Chromosomal Disorders

Oral Histology | Kristine Krafts, M.D.
Objectives

• Be able to give a ballpark figure on how common chromosomal abnormalities are, and know the relative incidence in all live births vs. births to mothers over 35 vs. 1st trimester miscarriages.

• Define euploidy, aneuploidy, and polyploidy.

• Describe the phenotypic features of Down syndrome, and explain its causative chromosomal abnormality.

• Compare and contrast trisomies 18 and 13.

• Describe the chromosomal abnormality and clinical features of cri du chat and DiGeorge syndromes.

• Describe the typical karyotype (e.g., 47,XXY) and clinical features of Klinefelter and Turner syndromes.

• Explain (in a general way) what the Philadelphia chromosome is, and describe the structural abnormality involved.
Chromosomal Disorders

Introduction

Autosomal disorders

Sex chromosome disorders

Acquired chromosomal abnormalities
Chromosomal Disorders

Introduction
Chromosomal abnormalities are pretty common!

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; trimester miscarriages</th>
<th>Mothers &gt;35</th>
<th>Live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence</td>
<td>1 in 2</td>
<td>1 in 50</td>
<td>1 in 160</td>
</tr>
<tr>
<td>Numerical abnormalities</td>
<td>96%</td>
<td>85%</td>
<td>60%</td>
</tr>
<tr>
<td>Structural abnormalities</td>
<td>4%</td>
<td>15%</td>
<td>40%</td>
</tr>
</tbody>
</table>
## Nomenclature of numerical abnormalities

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Euploidy</strong></td>
<td>Normal number of chromosome sets (humans: 2 sets of 23)</td>
</tr>
<tr>
<td><strong>Aneuploidy</strong></td>
<td>An abnormal chromosome number due to an extra or missing chromosome</td>
</tr>
<tr>
<td></td>
<td>monosomy: 45   trisomy: 47</td>
</tr>
<tr>
<td><strong>Polyploidy</strong></td>
<td>An abnormal chromosome number due to extra set(s) of chromosomes</td>
</tr>
<tr>
<td></td>
<td>triploidy: 69   tetraploidy: 92</td>
</tr>
</tbody>
</table>
Trisomy
Triploidy
Abbreviations you should know

+ gain    47,XY,+21   (trisomy 21)
- loss    45,XX,-22   (monosomy 22)
Balanced Translocation
Deletion
Duplication
Inversion
Ring chromosome
Chromosomal Disorders

Introduction

Autosomal disorders
46, XY

Autosomes
46, XY

Sex chromosomes
Down Syndrome

- Most common chromosomal disorder!
- Most common genetic cause of cognitive impairment!
- Overall incidence: 1 child in 800
- Incidence higher for mothers over 35
Facial Features

- Flat nasal bridge
- Epicanthal folds
- Upslanting palpebral fissures
- Upturned nose
- Smooth philtrum
- Open mouth with protruding tongue
Other Phenotypic Features

- Hypotonia in newborn period
- Short stature
- Brachycephaly (flat occiput)
- Brushfield spots around margin of iris
- Single palmar crease
Brachycephaly

None    Mild    Moderate    Severe
Brushfield spots
Single palmar crease
DeNiro has a single palmar crease!
So does Rainn Wilson...
...and Tony Blair.
Other Signs and Symptoms

- Cognitive impairment (IQ 30-60)
- Congenital heart disease
- Recurrent respiratory infections
- GI tract malformations
- Increased risk of leukemia
- Premature dementia
Etiology

• 95% of cases have trisomy 21 due to meiotic non-disjunction

• Rest have other other abnormalities involving 21 (like translocations)

• Maybe the older the oocyte, the greater the chance the chromosomes won’t separate correctly during meiosis
47,XY,+21 (Male with trisomy 21)
Meiotic nondisjunction

Failure of a pair of chromosomes to separate properly during one of the two meiotic divisions (usually meiosis I)
% of babies born with Down Syndrome

Maternal age
Trisomy 18 (Edwards Syndrome)

- 1 in 7500 births
- Most babies only live a few months
- Failure to thrive
- Characteristic head, hand, and foot findings
- Heart malformations
Infant with trisomy 18

- micrognathia (small jaw)
- low-set, malformed ears
- large occiput
clenched fist: fingers 2 and 5 overlap 3 and 4

prominent heels ("rocker-bottom" feet)

Infant with trisomy 18
Trisomy 13 (Patau Syndrome)

- 1 in 15,000 – 25,000
- Most babies only live a few months
- Failure to thrive
- Characteristic head, hand, foot findings
- Heart malformations
- Severe CNS findings (holoprosencephaly)
Infant with trisomy 13

- Polydactyly
- Prominent heels ("rocker-bottom" feet)
- Bilateral cleft palate
- Clenched fist: fingers 2 and 5 overlap 3 and 4
Cri du Chat Syndrome

• del 5p
• 1% of all institutionalized cognitively impaired patients
• “Cat cry” due to underdeveloped larynx
• Moderate to severe cognitive impairment
• Characteristic facial features
• Normal life expectancy (if no other malformations)
Child with cri du chat syndrome

- low-set ears
- micrognathia
- microcephaly
- hypertelorism (wide-set eyes)
DiGeorge Syndrome

- Microdeletion in 22q11.2
- 1 in 2000-4000 live births
- Pharyngeal arches/pouches don’t develop properly
- Abnormalities of face/palate, thymus, heart, parathyroids
- Cognitive impairment
Little boy with DiGeorge syndrome

- Hypertelorism
- Micrognathia
- Low-set ears
- Short philtrum ("fish-mouth")
Mnemonic: CATCH-22

- Cardiac abnormalities
- Abnormal facies
- Thymic aplasia
- Cleft palate
- Hypocalcemia/hypoparathyroidism
- Chromosome 22
Chromosomal Disorders

Introduction

Autosomal disorders

Sex chromosome disorders
Sex Chromosome Disorders

• Common! (1 in 400-500 births)
• Consider if patient has delayed puberty, amenorrhea, infertility
• Usually numerical but can be structural
• Less severe phenotype than autosomal disorders (X-inactivation and low gene content on Y)
Klinefelter Syndrome

- 1 in 1000 male births
- 47,XXY (most cases)
- Decreased secondary sex characteristics
- May have learning difficulties
- Adult habitus: normal, lanky or rounded
- Most patients infertile
Adolescent male with Klinefelter syndrome
Adult male with Klinefelter syndrome
Turner Syndrome

- 1 in 4000 female births
- 45,X (most)
- Short stature, “streak” gonads, webbed neck, broad chest, kidney and heart abnormalities
- May have learning difficulties
- Most patients infertile
Adolescent female with Turner syndrome
Adult female with Turner syndrome
Chromosomal Disorders

Introduction

Autosomal disorders

Sex chromosome disorders

Acquired chromosomal abnormalities
Acquired Chromosomal Abnormalities

- Most cancers have chromosomal abnormalities
- These are acquired and clonal
- Abnormalities are limited to the tumor cells
- Important to identify these (for diagnosis, treatment, prognosis)
The Philadelphia Chromosome

- t(9;22)
- Well-known and studied translocation
- Present in chronic myeloid leukemia
Normal chromosomes

Chromosomes in CML

9  22

\text{ABL\ oncogene}

\text{BCR\ locus}

\text{BCR-ABL\ hybrid\ gene}

\text{ABL\ oncogene}
Bad-ass tyrosine kinase

Normal chromosomes

Chromosomes in CML

BCR locus

ABL oncogene

BCR-ABL hybrid gene