Chromosomal Disorders

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.

Introduction

Chromosomal Disorders

Autosomal disorders
- Sex chromosome disorders
- Acquired chromosomal abnormalities

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

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>
Abbreviations you should know

- **gain**: 47,XY,+21 (trisomy 21)
- **loss**: 45,XX,-22 (monosomy 22)

**Balanced Translocation**

**Deletion**

**Duplication**
Chromosomal Disorders

Introduction

Autosomal disorders
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

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 abnormalities involving 21 (like translocations)
- Maybe the older the oocyte, the greater the chance the chromosomes won’t separate correctly during meiosis
Meiotic nondisjunction
Failure of a pair of chromosomes to separate properly during one of the two meiotic divisions (usually meiosis I)

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
- large occiput
- micrognathia (small jaw)
- low-set, malformed ears
- 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
- Prominent heels ("rocker-bottom feet")
- 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:
- Microcephaly
- Hypertelorism (wide-set eyes)
- Micrognathia
- Low-set ears

**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
- Micrognathia
- 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

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

Adult male with Klinefelter 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

46,XX,t(9;22)
Normal chromosomes
Chromosomes in CML

The Philadelphia chromosome

Bad-ass tyrosine kinase

Bad-ass tyrosine kinase