Cytogenetics
Chromosomal Disorders

• 50% of 1st trimester miscarriages
• 5% of stillbirths
• 0.5% of liveborns
  – Down syndrome—trisomy 21
  – Fragile X syndrome
• Somatic cell abnormalities in cancers

History

• Bateson (1916) “It is inconceivable that particles of chromatin….can posses the powers which must be assigned to our factors(genes).”
• (~1955) Human cells were thought to have 48 chromosomes
Cytogenetic Technology

- Peripheral blood lymphocyte culture
  - Phytohemagglutinin
  - Hypotonic swelling
- Banding---Giems
  - 350 – 550 bands/N (haploid set)
  - 850 in prometaphase
  - G-bands (dark): AT-rich, fewer transcribed genes, LINES
  - R-bands (light): GC-rich, more transcribed genes, SINES (Alu)

Metaphase spread
Prometaphase spread

Banding nomenclature
Chromosome morphology

Ideogram of human chromosomes
Human karyotype

Table 8.1. Chromosome Nomenclature*

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A–G</td>
<td>Chromosome groups</td>
</tr>
<tr>
<td>1–22</td>
<td>Autosome numbers</td>
</tr>
<tr>
<td>X, Y</td>
<td>Sex chromosomes</td>
</tr>
<tr>
<td>/</td>
<td>Diagonal line indicates mosaicism, e.g., 46/47 designates a mosaic with 46-chromosome and 47-chromosome cell lines</td>
</tr>
<tr>
<td>p</td>
<td>Short arm of chromosome, “petite”</td>
</tr>
<tr>
<td>q</td>
<td>Long arm of chromosome</td>
</tr>
<tr>
<td>del</td>
<td>Deletion</td>
</tr>
<tr>
<td>der</td>
<td>Derivative, a structurally rearranged chromosome</td>
</tr>
<tr>
<td>dup</td>
<td>Duplication</td>
</tr>
<tr>
<td>i</td>
<td>Isochromosome</td>
</tr>
<tr>
<td>ins</td>
<td>Insertion</td>
</tr>
<tr>
<td>inv</td>
<td>Inversion</td>
</tr>
<tr>
<td>r</td>
<td>Ring chromosome</td>
</tr>
<tr>
<td>t</td>
<td>Translocation</td>
</tr>
<tr>
<td>ter</td>
<td>Terminal (may also be written as pter or qter)</td>
</tr>
<tr>
<td>+</td>
<td>Placed before the chromosome number, these symbols indicate addition (+) or loss (−) of a whole chromosome, e.g., +21 indicates an extra chromosome 21, as in Down syndrome. Placed after the chromosome number, these symbols indicate gain or loss of a chromosome part, e.g., 5p− indicates loss of part of the short arm of chromosome 5. However, del(5p) is the preferred nomenclature.</td>
</tr>
</tbody>
</table>

Fluorescence in situ hybridization (FISH)

Locus-specific probes

Ch 15 centromere (green)
Ch 15 PWS critical region (red)
Centromeric probes

Trisomy 9 (leukemia)

Centromeric probes

(Ch 13 red, Ch18 pink, Ch 21 green, X yellow, Y white)
Centromeric probes
(Ch 8 red, Y yellow)

Chromosome painting probes
Chromosome painting probes

(Ch 9 green, der Ch 10)
Comparative Genomic Hybridization (CGH)
Chromosome Abnormalities

- Numerical
  - Euploid---multiple of haploid number (N)
  - Aneuploid---trisomy or monosomy
- Structural

Nondisjunction
Meiotic Nondisjunction

- Usually maternal (maternal age effect)
- Usually MI (meiosis I)
  - Starts at 20 weeks fetal
  - Arrests for 10 to 45 years
  - Finishes MI at ovulation
  - Meiosis II at fertilization

Meiotic nondisjunction
Translocations

- Reciprocal
- Robertsonian (Centric fusion)
  - Involves acrocentric chromosomes
- Balanced or unbalanced
Whole-chromosome painting probes: Ch 10 (red) and 17 (green) 
Arrows: translocation chromosomes

Centromeric probes: Ch 10 (green) and 17 (red) 
Arrows: derivative chromosomes

Locus-specific probes: Ch 15 centromere(green) Ch 15 PW/AS critical region (red) 
Arrow: unbalanced translocation
Table 8.2. Relative Frequencies of Different Abnormalities in Chromosomally Abnormal Abortuses

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 16</td>
<td>15</td>
</tr>
<tr>
<td>13, 18, 21</td>
<td>9</td>
</tr>
<tr>
<td>XXX, XXY, XYY</td>
<td>1</td>
</tr>
<tr>
<td>All others</td>
<td>27</td>
</tr>
<tr>
<td>45, X</td>
<td>18</td>
</tr>
<tr>
<td>Triploidy</td>
<td>17</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>
Trisomy 21 Down syndrome

Infant boy with severe anemia, neutropenia, dysmorphic features, growth retardation and developmental delay

46,XY, del(3)(q29)
Green: 3pter probe
Red: 3q29 probe
Microdeletion Syndromes

- Williams-Beuren Syndrome (WBS)
  - 1/20,000 all populations
  - Phenotype
    - Dysmorphic facies
    - Growth and mental retardation
    - Distinctive personality
    - Transient hypercalcemia
    - Arterial disease
  - “uniform” 1.5 MB deletion del(7)q11.23
  - Region flanked by duplicated genes---non-homologous recombination
  - 17 genes including ELN, which encodes tropoelastin
    (point mutation causes AD supravalvular aortic

Williams syndrome
FISH Diagnosis
Del(7)q11.23
Prader-Willi syndrome (PWS)

- 1/10,000
- Phenotype:
  - Mild to moderate MR
  - Hypotonia, poor feeding in infancy
  - Short stature, small hands and feet, small external genitalia
  - Hyperphagia (compulsive overeating), obesity
Prader-Willi syndrome (PWS)

PWS del(15)q11-q13
Prader-Willi syndrome (PWS)

- 1/10,000
- Phenotype:
  - Mild to moderate MR
  - Hypotonia, poor feeding in infancy
  - Short stature, small hands and feet, small external genitalia
  - Hyperphagia (compulsive overeating), obesity
- Del(15)q11-13.....Paternal
- Uniparental Disomy

Angelman syndrome

- Severe MR, absence of speech
- Jerky movements
- Inappropriate laughter
- Large jaw
- Del(15)q11-13----but Maternal
Genomic Imprinting

- Maternal and Paternal genetic contributions not equivalent
- Genetic contributions from both parents are needed for normal development
Evidence for Imprinting

- Mouse Embryos
  - Gynogenetic---poorly developed extra-embryonic membranes
  - Androgenetic—abnormal embryonic structures
- Human tumors
  - Hydatidiform moles—placental tumors with two paternal haploid sets of chromosomes
  - Ovarian teratomas---benign differentiated tumors with two maternal haploid sets

Mechanism of Imprinting

- Some genes are preferentially inactivated (imprinted) during gametogenesis in male and female parents
- Differential DNA methylation/histone acetylation
- Deletion of the active allele----functional nullisomy
- Uniparental disomy for the inactive allele—functional nullisomy
PWS/AS region