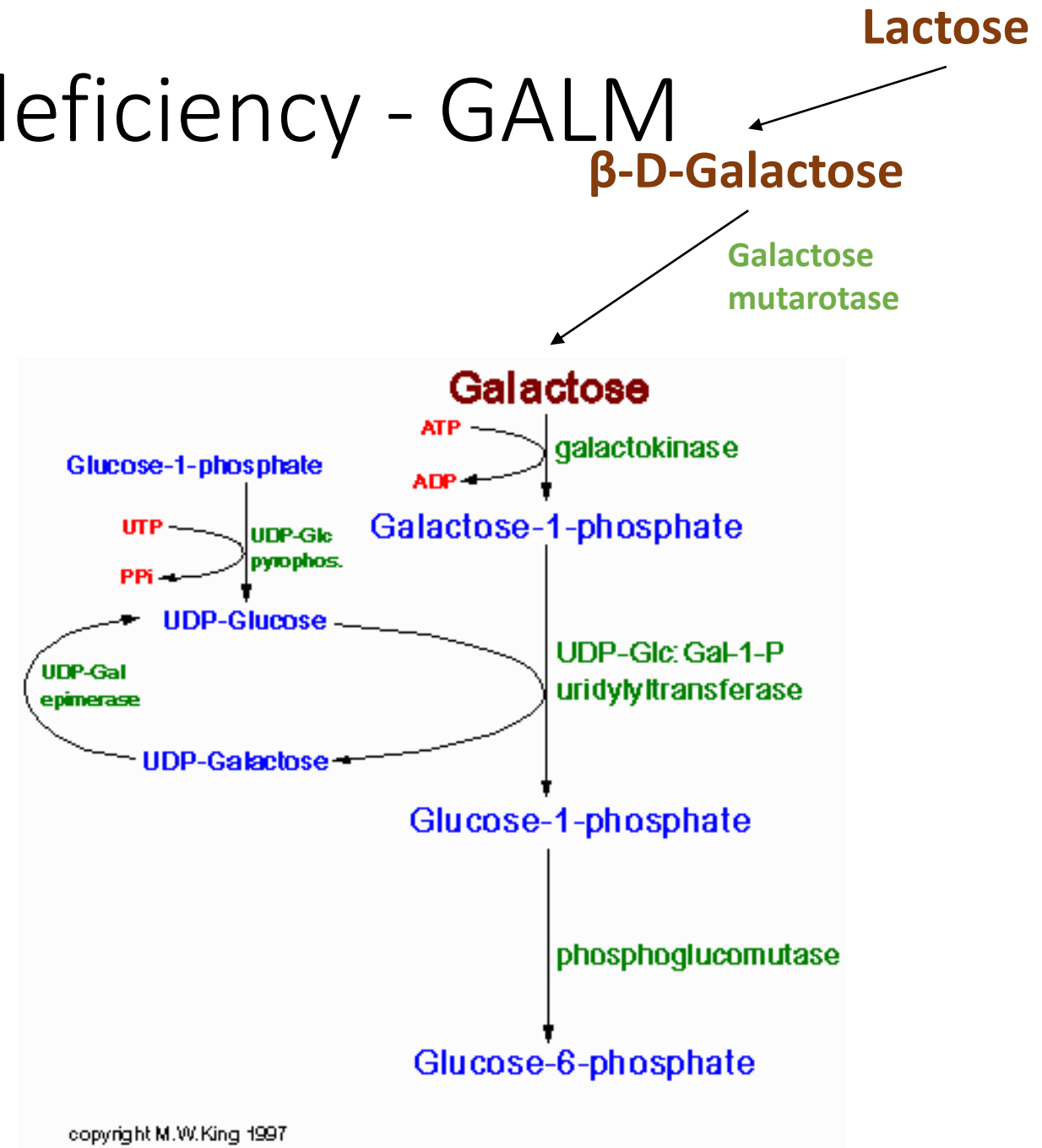


Epimerase deficiency

- Originally described as a benign condition in 1972 (Gitzelman) “peripheral”
- Then a patient was found to have symptoms like GALT galactosemia in 1981 (Holton)
- Finally, Openo in 2006 showed that patients are on a spectrum between these two extremes
- So some GALE patients need a restricted galactose diet, and some do not.
 - Diet cannot be completely restricted due to the place of the enzyme block
- Learning difficulties may occur
- Ovarian failure does NOT seem to occur

Galactose Mutarotase deficiency - GALM (Type IV)

- Chromosome 2p21
- GALM is the official gene name
- Only described this year by Dr Wada



Galactose Mutarotase deficiency - GALM (Type IV)

- increased blood galactose concentrations with no change in the levels of galactose 1-phosphate.
- None of the eight patients presented with gastrointestinal symptoms or severe liver dysfunction,
- Two patients presented with bilateral cataracts.
- No adult patients were examined
- All patients were treated with a galactose-restricted diet immediately after the diagnosis of galactosemia
- Two of these patients were allowed to resume a normal diet.

Galactosemia diet

- The diet should be low in lactose (dairy products)
- Babies
 - No breastfeeding
 - Formula for the first 4-6 months (Soy based or specialised eg Neocate)

Australasian Society for Inborn Errors of Metabolism

Handbook for Galactosaemia

Diet

- Avoid
 - Animal milks (Cows milk contains 2350mg of galactose per 100ml)
 - “Lactose free” dairy foods
 - Lactose in medicines (careful!)
 - Chickpeas (eg hummous, Besan flour)
 - Some fermented soy products
 - Offal
- Old “hard” cheeses are often OK

Low Galactose Food Pattern

<i>Food Group</i>	<i>Allowed</i>	<i>Not Allowed</i>
Milk & Milk Substitutes	Soy or MCT Formula: Neocate	Breast Milk, Animal Milk, Cheeses, Butter, Ice Cream, Yogurt
Fruits	Most Frozen, Fresh, Canned & Dried*	Dates, Papaya, Persimmon, Watermelon
Vegetables	Most Frozen, Fresh, Canned, & Dried*	Bell Peppers, Tomatoes
Meats & Meat Substitutes	Beef, Poultry, Lamb, Ham Pork, Fish, Game, Kosher Franks, Eggs, Nuts	None*
Breads	Rice, Pasta, Cereals, Breads	None*
Fats	Oil, Lard, Shortening, Mayonnaise	Butter, some margarines

Thank you!