GENOTYPE-PHENOTYPE CORRELATIONS IN GALACTOSEMIA

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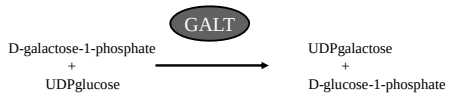
* No conflicts of interest to disclose

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

COMPLICATIONS

- What are the complications?
  - Developmental language delay
  - Speech defect
  - Learning problems in school
  - Cognitive deficits
  - Decreased bone mineralization
  - Poor growth
  - Infertility in females (Premature Ovarian Insufficiency or POI)

COMPLICATIONS

- What are the neurological complications?
  - Tremor
  - Ataxia
  - Dystonia

COMPLICATIONS

- Why are we worried about them?
  - Because we cannot prevent them with a lactose restricted diet
  - They may occur even if the patient's galactose-1-phosphate levels have been between 1-4 mg% and galactitol between 100-400 umol / mmol creatinine for life
  - They may occur even if mother restricted lactose during pregnancy and diet therapy was begun at birth

LONG-TERM CHRONIC COMPLICATIONS WITH NO CLEAR CAUSE

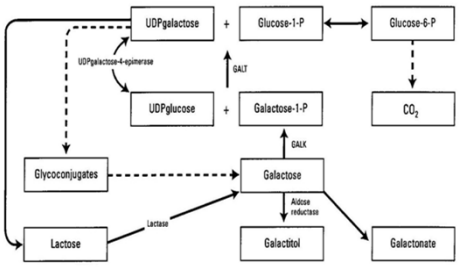
- Anxiety
- Depression
- Rare history of males who have been biological fathers
- Introverted or shy personalities (seems to affect males greater than females)

What causes the complications?

- Leading Hypotheses:
  - Chronic elevation of galactose-1-phosphate in brain, ovarian and bone cells due to endogenous synthesis of galactose

    Chronic deficiency of UDPgalactose in brain, ovarian and bone cells due to the inability to convert galactose-1-phosphate to UDPgalactose since that is what GALT does and it is absent in patients with classic galactosemia

Galactose Metabolism



When does this happen?

- Before birth when the fetus with galactosemia is growing in mother's womb
- After birth but only when the infant is exposed to large amounts of lactose in the newborn period
- After birth for the lifetime of the patient with classic galactosemia
- Both before and after birth

Okay, but given the fact that patients still develop chronic complications even if they are started on a diet as soon as they are born, what is the most likely hypothesis?

DESCRIPTION OF SAMPLE

AGE	Average: 32 years, (18-59 years)
GENOTYPE	15 subjects: Q188R/Q188R 13 subjects Q188R/other 5 other/other 1 Q188R/N314D (Duarte Variant)
HEALTH	Normal blood pressure in all but 2 subjects, majority in good health
HEIGHT	Average female height = 5 ft 5 in (US national average = 5 ft 4 in); Average male height = 5 ft 9 in (US national average =5 ft 9 in)
WEIGHT	58% normal weight; 2 subjects underweight; 11 subjects overweight
BONE DENSITY	20% with bone mineral density below lower limit of normal (5 women/2 males)

Adult Galactosemia Study (n=33 subjects with classic disease)

Gender	Male = 17, Female = 16
Mean age	33 $\pm$ 12 (range 18-59)
Mean Education	Two years of college
Mean SES	Lower middle class
Tried to conceive	3 males (18%); 5 female (31%)
Has a child	2 males (12%); 1 female (6%)

FEMALE FERTILITY

- 100% of females with classic galactosemia had POI and serum AMH (MIS) <0.3 ng/ml
- Average age of first menstruation was 15.1 +/- 1.8 years
- 11 women had secondary ammenorhea
- 5 women never had periods
- 4 women tried to have a baby; 1 succeeded after 60 months

MALE FERTILITY

- Testicular size is normal
- Mean hormone levels were within normal range
- Sperm count tended to be in the low normal range
- Semen volume was reduced in 6 out of 8 men
- Two men tried to have children. One of these men and one other man fathered one child each.

NUTRITION

- All subjects followed a dairy-free diet
- 90% did not receive nutrition counseling
- 67% took calcium supplement (irregularly)
- 38% took Vitamin D supplements (irregularly)
- 75%-80% had intakes below RDA guidelines
- Blood vitamin D level was low in 80%

Physiological outcomes, cont.

Primary ovarian insufficiency (POI)	16 females (100%)
Decreased bone mineral density (BMD)	8 (24%)

PSYCHOLOGICAL EVALUATION

- Mean FSIQ= 88+/-20 (Population norm = 100) with range of 55-122
- 24% had IQ </- 70 (intellectual disability)
- 21% had scores indicating difficulties in independent living on ABAS Questionnaire
- 46% lived independently
- 9 subjects were married or lived with partner
- Average years of schooling was 1-2 years college
- 21% were unemployed (and not in school)

INTELLIGENCE

Mean IQ	88 $\pm$ 20 (55-122)
Scores < 85 (Borderline Range)	13 subjects (39%)
Scores < 70 (Range of Intellectual Disability)	8 subjects (24%)
Verbal vs. Performance	No difference

PSYCHOLOGICAL EVALUATION

- Depression occurred in 12% of subjects at time of study (total of 39%>past episodes)
- Two subjects were being and 6 had been treated with anti-depressant medications
- One subject had received electro-convulsive therapy
- Anxiety occurred in 52% of subjects (total of 67%>past episodes); 3 subjects were being and 5 had been treated with a medication

PSYCHOLOGICAL OUTCOMES

Adaptive Behavior Deficits	7 (21%)
Executive Function Deficits	5 (15%)
Depression (observed or reported)	13 (39%)
Anxiety	17 (52%)

SPEECH & LANGUAGE

- Motor speech deficits: 25 subjects or 78%
- Dysarthria (articulation problems): 25%
- Apraxia of speech: 9%
- Reduced tongue strength: 73%
- Low phonation duration (breath support): 64%
- Reduced receptive vocabulary: 42%
- Hearing loss in 3 men (2 unilateral, 1 bilateral)

EEG

- In a small number (6 subjects), there were abnormal electrical signals or patterns in brain related to verbal tasks (especially voice onset latency of 5.5 seconds vs. 1.5 seconds in controls)

NEUROLOGICAL

- TREMOR 46%
  - Intention tremor in 8 subjects (24%)
  - Postural tremor in 5 subjects (15%)
  - Both kinds of tremor in 2 subjects (6%)
  - No subject exhibited a Parkinsonian tremor
- ATAXIA 15%
- DYSTONIA 6%

NEUROLOGICAL

- One subject experienced seizures; these first occurred during adulthood
- No subject had upper motor neuron disease (such as spastic paraparesis and spastic quadriplegia)

AGE AND OUTCOME

Outcome Variable (Logistic regression analyses)	p value
IQ	0.56
Beck Depression Inventory	0.64
Beck Anxiety Inventory	0.96
ABAS Composite	0.87
Peabody Picture Vocabulary	0.87
Articulation Test	*0.01
Bone Density Mass	0.72
Body Mass Index (increase)	*0.01

* Statistically significant

FINDINGS

- Older subjects were no more likely than younger subjects to experience low IQ, depression, anxiety, low bone density, tremor, ataxia, dystonia, dysarthria, verbal dyspraxia, low tongue strength or poor phonation.
- Older subjects had more normal articulation and a higher body mass index (BMI)

GENOTYPE AND OUTCOME

- Subjects homozygous for the common Q188R mutation experienced a similar range of scores on IQ tests and measures of depression and anxiety as subjects with deletions or other mutations on one allele.
- Percentage of patients with tremor, ataxia or speech defects did not differ with genotype

GENDER AND OUTCOME

	Men (n=17)	Women (n=16)
IQ ≤ 85	7 (44%)	6 (35%)
Depression	2 (13%)	2 (12%)
Anxiety	9 (56%)	8 (48%)
Dysarthria	4 (24%)	4 (27%)
Apraxia	1 (1/17)	2 (2/15)
Tremor	8 (50%)	6 (35%)
Ataxia	4 (24%)	1 (6%)

FINDINGS

- Males and females experienced low IQ, anxiety, depression, speech deficits and neurological symptoms at similar rates

NEWBORN SCREENING AND OUTCOME
(NOT ACCURATE!!!)

	Newborn Screened (6)	Not newborn screened (27)
Average IQ	91	88
Depression	0	11%
Anxiety	33%	52%
Tremor	0	52%
Ataxia	0	19%
Dysarthria	20%	26%
Apraxia	20%	7%

FINDINGS

- Only one subject identified by newborn screening showed evidence of tremor/ ataxia/dystonia
- Speech and intellectual functioning did not differ between those identified by newborn screening and those not identified by newborn screening

SUMMARY

- Individuals with galactosemia experience challenges in adulthood that may affect
  - Living independently
  - Social relationships
  - Becoming parents
- Included in this sample, however, were successful college students, teachers and many with successful marriages

CONCLUSIONS

- Galactosemia is not a progressive neurodegenerative disease
- Subjects appear to overcome handicaps over time
- The impact of newborn screening on the health and outcome of patients with galactosemia needs to be further examined

CONCLUSIONS

- POI is the one complication that is almost universal in women with galactosemia and appears completely resistant to diet therapy
- The structure and function of the male reproductive tract does not appear to be severely affected and does not easily explain why so few men have become fathers

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

THANK YOU!

- We greatly thank the Galactosemia Foundation for supporting our work.