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>1st 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>
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</tbody>
</table>
Nomenclature of numerical abnormalities

**Euploidy**  Normal number of chromosome sets (humans: 2 sets of 23)

**Aneuploidy**  An abnormal chromosome number due to an extra or missing chromosome

- monosomy: 45  
- trisomy: 47

**Polyploidy**  An abnormal chromosome number due to extra set(s) of chromosomes

- triploidy: 69  
- tetraploidy: 92
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

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
Infant with trisomy 18

- Clenched fist: fingers 2 and 5 overlap 3 and 4
- Prominent heels ("rocker-bottom" feet)
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
- Bilateral cleft palate
- Clenched fist: fingers 2 and 5 overlap 3 and 4
- Prominent heels ("rocker-bottom" feet)
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
- low-set ears
- short philtrum ("fish-mouth")
- micrognathia

Little boy with DiGeorge syndrome
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

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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
The Philadelphia chromosome
Normal chromosomes

Chromosomes in CML

9  22

BCR locus

ABL oncogene

BCR-ABL hybrid gene
Bad-ass tyrosine kinase
Bad-ass tyrosine kinase