

New insights into possible pathways: growth hormone issue

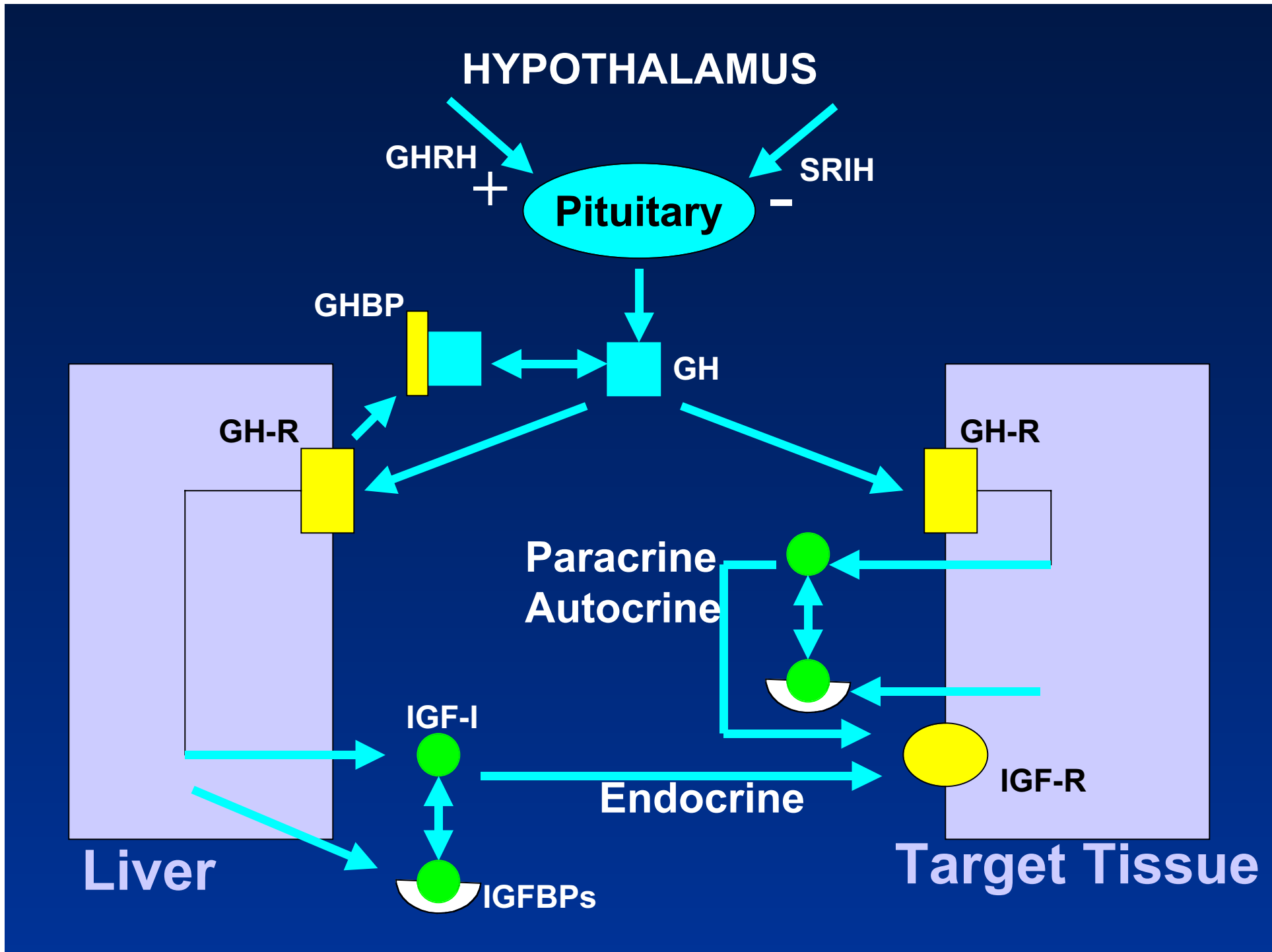
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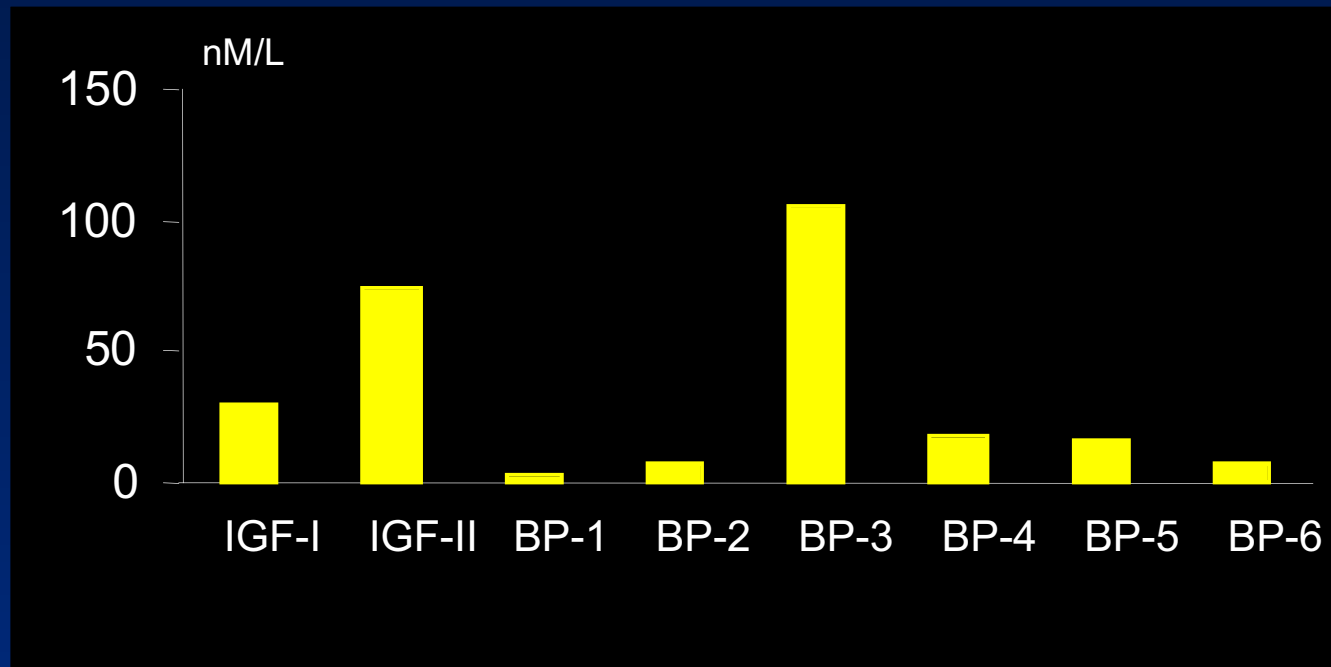
*International Alström Syndrome Workshop
“Pieces of the puzzle - Putting it Together”
August 13-15, 2001
Morrisburg, Ontario, Canada*

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- General aspects of GH & IGF-I axis
- Growth Hormone Deficiency
- GH & IGF-I axis in ALMS
- Effect of treatment with rGH in ALMS
- Conclusion

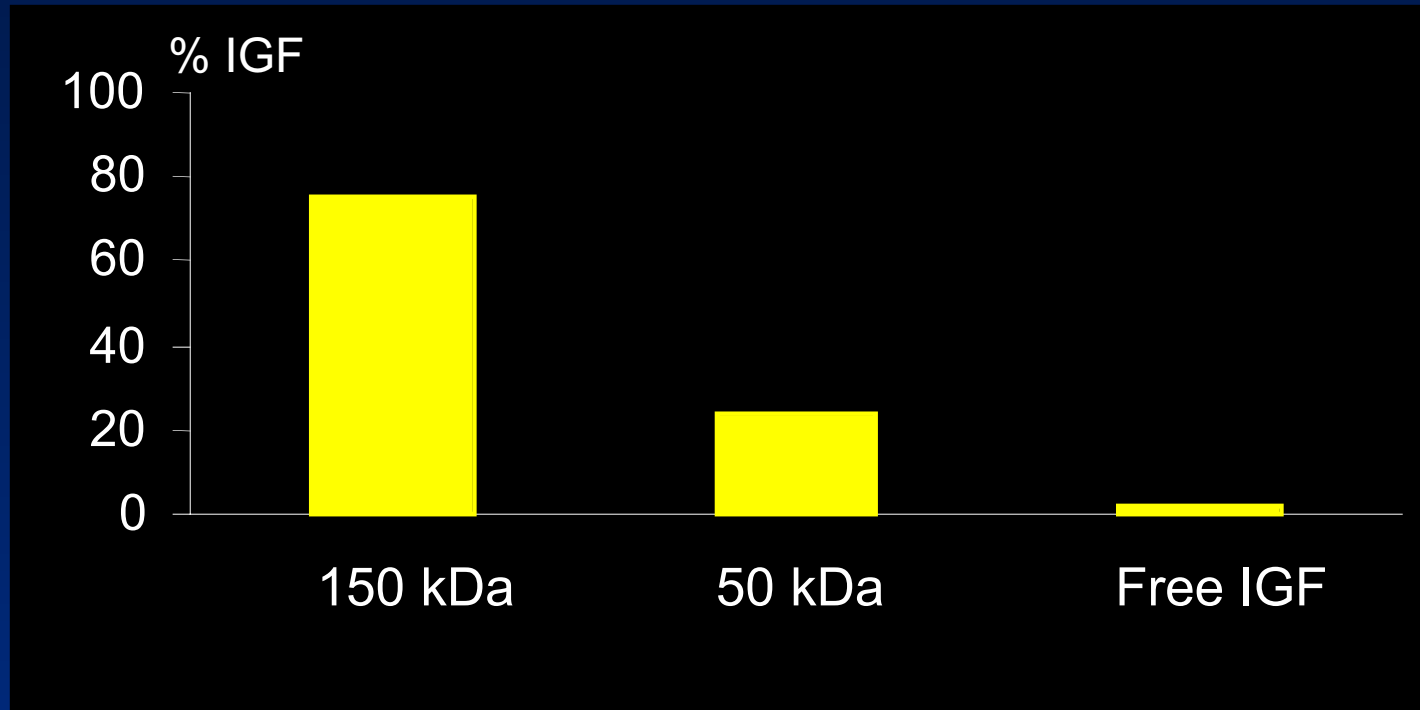


IGF & IGFBPs concentration - correlation



	<u>IGF-I</u>	<u>IGF-II</u>
IGFBP-1	Negative	Negative
IGFBP-2	Negative	Negative
IGFBP-3	Positive	Positive
IGFBP-4	NS	NS
IGFBP-5	Positive	Positive
IGFBP-6	?	?

Distribution of IGF pools



150 Kda

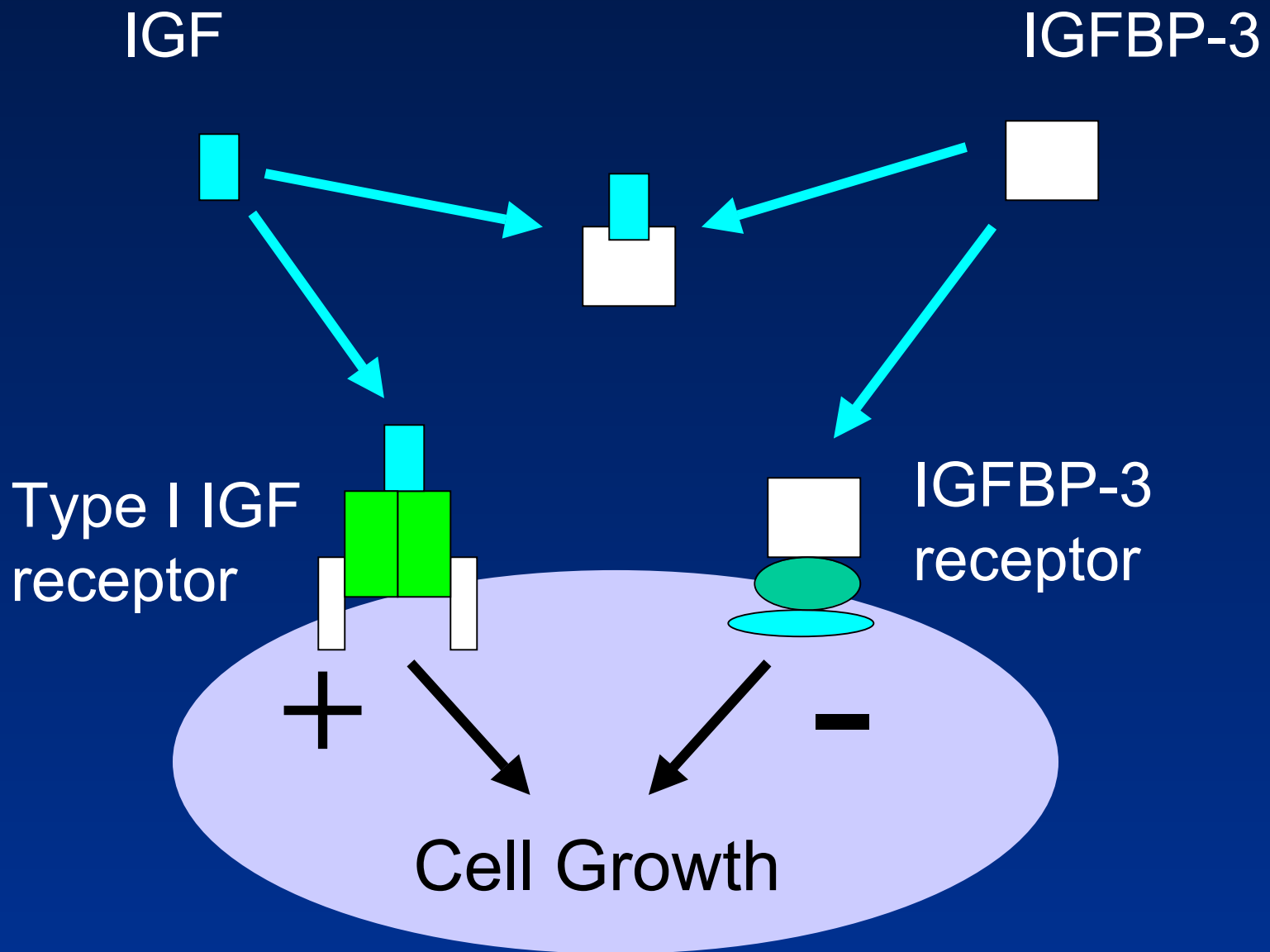
ALS+BP3+IGF

50 Kda

BP1/IGF
BP2/IGF

....

Free IGFs



Genetic of GH

	Chromosome
GH	17q22q24
GH receptor	5 p13.1-p12
GHRH	20 q11.2
GHRH receptor	7 p15-p14
GH-RELIN	3 p26-p25
Pit 1	5 q
Pou domain	3 p11
Prophet of Pit 1	5q
STAT 1 and 3	2 q32.2-q32.3
JAK 1, 2, 3	1 p31.3; 9 p24; 19 p13.1
Leptin	7q 31.3

Genetic of IGF

	Chromosome
IGF-I	12 q22-q24.1
IGF-I receptor	15 q25-q26
IGF-II	11 p15.5
IGF-II receptor	6 q26
IGFBP 1	7 p14-p12
IGFBP 2	2 q33-q34
IGFBP 3	7 p14-p12
IGFBP 4	17 q12-q21
IGFBP 5	2 q33-q36
IGFBP 6	?
IGFBP 7	4 q12

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GH treatment of children with short stature

Idiopathic GHD (IGHD)	40%
Organic	13 %
Idiopathic short stature (ISS)	17%
Turner syndrome	10%
Chronic renal failure	6%
Other	14%
Total number	34.426 patients

Aims of GH treatment in children

- To improve final height
- To reach a normal peak of bone mass
- To modify the phenotype
- To stimulate muscle mass and reduce visceral fat
- To prevent fasting hypoglycemia

Growth Hormone Deficiency in Adults: Cardinal Clinical Features

- Increased weight and body fat mass;
decreased lean body mass
- Decreased exercise capacity
- Decreased muscle mass and strength
- Reduced cardiac performance
- Reduced bone density and increased
fracture rate
- Poor sleep
- Impaired sense of well-being

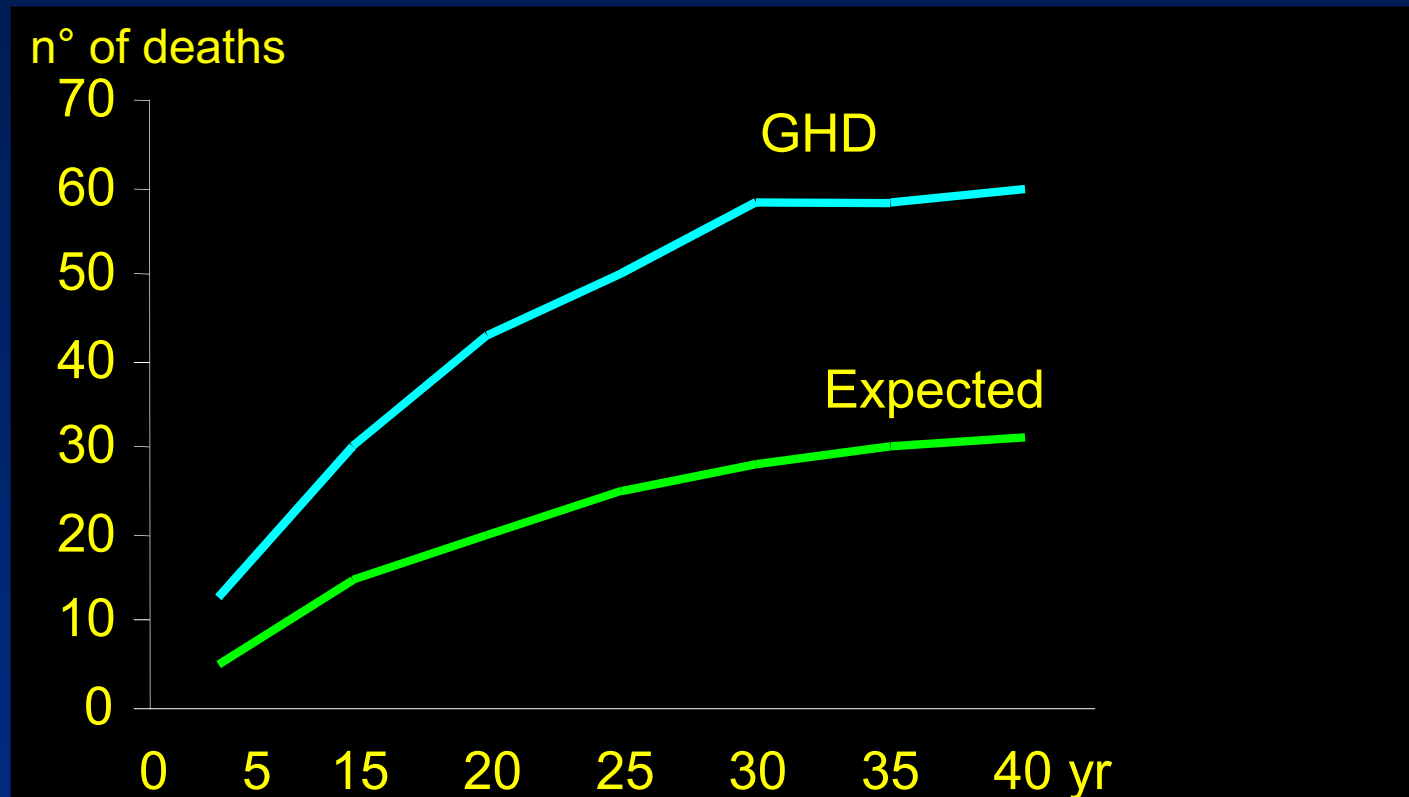
Body composition in GHD adults

	Untreated GHD	rGH Therapy	
Total body fat	increased	↓	
Subcutaneous	increased	↓	
Visceral	increased	↓	
Lean body mass	decreased		↑
Cell mass	decreased		↑
ICW	?	?	
ECW	decreased		↑
Muscle mass	decreased		↑
Bone density	decreased		↑
Muscle strength	decreased		↑
Exercise performance	decreased		↑

Metabolic characteristics in GHD adults

	Untreated GHD	rGH Therapy
Lipids		
Total Cholesterol	increased	↕↔
LDL	increased	↕↔
HDL	reduced	↑↔
Apo B	increased	↕↔
Lp(a)	normal	↑↔
Triglycerides	increased	↔
Fasting glucose	normal	↑↔
Fasting insulin	increased	↑↔
Insulin sensitivity	reduced	↑↔
Fasting C-peptide	normal	↑↔
HbA1c	normal	
glycogen stores	reduced	

Mortality in GHD adults



333 patients with hypopituitarism (diagnosis: 1956 - 1987)

Routine replacement therapy without GH (104 deaths compared with 57 expected)

Increase in death for cardiovascular disease (60 in GHD versus 31 expected)

Diagnosis of GHD

- Clinical features and medical history
- Dynamic tests of GH secretion:
 - Insulin induced hypoglycemia (0.1 U/Kg i.v.)
 - GHRH (1 ug/kg i.v.) + Arginine (0.5/Kg i.v. over 30 m')
 - Arginine
 - L-Dopa
 - Clonidine

ITT

GHRH + Arginine

child

GH > 5 ug/L

GH > 20 ug/L

adult

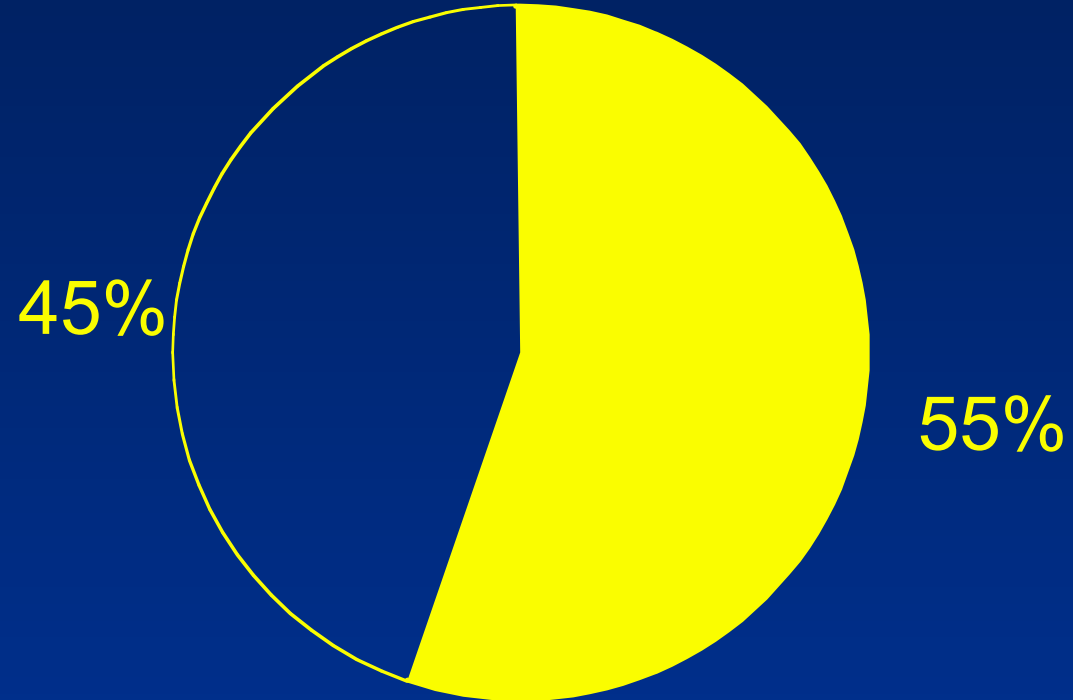
GH > 5 ug/L

GH > 16.1 ug/L

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Short Stature



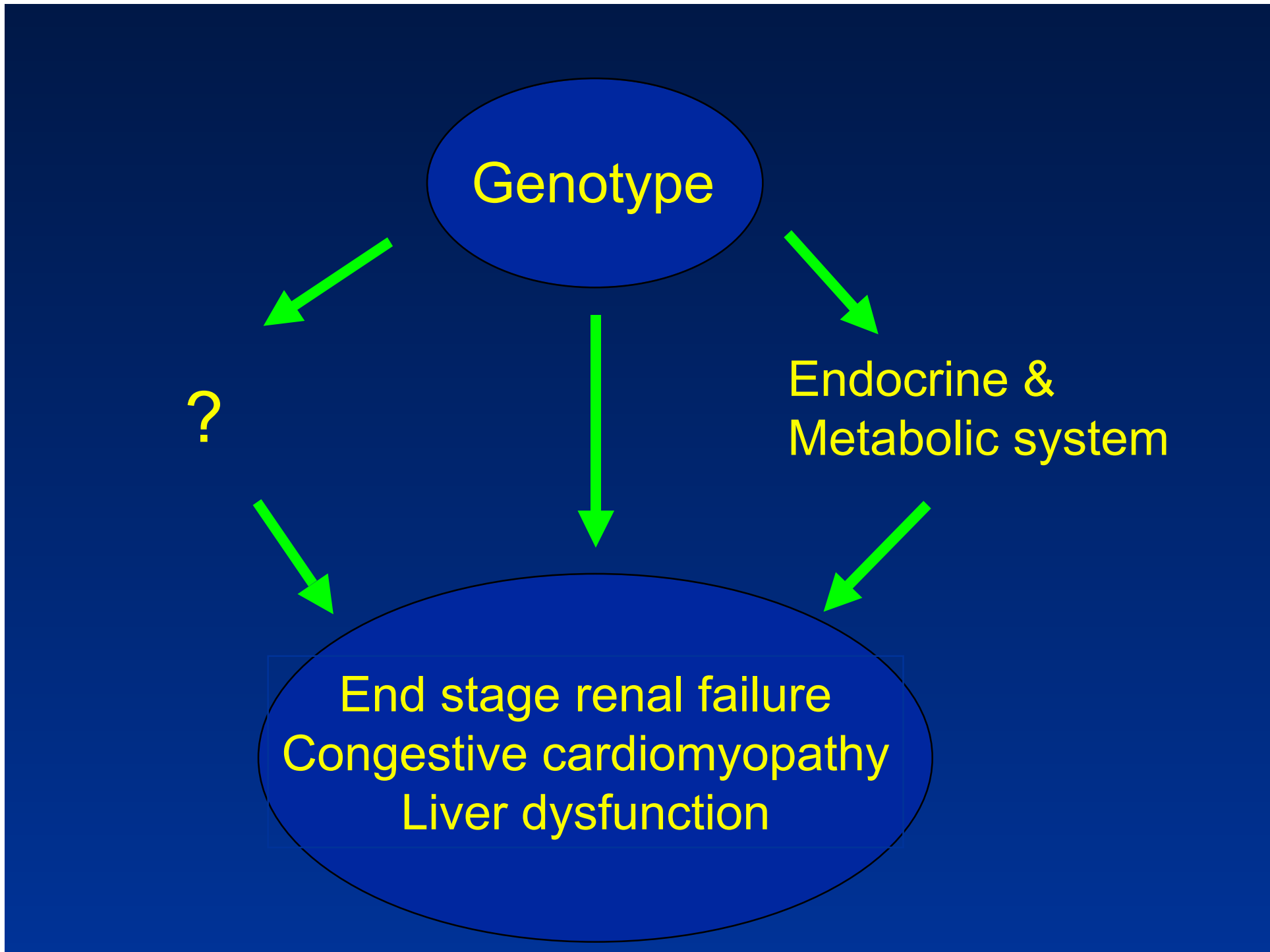
Jackson Laboratory, 1999

Genotype

Endocrine &
Metabolic system

?

End stage renal failure
Congestive cardiomyopathy
Liver dysfunction



GHD in Two Siblings with ALMS

Patient	GH stimulant	Basal GH	Peak GH
11 yr/M	Arginine	2.4	5.1
	Clonidine	0.5	0.7
9 yr/F	Arginine	4.9	4.9
	Clonidine	0.5	2.0

- Advanced bone age
- Low serum GH concentration in pooled 12-h overnight samples
- Low-normal IGF-I values
- Glucose intolerance and hyperinsulinemic

Anthropometric Parameters (Padua)

	height (centile)	\pm SD
PATIENT 1	< 3	< - 2
PATIENT 2	< 3	< - 2
PATIENT 3	< 3	- 3
PATIENT 4	< 3	< - 2
PATIENT 5	< 3	< - 2

Summary of GHD in ALMS

- Severe GHD in 2 out of 5 patients
- Mild GHD in 1 out of 5 patients
- Low-normal GH response in 2 out of 5 patients

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rGH Therapy

The USA FDA has approved GH for use in the following conditions:

- Growth hormone deficiency (pediatric and adults)
- Turner syndrome
- Chronic renal insufficiency
- AIDS-associated wasting

rGH Therapy (adults)

Under investigation:

- Somatopause (older adults)
- Infertility
- Chronic catabolic states (IBD, respiratory failure...)
- Burn injury
- Obesity
- Other causes of extreme short stature
- Constitutional delay of growth and development
- Prader-Willi Syndrome
- Growth retardation due to glucocorticoid treatment

Side Effects of rGH Treatment

- Fluid retention, edema (37.4 %)
- Arthralgia (19.1 %)
- Myalgia (15.7 %)
- Paresthesias (7.8 %)
- Carpal Tunnel Syndrome (1.7 %)
- Pseudotumor cerebri/benign intracranial hypert...
- Slipped capital femoral epiphysis
- Lipoatrophy (injection sites)
- Transient resistance to the action of insulin
- Pancreatitis
- Transient gynecomastia

rGH Therapy is Contraindicated

- Active malignant diseases
- Benign intracranial hypertension
- Proliferative/preproliferative diabetic retinopathy
- Pregnancy
- Critically ill patients (intensive-care units)

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- 1) All ALMS patients should be tested for GHD
- 2) rGH therapy in ALMS could prevent or delay further derangement of some target organs or metabolic pathways
- 3) The mechanisms of GHD still remain unknown:
 - primary genetic ? At which level ?
 - primary pituitary-hypothalamus involvement ?
- 4) When should we start rGH and at which dosages ?

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