GROWTH:
A Clinical Perspective

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GH-IGF Axis: Sites of Defects

HYPOTHALAMUS
- Hypothalamic dysfunction
- Transcription factors
- GHRH or ghrelin genes

PITUITARY
- Pituitary dysfunction
- Transcription factors
- GHRH receptor
- GH genes

GROWTH PLATE
- Defects of IGF-I synthesis
- Defects of IGF-I receptor
- Defects of IGF transport/clearance
- Growth
- Post-receptor defects

LIVER
- Abnormal GH–signal transduction
- JAK/STAT/MAPK

Other IGFBPs

GHBP
GH receptor
IGF-1
IGFBP-3
AL5


Figure 1-6. Linear growth in human infants during fetal life and for the first postnatal year, shown as a distance curve (above) and as a velocity curve (below). The broken line (below) provides a smooth average velocity rate. The slowing of late fetal growth rate with postnatal catch-up is compatible with the concept of late fetal slowing of growth due to uterine restraint. (Redrawn from Thompson, D’Arey W. On Growth and Form. Cambridge: Cambridge Uni.)
Figure 1-9. Mean and percentiles for the linear growth of male infants and mean for female infants, derived from longitudinal growth values of 90 middle-class white babies. The rate of growth of the males is more rapid than that of the females during the first 3 to 6 months. (From Smith, D. W., Harvey, M. A. S., Rogers, J. K., Greitzer, L. G., and Skinner, A. L.: Unpublished observations.)
## Expected Growth Rate Per Year

<table>
<thead>
<tr>
<th>Age</th>
<th>Inches/Year</th>
<th>Cm/Year</th>
<th>Frequency of Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>9-11</td>
<td>18-25</td>
<td></td>
</tr>
<tr>
<td>12 to 24 months</td>
<td>4-5</td>
<td>10-13</td>
<td>3 to 4 times/year*</td>
</tr>
<tr>
<td>24 to 36 months</td>
<td>3-4</td>
<td>7.5-10</td>
<td></td>
</tr>
<tr>
<td>3 years to puberty</td>
<td>2-2.5</td>
<td>5-6</td>
<td>Annually</td>
</tr>
</tbody>
</table>

* More frequently if growth abnormality is suspected
Fig. 1. Growth hormone secretory pattern in a prepubertal 12-yr-old male. Shaded area indicates the period of nocturnal sleep.
Fig. 2. Growth hormone secretory pattern in a 12-yr-old male with moderate sexual maturity. Shaded area indicates the period of nocturnal sleep.
What is Short Stature?

**Definition**
- Height SDS < -2 for age and sex
- Approximately 3% of all children

![Diagram of Short Stature]

**Normal Variants**
- Familial short stature
- Constitutional delay

**Pathologic**
- Disproportionate
  - Skeletal dysplasia
  - Rickets

**Prenatal**
- IUGR
- Placental Diseases
- Infections
- Teratogens
- Dysmorphic syndromes
- Chromosomal disorders

**Postnatal**
- Endocrine disorders
- Psychosocial disorders
- Malnutrition
- Gastrointestinal diseases
- Cardiopulmonary diseases
- Chronic anemia
- Renal disorders

Figure 2. Differential diagnosis of short stature. IUGR = intrauterine growth retardation. (Modified from Rimoin DL, Borochowitz Z, Horton WA. West J Med 144:710, 1986, with permission)
Obtaining Accurate Measurement of Length

Birth to 24 Months

Obtaining Accurate Measurement of Height

Children Aged 2 to 18 Years
Assessment of Suspected Growth Abnormalities

**Auxologic Data**

- Abnormally slow growth rate
  - Ages 3 to 12 years: Less than 2 inches/year (5 cm/year)
- Downwardly crossing centile channels on growth chart after the age of 18 months
- Height below third percentile (-2 SD)
- Height significantly below genetic potential (-2 SD below midparental height)

**History and Physical Examination**

- Birth History – Small for Gestational Age, Intrauterine Growth Retardation
- General History – Chronic Illness
- Family History – Genetic, Psychosocial
- Physical Examination – Proportions, Abnormalities
- Growth Chart – Growth Velocity, Age of Onset, Change in Growth Pattern
Blood Tests

- Complete Blood Count
- Erythrocyte Sedimentation Rate
- Serum Electrolytes and Chemistries
- Thyroid Hormone Levels
- Exercise-Induced GH Level
- IGF-1 Level
- Chromosomal Analysis (Karyotype)
- Tissue Transglutaminase Antibody
- Gliadin Antibodies (IGG, IGA)

Additional Measurements in Assessing Short Stature

- Head Size
- Body Proportions
- Sexual Maturation
- Skeletal Maturation
Calculating Midparental and Target Heights

Midparent Height (in inches)

<table>
<thead>
<tr>
<th></th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midparental height for girls</td>
<td>(Father’s height – 5 inches) + (Mother’s height)</td>
</tr>
<tr>
<td>Midparental height for boys</td>
<td>(Mother’s height + 5 inches) + (Father’s height)</td>
</tr>
</tbody>
</table>

Target Height
Midparental Height ± 2 SD
(1 SD = 2 inches)
Assessment of Growth Hormone Secection

**Provocative stimuli**
- Arginine-insulin
- Clonidine
- L-dopa ± propranolol
- Glucagon
- Others

**Physiologic tests**
- Exercise-stimulated
- Serial sampling
Growth Deficiency-Prenatal Onset

**Exogenous Causes-Secondary Growth Deficiencies**
- Maternal Malnutrition
- Toxemia
- Hypertension
- Renal or Cardiac Disease
- Nicotine
- Ethanol
- Hydantoins

May or may not show post-natal catch-up growth

**Endogenous Causes-Primary Growth Deficiencies**
- Chromosomal Abnormalities, e.g. Turner’s Syndrome
- Osteochondrodysplasias
- Multiple Malformation Syndromes

Do not show post-natal catch-up growth
Postnatal Growth Deficiency

- Nutritional
  - Neglect, Malabsorption
- Cardiac Defect
- Renal Dysfunction
- Growth Hormone Deficiency
- Thyroid Hormone Deficiency
- Metabolic Disorders
  - Hypercalcemia, Glycogen Storage Disease, Poorly Controlled Diabetes Mellitus, Salt Wasting Syndrome

Specific treatment results in catch-up growth
Familial Short Stature

- Annual Growth Rate Normal
- Height at or Below 3rd Percentile
- No Systemic or Endocrine Disease
- Pubertal Growth Spurt at Normal Age
- Skeletal Age Equal to Chronological Age
- Ancestors Relatively Short
Constitutional Growth Delay

- Delayed Puberty
- Retarded bone age
- Normal predicted adult height in context of family pattern
- No organic or emotional cause for growth failure
Table 1. Principal Clinical Features in 13 Cases of Cushing’s Syndrome in Children*  

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncal Obesity, moon face, buffalo hump</td>
<td>13</td>
</tr>
<tr>
<td>Short Stature (10&lt;sup&gt;th&lt;/sup&gt; percentile or less)</td>
<td>11</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>11</td>
</tr>
<tr>
<td>Acne</td>
<td>11</td>
</tr>
<tr>
<td>Flushed cheeks</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10†</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7</td>
</tr>
<tr>
<td>Cutaneous striae</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
</tbody>
</table>


† Diastolic pressure of 90 mm Hg or higher
PATHOPHYSIOLOGICAL MECHANISMS OF BIPOTENTIAL GLUCOCORTICOID ACTIONS ON GH SECRETION IN THE RAT

Fig. 13. Schematic representation of the authors’ concept of pathophysiological mechanisms of the biphasic dose-dependent effects of glucocorticoids on the somatotropic axis. Smaller (physiological) amounts of cortisol are required to support pituitary GH gene transription and maintain the GHRH receptor, whereas excessive glucocorticoid suppresses GH secretion via augmenting somatostatin release, and reducing GHRH secretion, as inferred based on data in the rat. Giustina and Veldhuis, 1998 Endo Rev.
Height curve in a girl with Crohn’s disease accompanied by undernutrition. Sizonenko, 1981
Fig. 1. Hypograms obtained for case C. (A) second sleep recording 40 days later (Stage III wakefulness, sleep stages). 1, 1.5, 1.5, = 7, 5. Long periods of wakefulness and absence of slow IV characterized the initial sleep recording (A). The second sleep recording exhibits a normal sleep organization. Gullin, A. A., Fed. Proc., 1962.
Prevalence of GHD: Utah Growth Study

- 114,881 measurements available for evaluation in 1st year
  - 1,334 children with heights > 2 SD below the mean
  - 52 children referred for further evaluation of growth problems
- 79,495 measurements available for evaluation in 2nd year
  - 578 children with height < 3rd percentile and growth rate < 5 cm/y
  - 503 of 578 children available for follow-up were evaluated further
- 16 new cases of GHD diagnosed
- 17 GH-treated GHD children not identified because of normal growth rates
- Estimated prevalence of GHD in the United States: 1:3,480
Established Genetic Defects Causing IGF Deficiency (1)

<table>
<thead>
<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Murine Homolog</th>
</tr>
</thead>
<tbody>
<tr>
<td>HESX1</td>
<td>AR</td>
<td>Septo-optic dysplasia. Variable involvement of pituitary hormones</td>
<td>Hesx1/Rpx</td>
</tr>
<tr>
<td>PROP1</td>
<td>AR</td>
<td>GH, PRL, TSH, LH and FSH deficiencies. Variable degree of ACTH deficiency</td>
<td>Prop1 (Ames mouse)</td>
</tr>
<tr>
<td>POU1F1</td>
<td>AR, AD</td>
<td>GH and PRL deficiencies. Variable degree of TSH deficiency</td>
<td>Pit1/Ghf1 (Snell mouse, Jackson mouse)</td>
</tr>
<tr>
<td>RIEG1</td>
<td>AD</td>
<td>Reiger’s syndrome. IGHD</td>
<td>Rieg/Ptx2</td>
</tr>
<tr>
<td>GHRHR</td>
<td>AR</td>
<td>IGHD</td>
<td>Ghrhr (little mouse)</td>
</tr>
<tr>
<td>GH1</td>
<td>AR</td>
<td>Type 1A form of IGHD</td>
<td>Gh (spontaneous dwarf rat)</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>Type 1B form of IGHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Type II form of IGHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>Type III form of IGHD, Hypogammaglobulinemia²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Bioinactive GH molecule</td>
<td></td>
</tr>
</tbody>
</table>

GHD owing to hypothalamic-pituitary dysfunction

Developmental abnormalities

The genetic defect for this syndrome is unknown

The GH/IGF axis in GHIS
Established Genetic Defects Causing IGF Deficiency

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<tr>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Murine Homolog</th>
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<tbody>
<tr>
<td>GHI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GHR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracellular domain</td>
<td>AR</td>
<td>IGF deficiency. Decreased or normal GHBP</td>
<td></td>
</tr>
<tr>
<td>Transmembrane domain</td>
<td>AR</td>
<td>IGF deficiency. Increased GHBP</td>
<td></td>
</tr>
<tr>
<td>Intracellular domain</td>
<td>AD</td>
<td>IGF deficiency. Increased or normal GHBP</td>
<td></td>
</tr>
<tr>
<td>Intracellular domain (cytoplasm)</td>
<td>AR</td>
<td>IGF deficiency. Normal GHBP</td>
<td>Stat5b knockout</td>
</tr>
</tbody>
</table>

**Primary defects of IGF synthesis**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF1</td>
<td>AR</td>
<td>IGF deficiency</td>
<td></td>
</tr>
</tbody>
</table>

* Lopez-Bermejo A, Buckway CK, Rovender LE. TEM 11:39-49, 2000*
Response of serum somatomedin to administration of human growth hormone, 2.5 mg bid, for 4 days in patients with hypopituitary dwarfism (○) and Laron dwarfism (●). (Reprinted from Daughaday et al., 1969.)
Figure 1. The Family of Patients 8, 9, and 10.
From left to right, this photograph shows a sister, 25 years old (height, 156.8 cm); a brother, 18 years old (164.7 cm); Patient 9; the father, 52 years old (165 cm); Patient 8; a brother, 12 years old (130.9 cm); a sister, 8½ years old (116.4 cm), and the mother, 46 years old (156.7 cm), holding Patient 10.

IUGR and Postnatal Growth Failure with IGF-I Gene Deletion

- 15-year-old with severe prenatal and postnatal growth failure with homozygous partial deletion of IGF-I gene
- No response to GH therapy administered from age 11 to 12.7 years

Growth Hormone-Activated Intracellular Signaling

IGF-I receptor mutations:
IGF-I Receptor Mutations: Pre and Postnatal Growth Retardation
**IGF-I receptor mutations:**

*IGF-I Receptor Mutations: Pre and Postnatal Growth Retardation*

**Patient 1**

- Patient 1 – nonconsanguinous, 1.4 kg, 38 week pregnancy, normal serum IGF-I, normal GH to provocation.
- Patient was a compound heterozygous for mutations in exon 2 of the IGF-IR gene → binding of IGF-I to IGF-I receptor.


**Patient 2**

- Patient 2 - At birth, weight of 2000 grams, length of 40 cm, and microcephaly. Normal GH and IGF-I high for age.

Heterozygous for a potential mutation in exon 2. Exon 2 is the first exon to encode a substantial portion of the mature receptor → no visible receptor protein was made.


Inactivating mutations of the IGF-I gene: A Novel Insulin-Like Growth Factor-I Mutation

Inactivating mutations of the IGF-I gene:
A Novel Insulin-Like Growth Factor-I Mutation

This is the first report on a homozygous missense mutation in the human IGF-I gene resulting in an IGF-I protein that is hardly capable of interacting with the IGF-IR but with relatively unaffected binding capacity for IGFBPs. This leads to severe effects on growth and development in utero and during childhood.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Growth Factor</th>
<th>Genomic Organization</th>
<th>Clinical/Lab Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>GHRH↓</td>
<td>PTX 1, HESX 1↓</td>
<td>• Hypothalamic (idiopathic GH deficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypothalamic infiltrative disease</td>
</tr>
<tr>
<td>Pituitary</td>
<td>GH↓</td>
<td>PROP 1, PIT 1, LHX 3, GH 1, POU1F1</td>
<td>• Pituitary tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypoplasia</td>
</tr>
<tr>
<td>Hepatocytes, Osteoblasts</td>
<td>GH Receptor↓</td>
<td>+GHR 1</td>
<td>• Growth hormone resistance</td>
</tr>
<tr>
<td></td>
<td>J2K, Stat 5b</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IGF1, IGFBPs, AL5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>IGF1 Receptor</td>
<td>+IGF1 mRNA gene, IGF1 receptor gene</td>
<td>• IGF1 resistance</td>
</tr>
</tbody>
</table>

Table: Growth Failure Resulting from Reduced GH Secretion or Action.
Five girls with the XO syndrome. Note the variability of such features as webbed neck and broad chest.

GROWTH VELOCITY IN TURNER SYNDROME

Height velocity in patients with Turner syndrome compared to the normal range; single measurements.

AGA vs SGA

- **AGA**
  - Birth weight and length within 2 SD of mean for gestational age

- **SGA**
  - Birth weight and/or length at least 2 SD below mean for gestational age
  - Other definitions
    - Birth weight <2500 g, gestational age ≥37 wk
    - Birth weight or length <3rd, <5th, or <10th percentile for gestational age
    - Ponderal index less than –2 SD

Figure 5-1. Linear growth of a child with Russell-Silver syndrome who was small from prenatal life, had a consistently low rate of linear growth with attainment of short adult height, and showed no acceleration of growth during two trials of human growth hormone therapy. (From J. M. Tanner and R. H. Whitehouse.)
Causes of Tall Stature and Excessive Growth

- Normal variants: Constitutional tall stature
- Endocrine disorders
  - Growth hormone excess
  - Disorders of sexual maturation
    - Precocious puberty
    - Virilization
    - Feminization
    - Hypogonadism
- Nonendocrine disorders
  - Cerebral Gigantism (Sotos syndrome)
  - Klinefelters syndrome
  - XYY males
  - Marfan syndrome
  - Homocystinuria

# Large Size in Childhood

## Normal Variants

<table>
<thead>
<tr>
<th></th>
<th>Familial Tall Stature</th>
<th>Familial Rapid Maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental stature</td>
<td>Tall</td>
<td>Average</td>
</tr>
<tr>
<td>Onset of rapid growth</td>
<td>Infancy</td>
<td>Infancy</td>
</tr>
<tr>
<td>Facial appearance and bone age in childhood</td>
<td>Normal</td>
<td>Advanced</td>
</tr>
<tr>
<td>Onset of adolescence</td>
<td>Normal</td>
<td>Early</td>
</tr>
<tr>
<td>Final height attainment</td>
<td>Usual age</td>
<td>Early age</td>
</tr>
<tr>
<td>Adult stature</td>
<td>Tall</td>
<td>Average</td>
</tr>
</tbody>
</table>

![Graph showing growth patterns](image)
### Causes of Increased Statural Growth

<table>
<thead>
<tr>
<th>Prenatal Onset</th>
<th>Postnatal Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal diabetes mellitus</td>
<td>Exogenous obesity</td>
</tr>
<tr>
<td>Beckwith-Wiedemann Syndrome</td>
<td>Pituitary GH excess</td>
</tr>
<tr>
<td>Cerebral Gigantism</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td></td>
<td>Sexual precocity and virilizing syndromes</td>
</tr>
<tr>
<td></td>
<td>McCune-Albright syndrome</td>
</tr>
<tr>
<td></td>
<td>Homocysteinuria</td>
</tr>
<tr>
<td></td>
<td>Total lipodystrophy</td>
</tr>
<tr>
<td></td>
<td>Klinefelter syndrome (47, XXY)</td>
</tr>
<tr>
<td></td>
<td>XYY karyotype</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism</td>
</tr>
</tbody>
</table>


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Wise nature did never put her precious jewels into a garret four stories high: and therefore... exceeding tall men had ever very empty heads.

Francis Bacon