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Chromosomal Disorders

MGL-4
July 9th 2013
Chromosomal Disorders

- Cell division
- Disorders of the autosomes
- Disorders of the sex chromosomes
- Chromosomal Breakage syndromes
Types of chromosome abnormalities

- **Numerical**
  - Aneuploidy (monosomy, trisomy, tetrasomy)
  - Polyploidy (triploidy, tetraploidy)

- **Structural**
  - Translocations
  - Inversions
  - Insertions
  - Deletions
  - Rings
  - Duplication
  - Isochromosomes
Chromosome Abnormalities
Numerical Autosomal Disorders

AGE OF ONSET OF GENETIC DISORDERS

chromosomal

number of affected individuals

birth puberty adult

single-gene (Mendelian)
multifactorial
Aneuploidy

- Almost all been found in oocytes and early embryos, trisomies and monosomies
- Most lethal (miscarry)
- Do not see in pregnancy or live born
- Exceptions sex chromosomes and Down
- Some aneuploidy is age related
Autosome Chromosomal Abnormalities
Numerical Abnormalities

- **Polyplody**
  - Triploidy (69,XXY)
  - Tetraploidy (92,XXYY)

- **Aneuploidy**
  - Monosomy (45,X : Turner Syndrome)
  - Trisomy (47,XY,+21 : Down Syndrome)
  - Tetrasomy (48,XXXX)
TRIPLOIDY
(all chromosomes threefold)

Triploidy (all chromosomes threefold)

Origin of triploidy

<table>
<thead>
<tr>
<th>Oocyte</th>
<th>Spermatozoon</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>normal</td>
</tr>
</tbody>
</table>

46, XX
23, X or 23, Y

69, XXX or 69, XXY
Maternal origin

69, XXY
Paternal origin
Aberrant euploidy (polyploidy)

(A) Triploidy

(B) DNA duplication but no cell division (endomitosis)

(C) 24%

(D) Tetraploidy
Aneuploidy Caused by

- **Non-disjunction**
  - failure of homologous chromosomes to separate in anaphase I
  - failure of sister chromatids to separate at meiosis II

- **Anaphase lag**
  - Chromosomal loss via micronucleus formation caused by delayed movement of chromosome /chromatid during anaphase
    - results in daughter cell deficient of that chromosome or chromatid
MONOSOMY & TRISOMIES

Diagram showing the process of meiosis and the outcomes of nondisjunction at meiosis I and meiosis II, resulting in monosomic, trisomic, and euploid zygotes.
Genetic diversity

1. Crossing over in MI
   - swap pieces of DNA between maternal and paternal homologous chromosomes

2. Independent assortment at end of MI
   - paternally and maternally derived homologues assort randomly
### Distribution of non-disjunction

<table>
<thead>
<tr>
<th></th>
<th>Meiosis I</th>
<th>Meiosis II</th>
<th>Mitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>21, 15, 16</td>
<td>18</td>
<td>15, 18, 21, 8</td>
</tr>
<tr>
<td>Paternal</td>
<td>-</td>
<td>18, 21</td>
<td>18, 21</td>
</tr>
</tbody>
</table>
Aneuploidy

- Autosomal monosomy is rarely observed in spontaneously aborted fetuses or in live births.

- Most autosomal trisomies are also lethal with one notable exception.

- Trisomy 13: Patau syndrome
- Trisomy 18: Edward syndrome
- Trisomy 21: Down’s syndrome
Trisomy 21 (1 in 800 live births; incidence greater if mat. age >35)

- Hypotonia
- Short neck with loose skin at nape
- Flat nasal bridge
- Brushfield spots around edge of iris
- Epicanthal folds
- Short, broad hands with single transverse palmar crease
- Congenital heart disease
- Mental retardation
- Increased risk for leukemia
Nondisjunctional phenomenon on meiosis
Down Syndrome

Wide “sandal” gap

epicanthische vouwen

Brushfield spots

Simian crease (bilateral single palmar crease)
NON-DISJUNCTION FEATURES OF CHROMOSOME 21

- Occurs in all populations approximately at the same rate
- There is a significant loss of trisomy 21 pregnancy 1/150
- The risk of having pregnancy affected with DS is increased with maternal age
Changes in the Genome...

- **Trisomy**: The zygote has three copies of a chromosome.
Recurrence Risks: Trisomy 21

- Trisomy 21
  - 1\% or age-related risk (whichever is greater)
    - Occult somatic or gonadal mosaicism
- 46,i(21q) recurrence risk is low (if not a carrier)
- t(14;21)
  - 15\% if female carrier
  - <1\% if male carrier
Trisomy 13, Patau syndrome

Clinical Features (1 in 15 - 25,000 births)
- Microcephaly and mental retardation,
- scalp defect,
- microphthalmia, often blind
- Cleft lip/palate,
- polydactyly,
- rocker-bottom feet,
- abnormal ears,
- apneic spells and myotonic seizures,
- cardiac dextroposition and VSD,
- extensive visceral defects
- CNS malformations presence of a single forebrain hemisphere or lobe

Half of such individuals die within the first month-- the remainder by 1 year
cleft palate, atrial septal defect, inguinal hernia, and postaxial polydactyly of the left hand.

Polydactyly, particularly of all extremities, strongly suggests trisomy 13.
## Trisomy 13, Patau syndrome

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13 47,XX,+13</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>R. Translocation 46,XX,der(13;14)+13</td>
<td>20%</td>
</tr>
<tr>
<td>Mosaicism 47,XX,+13/46,XX</td>
<td>5%</td>
</tr>
</tbody>
</table>
Clinical Features: Trisomy 18
Clinical feature (1 in 7,500 births)

- Prominent occiput
- Short palpebral fissures
- Micrognathia
- Low-set, malformed ears
- Profound Mental Retardation
- Rocker-Bottom Feet
- Short Sternum
- Small Pelvis
- Clenched Hands
- Renal anomalies
- Cleft Lip/Palate
- Hypoplastic thumbs
- Dorsiflexed halus (hammer toe)
- Renal Anomalies
Trisomy 18 – Edwards syndrome
Karyotype: 47, XX (or XY), +18
Survival – 50% within 1 month, 50% within less than 1 year
# Edwards Syndrome (Trisomy 18)

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 18</td>
<td>47,XX,+18</td>
</tr>
<tr>
<td>Translocation</td>
<td>46,XX,+18,t(?;18q)</td>
</tr>
<tr>
<td>Mosaicism</td>
<td>47,XX,+18/46,XX</td>
</tr>
</tbody>
</table>

![Image of karyotype with chromosomes 13, 21, X, Y, and 18 highlighted]
Sex Chromosomes
Abnormalities
Sex Chromosome Aneuploidy

- Sex Chromosome Aneuploidy is more common than Autosomal Aneuploidy!
- In order to survive and develop, the embryo needs at least one X chromosome.
- In healthy females, one X chromosome will be inactivated in each somatic cell. The inactivated X chromosome is referred to as a “Barr body”.
- An individual who has an intact Y-chromosome will be male, regardless of the number of X chromosomes he possesses.
- In the absence of an intact Y chromosome, an individual will be female.
X-Chromosomal Disorders

- Imbalances of X-chromosomes are better tolerated than those of autosomes
- Increased number of X-chromosomes in either males or females lead to mental retardation
- Lyonization – Mary Lyon
  - during 16\textsuperscript{th} day of embryonic life one X-chromosome in females is randomly inactivated
  - inactivation persists in all subsequent cells
A woman with the chromosome constitution 47, XXX should have 2 Barr bodies in each cell.

XXY individuals are male, but have a Barr body.

XO individuals are female but have no Barr bodies.
<table>
<thead>
<tr>
<th>Gametes</th>
<th>Sperm</th>
<th>X</th>
<th>Y</th>
<th>XY</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>46,XX</td>
<td>46,XY</td>
<td>47,XXY</td>
<td>45,X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal ♀</td>
<td>Normal ♂</td>
<td>Klinefelter ♂</td>
<td>Turner ♀</td>
<td></td>
</tr>
<tr>
<td>XX</td>
<td>47,XXX</td>
<td>47,XXY</td>
<td>48,XXXXY</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♀</td>
<td>Klinefelter ♂</td>
<td>Klinefelter ♂</td>
<td>Normal ♀</td>
<td></td>
</tr>
<tr>
<td>XXX</td>
<td>48,XXXXX</td>
<td>48,XXXXY</td>
<td>49,XXXXXY</td>
<td>47,XXX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>♀</td>
<td>Klinefelter ♂</td>
<td>Klinefelter ♂</td>
<td>Triple X ♀</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>45,X</td>
<td>45,Y</td>
<td>46,XY</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Turner ♀</td>
<td>LETHAL</td>
<td>LETHAL</td>
<td>LETHAL</td>
<td></td>
</tr>
</tbody>
</table>

- **X chromatin (Barr body)**
- **Y chromatin**
Nondisjunction of X chromosome
## Sex Chromosome Aneuploidy

<table>
<thead>
<tr>
<th>Situation</th>
<th>Oocyte</th>
<th>Sperm</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>X</td>
<td>Y</td>
<td>46, XY normal male</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>46, XX normal female</td>
</tr>
<tr>
<td><strong>Female Nondisjunction</strong></td>
<td>XX</td>
<td>Y</td>
<td>47, XXY Klinefelter syndrome</td>
</tr>
<tr>
<td></td>
<td>XX</td>
<td>X</td>
<td>47, XXX triplo-X</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td></td>
<td>45, Y nonviable</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
<td>45, X Turner syndrome</td>
</tr>
<tr>
<td><strong>Male Nondisjunction</strong></td>
<td>X</td>
<td></td>
<td>45, X Turner syndrome</td>
</tr>
<tr>
<td>(meiosis I)</td>
<td>X</td>
<td>XX</td>
<td>47, XXX triplo-X</td>
</tr>
<tr>
<td><strong>Male nondisjunction</strong></td>
<td>X</td>
<td>YY</td>
<td>47, XYY Jacobs syndrome</td>
</tr>
<tr>
<td>(meiosis II)</td>
<td>X</td>
<td></td>
<td>45, X Turner syndrome</td>
</tr>
</tbody>
</table>
Turner syndrome
Monosomy X or X0

- 1 in every 5000 births
- varied degree of effects
- webbed neck
- short stature
- sterile

KARYOTYPING:
- Classical 45X
- 46,X,i(Xq)
- 46XXq-
- 46XXp-
- 46,X r(X)
- 45,X/46,XX
Turner Syndrome

- Results from complete or partial monosomy of the X-chromosome in females
- Most common sex chromosome abnormality in females, incidence 1 in 1000 live births
- Classical cytogenetics
  - 45,X (57%)
  - Structural abnormalities of X-chromosomes (14%)
  - Mosaics (29%)
Mosaicism in Turner Syndrome

- 99% of conceptuses with 45,X are nonviable
- FISH and PCR studies show much higher incidence of mosaics than conventional studies
- Some authorities believe that there are no truly nonmosiac Turner syndrome patients
- Patients with a high proportion of 45,X cells are more severely affected
TURNER SYNDROME

KARYOTYPING:

- Classical 45X
- Isochromosome 46,X,i(Xq)
- Deletion 46XXq-
- Deletion 46XXp-
- Ring 46,X r(X)
- Mosaic e.g. 45,X/46,XX
47,XXY - Klinefelter syndrome

Clinical Features

- Tall, thin, long legs, hypogonadism, underdeveloped secondary sex characteristics, gynecomastia - excessive development of the male mammary glands. Usually infertile
- Verbal comprehension and ability slightly lower than average
- Increased risk of learning difficulties, esp. in reading

Karyotyping:
- 60% are of maternal nondisjunction and maternal age increases the possibilities
- 47 XXY
- Mosaics XY / XXY
- XXXY, XXYY, XXXXY. Severely mentally retarded

1/1000 male births
Klinefelter Syndrome

- A male hypogonadism that occurs when there are two or more X-chromosomes and one or more Y-chromosomes
- Incidence is 1 in 500 male births
- Usually (82% of cases) 47,XXY
  - maternal (60%) or paternal (40%) nondisjunction during meiotic divisions
- 15% are mosaics, usually 46,XY/47,XXY
Clinical Features

- Testicular abnormality does not develop before puberty
  - seminiferous tubules are atrophic resulting in reduced spermatogenesis, infertility, small firm testes, and increased FSH
  - testosterone levels are reduced
    - impotence and increased LH
    - lack of secondary male sexual characteristics
- Mental retardation is unusual but IQ may be below normal
- Mosaics are less severely affected
47,XYY

Clinical Features

- Not obviously abnormal
- No marked physical or behavioral phenotype
- Tall, fertile, may have severe acne during adolescence

Incidence 1/1000

- Increased risk of educational or behavioral problems
- IQ scores about 10 pts below average
  - Attention deficits
  - Hyperactivity
  - Impulsiveness
Origin of the error that leads to XYY karyotype must be paternal nondisjunction at meiosis II producing YY sperm.

Fertilization of this sperm by an egg will lead to Turner syndrome.
Sex Chromosome Tetrasomy
Males: 48, XXXY

Clinical Features

- Reduction in intellectual functioning – IQ between 20-80
- Coarse facial appearance, gonadal hypoplasia common
- As a rule: additional X chromosomes cause a more abnormal phenotype-more defective sexual development and mental impairment.
Sex Chromosome Tetrasomy
Males: 48,XXXY

Clinical Features

- Reduction in intellectual functioning – IQ between 20-80
- Coarse facial appearance, gonadal hypoplasia common
- As a rule: additional X chromosomes cause a more abnormal phenotype-more defective sexual development and mental impairment
Sex Chromosome Pentasomy
49,XYYYY

Clinical Features

- Tall stature
- Aberrant behavior (impulsivity, low frustration tolerance)
- Low-normal or subnormal intelligence
- Developmental delay
- Testicular abnormalities
- Some craniofacial dysmorphisms (more common for 49,XYYYY)
48,XXXY: X (green), Y (red), 18 (blue),
INSTABILITY OF CHROMOSOMES
Chromosome breaks

- Once chromosome broken by some means
- Unstable situation as telomeres not at end
- Usually join up to other piece
Defects in DNA Repair or Replication

All are associated with a high frequency of chromosome and gene (base pair) mutations; most are also associated with a predisposition to cancer, particularly leukemias

- **Xeroderma pigmentosum**
  - caused by mutations in genes involved in nucleotide excision repair
  - associated with a >1000-fold increase of sunlight-induced
  - skin cancer and with other types of cancer such as melanoma
Main Features Ataxia Telangiectasia

- Cerebellar ataxia
- Immune defects
- Telangiectases of the conjunctivae
- Predisposition to tumors (lymphoma, leukemia)
- Extreme radiation sensitivity
- Autosomal recessive
- Several gene loci

Ataxia telangiectasia caused by gene that detects DNA damage increased risk of X-ray associated with increased breast cancer in carriers
Main features of Bloom syndrome (BS)

- Extreme intrauterine and postnatal growth retardation
- Chromosomal instability
- Predisposition to leukemias, lymphomas, and other tumors
- Immune defects
- Sunlight-induced erythema of the face
- Hypo- and hyper-pigmented skin areas
- Autosomal recessive
- Gene locus on chromosome 15
Main features of Fanconi Anemia (FA)

- Growth retardation
- Skeletal defects (e.g., radius and thumb)
- Bone marrow failure
- Skeletal and kidney malformation
- Localized pigment changes
- Increased risk of X-ray and sensitivity to sunlight
- Autosomal recessive
- Several gene loci.

Caused by a gene involved in DNA repair.
Defects in DNA Repair or Replication

- **Cockayne syndrome**
  - caused by a defect in transcription-linked DNA repair
  - sensitivity to sunlight

- **Werner’s syndrome**
  - caused by mutations in a DNA helicase gene
  - premature aging
Structural Chromosomal Abnormalities