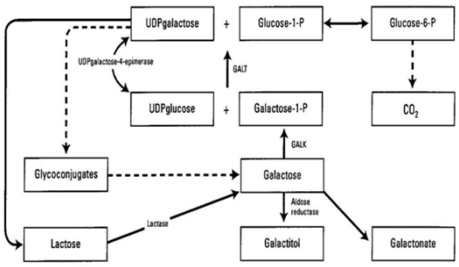
2012 Galactosemia Foundation CONFERENCE "Empowering Our Future" Dallas, Texas • July 19-21

EXPANDED RESEARCH IN GALACTOSEMIA

DIVISION OF GENETICS
BOSTON CHILDREN'S HOSPITAL
HARVARD MEDICAL SCHOOL

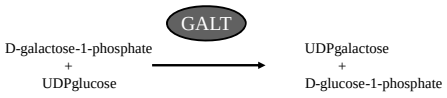
Gerard T Berry*, MD
*no conflicts of interest to disclose

Galactose Metabolism



Galactosemia

Deficiency: galactose-1-phosphate-uridyltransferase(GALT)



Gene: GALT on chromosome 9p13

Frequency: 1/35,000 to 1/60,000 (1/16,476 in Ireland)

Inheritance: autosomal recessive

Long-term Prognosis in Galactosaemia: Results of a Survey of 350 Cases

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Summary: An international survey of the long term results of treating galactosaemia has shown poor results. These do not seem to be related to any of the relevant variables studied, for example delayed diagnosis or poor dietary compliance.

Table 10 Sibling cases: older sibling diagnosed because of clinical symptoms or newborn screening, younger sibling treated within first two days of life

	Proband ($n = 28$) *Result* (n)	*Sibling* ($n = 31$) *Result* (n)	p
Age			
Mean (range)	14 y (3–33 y)	10 y (0–31 y)	0.1
Neonatal history			
Symptomatic	100%	3%	0.0001
Age diet begun			
Mean (range)	63 d (7–400 d)	1 d (1–2 d)	
Milk restriction during pregnancy	0% (22)	76% (25)	0.0001
DQ/IQ (Mean ± SD)			
IQ 3–5 y	87 ± 8 (9)	96 ± 20 (13)	0.2
IQ 6–9 y	83 ± 23 (11)	93 ± 21 (12)	0.3
IQ 10–16 y	69 ± 19 (9)	84 ± 15 (9)	0.1
Speech			
Abnormal	64% (25)	62% (26)	0.9
Ovarian function (F ≥ 14 y)			
Abnormal	75% (8)	71% (7)	0.7

from Waggoner D.D. et al 1990

J Inherit Metab Dis
DOI 10.1007/s10545-011-9372-y

ORIGINAL ARTICLE

The adult galactosemic phenotype

Susan E. Waisbren • Nancy L. Potter • Catherine M. Gordon • Robert C. Green • Patricia Greenstein • Cynthia S. Gubbels • Estela Rubio-Gozalbo • Donald Schomer • Corrine Welt • Vera Anastasoaie • Kali D'Anna • Jennifer Gentile • Chao-Yu Guo • Leah Hecht • Roberta Jackson • Bernadette M. Jansma • Yijun Li • Va Lip • David T. Miller • Michael Murray • Leslie Power • Nicolle Quinn • Frances Rohr • Yiping Shen • Amy Skinder-Meredith • Inge Timmers • Rachel Tunick • Ann Wessel • Bai-Lin Wu • Harvey Levy • Louis Elsas • Gerard T. Berry

J Inherit Metab Dis. 2012 Mar;35(2):279-86. Epub 2011 Jul 21.

SO, AS YOU CAN SEE, EXCEPT FOR POI IN FEMALES WITH CLASSIC GALACTOSEMIA, ALMOST ALL OF THE OTHER CHRONIC COMPLICATIONS ARE VARIABLE IN THEIR EXPRESIVITY

DOES THE GALT GENOTYPE PROVIDE AN EXPLANATION?

- NO

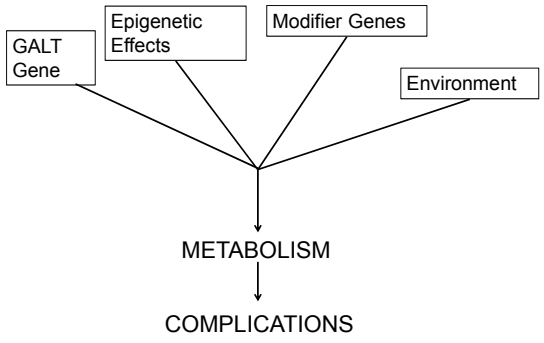
Common GALT Mutations

- N314D
- Q188R
- S135L
- K285N
- L195P
- 5.2 kb deletion
- More than 230 GALT gene mutations have been detected

Postulated Mechanisms of Disease Pathogenesis in Galactosemia

- Phosphate trapping due to galactose-1-phosphate excess
- Galactose-1-phosphate inhibition of enzymes/transporters
- Galactitol (cytotoxic edema, NADPH deficiency)
- Galactonate toxicity
- Unidentified galactose metabolite
- Myo-inositol deficiency
- Reduced concentration of the GALT-product, UDP-galactose
- Reduced synthesis of galactose-containing glycoproteins, galactocerebrosides and glycosaminoglycans due to ER and/or Golgi lesions
- Moonlighting function of GALT protein
- Effect of GALT gene mutation on IL-11Rα gene

- Data support galactose-1-phosphate as the key pathogenic factor



Clinical Research: An Evidence-Based Medicine Approach Is Mandatory

Establish an International Consortium for Galactosemia

- International Database
- Repository
- Patient care
- Education
- Multicenter Research Studies

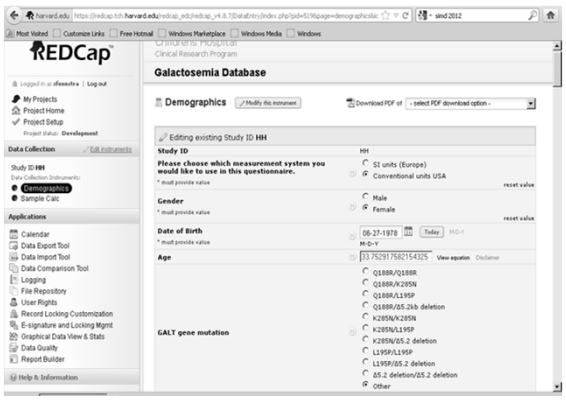
Research Targets

- Determine the developmental / time dependent tolerance of patients to dietary lactose (or galactose).
- Determine the developmental / time dependent rates of de novo galactose synthesis in patients using stable isotopically labeled sugars, mass spectrometry and in vivo kinetic analyses.
- Determine the developmental / time dependent relationship between galactose-containing glycoconjugate formation and de novo galactose synthesis in patients with and without dietary lactose intake.

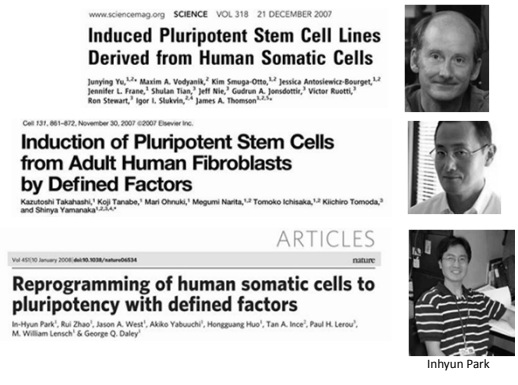
International Consortium for Galactosemia

Patient Care
Education
Research

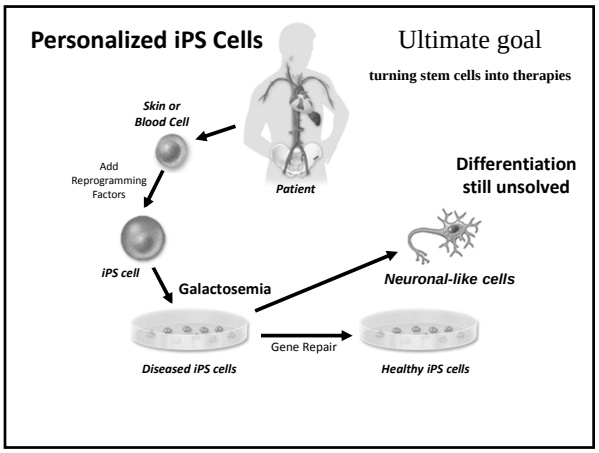
Initiate Multicenter Clinical Study of Dietary Galactose Tolerance in adolescents and adults, and assess the effect of Exogenous Galactose Exposure on Glycoconjugate formation and Endogenous galactose synthesis



Human iPS cells (2007)



Inhyun Park



THANK YOU!

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