Why do we study human chromosomes?
- Chromosome disorders - major category of genetic disease
- Responsible for >100 identifiable syndromes
- More common than all mendelian single gene disorders!
- 1% livebirths
- 2% pregnancies

Clinical Indications for Chromosome Analysis
- Problems of early growth and development
- Stillbirth/neonatal death
- Fertility problems
- Family history of chromosome rearrangement
- Pregnancy indications – LMA, U/S abn etc
- Neoplasia

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

Non-disjunction during meiosis

History
- 1890-1920: techniques of plant and insect cell staining applied to human cells
- 1923: XX/XY was postulated to be the sex-determining mechanism
- 1956: 46 chromosomes in human cells
  - First karyotype
- 1959: Down Syndrome (extra small chr.), Turner Syndrome, Kleinfelter Syndrome other trisomies visualized
- 1960: phytohemoglobin (PHA)—stimulates blood cells to divide
  - When they divide, they condense to we can see them better

History
- 1970: chromosome banding
- 1977: high resolution banding
- 1986: fluorescence in situ hybridization (FISH)
Distribution of non-disjunction

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

Aneuploidy

- As women age
- Some chromosomes exhibit non-disjunction in oocytes
- Many theories why
- 13, 18, 21 associated with age
- 16 and X only first meiotic division associated with age
- Most chromosome abnormalities incompatible with life
- Willmiscarry

Differences in Gametogenesis

**Male**
- Puberty
- 60-65 days
- 30-500 mitoses
- 4 spermatids
- 100-200 million /ejaculate

**Female**
- Early embryonic development
- 10-50 years
- 20-30
- 1 ovum and polar bodies
- 1 ovum / menstrual cycle
Maternal age specific estimates of trisomy among all clinically recognisable pregnancies

Maternal age specific estimates of trisomy among all clinically recognisable pregnancies

Parental origin of aneuploidy

<table>
<thead>
<tr>
<th></th>
<th>Paternal %</th>
<th>Maternal %</th>
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<tbody>
<tr>
<td>Trisomy 13</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>45,X</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>47,XXX</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>47,XXY</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>47,XYY</td>
<td>100</td>
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Parental origin of aneuploidy

Chromosome abnormalities in miscarriages

<table>
<thead>
<tr>
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<th>Incidence %</th>
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<tbody>
<tr>
<td>Trisomy 13</td>
<td>2</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>15</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>3</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
</tr>
<tr>
<td>Other Trisomy</td>
<td>25</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>20</td>
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<tr>
<td>Triploidy</td>
<td>15</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>

Chromosome abnormalities in humans

- Spermatozoa: 10%
- Mature oocytes: 25%
- Spontaneous miscarriage: 50%
- Live births: 0.5-1%
- Most due to maternal meiotic non disjunction
- Strongly related to maternal age
- Natural selection at work

Chromosome abnormalities in newborns

<table>
<thead>
<tr>
<th></th>
<th>Incidence / 10,000</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>births</td>
</tr>
<tr>
<td>Trisomy 13</td>
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<tr>
<td>Trisomy 18</td>
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<td>Trisomy 21</td>
<td>15</td>
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<tr>
<td>45,X</td>
<td>1</td>
</tr>
<tr>
<td>47,XXX</td>
<td>10</td>
</tr>
<tr>
<td>47,XXY</td>
<td>10</td>
</tr>
<tr>
<td>Unbalanced</td>
<td>10</td>
</tr>
<tr>
<td>Balanced</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
</tr>
</tbody>
</table>

Chromosome abnormalities

- Triploidy: rare at birth – lethal
- Trisomy 16: Most common in spontaneous miscarriages
- Trisomy 13 &18: Completely lethal. Cause unknown
- Trisomy 21: 80% miscarriage
- Klinefelters: 50% miscarriage
- 45X: 1% at conception
- 45Y: 98% miscarry, probably mosaic survive

Chromosome abnormalities

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TRISOMY 21

- Most common postnatal autosomal trisomy
- Complete trisomy = 95%
- Robertsonian Translocated = 4%
  - Rob(14q21q) = 1:10000
  - Rob(21q21q) = 1:30000
    - mostly isochromosome
    - 1:3 hereditary (usually mother)
    - 7% of such patients has a carrier parent (usually mother)
  - De novo Rob(14q21q) – most often maternal germ cell - due to meiosis NDJ as a result of an unusual genetic recombination in meiosis I
- Mosaic trisomy = 1%
  - General tendency of trisomic cells to be higher in fibroblasts and early life

Clinical features

- Short stature
- Hypotonia – improves by age
- Moderate-to-severe mental retardation
  - IQ range of 20–85 (mean IQ is approximately 50)
- Seizure disorders (5-10%)
  - Infantile spasm (most common type in infancy)
  - Tonic-clonic seizures (most commonly seen in older patients)
- Obesity

Eye dysmorphism features

- Up-slanting palpebral fissures
- Bilateral epicanthal folds
- Brushfield spots (speckled iris)
- Refractive errors (50%)
- Strabismus (44%)
- Nystagmus (20%)
- Blepharitis (33%)
- Congenital cataracts (3%)

Behavioral disorders

- Children and adolescents at a higher risk for
  - Autism
  - Attention deficit hyperactivity disorder
  - Conduct disorder
  - Obsessive-compulsive disorder
  - Tourette syndrome
  - Depressive disorder during the transition from adolescence to adulthood
Ears

- Small
- Over-folded helix
- Chronic otitis media
- Hearing loss common. Between 66–89% of children
- have hearing loss of greater than 15–20 dB in at least one ear by auditory brainstem response

Clinical diagnosis

- Radiologic study
- Brachycephaly
- Absence of nasal bone ossification
- Hypoplasia of middle phalanx of the fifth finger

Eight cardinal dysmorphism

- Abundant neck
- Mouth corners turned downward
- Hypotonia
- Flat face
- Dysplastic ears
- Epicanthic eye fold
- "sandal gap" between first and second toes
- Protruding tongue
Genetic

- Chr 21 has 47 million nucleotides
- Chr 21 likely contains between 300 and 400 genes
- 52 genes associated with diseases have been found
- Down syndrome critical region
  - DSCR1 on chromosome 21q22.3
  - DSCR2 on chromosome 21q22.2
  - DSCR3 on chromosome 21q22.2
  - DSCR4 on chromosome 21q22.2
  - DSCR5 in chromosome 21q22.1-q22.2
- 21q22.1-q22.3 region > congenital heart disease
  - (DSCR1) > 21q22.1-q22.2

Differential diagnosis

- Newborn
  - Zellweger syndrome
  - Tetrasomy 12p
- Older patients
  - Smith-magenis syndrome
  - Subtelomeric deletion of 9q34
Trisomy 18 (EDWARDS SYNDROME)
- Hypertonia
- Prominent occiput
- Atheli/hypothelia (nipple hypoplasia)
- Overlapping fingers
- rocker bottom feet
- Small pelvis
- Arthrogryposis congenita
- Hip movement limitation
- Omphalocele
- Cryptotia (uncommon)

Laboratory findings
- Thrombocytopenia (occurs in 83% of cases)
- Neutropenia
- Abnormal erythrocyte values
  - Anemia (40%)
  - Polycythemia (17%)

Skeletal radiography
- absent radius
- tight flexion of the fingers with the second over the third and the fifth over the fourth
- talipes equinovarus
- short sternum
- Hemivertebrae
- fused vertebrae
- short neck
- Scoliosis
- rib anomaly.
- dislocated hip

Imaging
- Echocardiography:
  - ventricular septal defect (94%)
  - patent ductus arteriosus (77%)
  - atrial septal defect (68%)
  - complex congenital heart defects (32%)
- brain ultrasonography
  - cerebellar hypoplasia (32%)
  - brain edema (29%)
  - enlarged cisterna magna (26%)
  - choroid plexus cysts (19%)
- Ultrasonography is also indicated for genitourinary anomalies
Differential diagnosis
- Pena-Shokeir syndrome (has overlapping finger)
- Arthrogryposis
- Other Problems to Be Considered
  - Fetal akinesia sequence
  - Mental retardation syndromes
  - Multiple congenital anomalies
  - Other autosomal trisomies and monosomies
  - Pseudo-trisomy 18 syndrome

Prognosis
- A small number of children with trisomy 18 survive beyond the first year
- Newborns have a 40% chance of surviving to age 1 month.
- Infants have a 5% chance of surviving to age 1 year.
- Children have a 1% chance of surviving to age 10 years
- Cause of death
  - Congenital heart malformations
  - GI and genitourinary anomalies
  - Feeding difficulties
  - Associated CNS defects that produce central apnea

Prenatal feature
- Posaxial polydactyly
- Microcephaly
- Mental retardation
- Scalp defect
- Microphthalmia
- Cleft palate
- Polydactyly
- Rocker-bottom feet
- Low birth weight <2.6

Trisomy 13
- Antenatally
  - History of
    - Preeclampsia
    - Abnormal placenta like a partial mole

• all older children with trisomy 18
  • Smile
  • Laugh
  • Interact
  • Relate to their families
  • Achieve some psychomotor maturation.
  • Mosaic cases may show milder phenotypic expression and prolonged survival
TRISOMY 13

- distinctive central dysmorphic midline structural anomaly
- Microphthalmia
- Cyclops
- cleft lip
- omphalocele

TRISOMY 8

- Complete trisomy 8 frequently results in miscarriage
- 100 cases (most of them are mosaic)
- The male-to-female ratio is 2–3:1
- Mild to severe retardation
- Complete trisomy 8 frequently results in miscarriage;
  those with "trisomy # mosaic" are more likely to survive
- Most common trisomy in hematopoietic malignancy
- Retarded psychomotor development
- Moderate to severe mental retardation
- variable growth patterns
- can result in either abnormally short or tall stature
- an expressionless face

Skeletal abnormalities

- long, thin trunk
- Hemivertebrae
- spina bifida
- Kyphoscoliosis
- hip dysplasia
- multiple joint contractures
- Camptodactyly
- dysplastic nails
- absent or dysplastic patella
- Narrowed pelvis
- The presence of deep palmar and plantar furrows is characteristic
Craniofacial dysmorphism

- Prominent forehead
- Deep-set eyes
- Strabismus
- Broad nasal bridge
- Uptorned nares
- Long upper lip
- Thick and everted lower lip
- High arched or cleft palate
- Micrognathia
- Large dysplastic ears with prominent antihelices

TRISOMY 9

- More than 40 cases of liveborns or term stillborns from 1973
- Male-to-female ratio > close to 1:1
- Dysmorphisms in the skull
  - High narrow forehead
  - Short nose, shallow nasal dome
  - Anterriorly placed ears
  - Deep-set eyes, microphthalmia
  - Underdeveloped auricles
  - Prominent upper lip
  - Nystagmus
- Nervous system
- Mental retardation
- Dysmorphisms in the heart, kidneys, may also occur

TRISOMY 16

- More than 1% of pregnancies
- Most common chromosomal cause of miscarriage during the first trimester of pregnancy
- Sometimes occur in mosaic livebirths

- Musculoskeletal system
  - Abnormal position/function of various joints
  - Bone dysplasia
  - Narrow chest
  - 13 ribs
  - Overlapping fingers
  - Hypoplastic external genitalia
- Cryptorchidism
  - Cardiac anomalies: 60% of cases
  - Most frequently VSD
  - Renal malformations: ~40% of patients
  - Congenital hydrocephalus
  - Majority of patients die in the early postnatal period (with rare exceptions)
TRISOMY 20
- Unusual facial features
- Multiple congenital malformations
- Death soon after birth
- Severe gastrointestinal anomalies
- Spinal dysplasia
- Large mouth/macrostomia
- Large tongue/macroglossia
- Snoring
- Coarsened facial features
- Dysmorphic appearance/face

Mosaic forms
- Poor growth of the fetus during pregnancy
- Congenital heart defects, such as ventricular septal defect (16% of individuals) or atrial septal defect (10% of individuals)
- Unusual facial features
- Underdeveloped lungs or respiratory tract problems
- Musculoskeletal anomalies
- Urethral opening too low (hypospadias) (7.6% of boys).
- Increased risk of premature birth

TRISOMY 22
- Craniofacial anomalies
- Microcephaly
- Brachycephaly
- Arhinencephaly
- Holoprosencephaly
- Microphthalmia
- Small palpebral fissures
- Prominent eyes
- Coloboma
- Cleft palate/cleft lip

Trisomy 22
- Second most common finding in miscarriages
- There are 3 types
  - Non-mosaic trisomy 22
  - Unbalanced 11;22 translocations
  - Mosaic trisomy 22
- Full trisomy symptoms:

Facial dysmorphism
- Thin upper lip
- Cranial / facial asymmetry
- Frontal bossing
- Depressed supraciliary region
- Occipital anomaly
- Sparse hair
- Hypertelorism
- Downslanting eyes
- Epicanthal folds
- Broad flat nasal bridge
- Broad nose, flat nose
- Occipital hypertelorism
- Long philtrum
- Webbed neck
- Micrognathia
- Hypertelorism
- Frontal bossing
- Bulbous nose
- Antimongoloid slant of the palpebral fissures
- Strabismus
- Large rotated protruding low-set auricles
- Goldenhar syndrome (facioauriculo-vertebral dysplasia)
- Low set ears
- Malformed ears
- Webbed neck