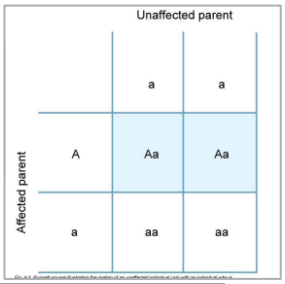
Genetics Summary (7-12)

By: Shahd Alahmad & ChatGPT

Lecture 7 : Autosomal Dominant Inheritance

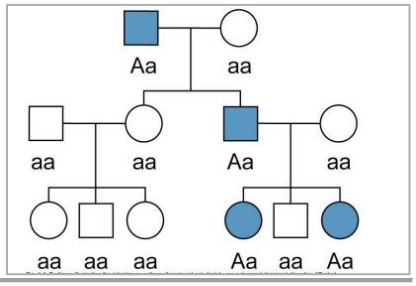
🧬 AUTOSOMAL DOMINANT INHERITANCE

Feature	Description
Total Known Traits	Over 4,400 traits (most of these diseases are rare ones)
Frequency (rare)	Most common dominant traits have a gene frequency ~0.001
Inheritance	One mutant allele is sufficient to cause disease
Typical Mating Pattern	Affected heterozygote x Unaffected individual
Transmission Probability	50% chance per child to inherit the disease
Sex Distribution	Equal in males and females
Generational Pattern	No skipping , vertical transmission seen مهمة
Father-Son Transmission	observed (which rules out X-linked inheritance)
Homozygous Dominant	Very rare, usually more severe disease



🧬 Example: Postaxial Polydactyly

Alleles	Description
A	Gene for polydactyly (extra digits)
a	Normal allele
Inheritance	Autosomal dominant
Trait Visibility	Seen in both sexes equally



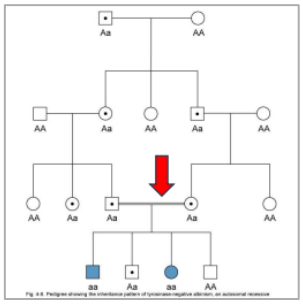
📊 Recurrence Risk (Autosomal Dominant)

Parent Genotype	Recurrence/Occurrence Risk
Heterozygous x Normal	1/2 (50%) per child
Each Birth	Independent event (such as coin toss experiment)

🧬 AUTOSOMAL RECESSIVE INHERITANCE

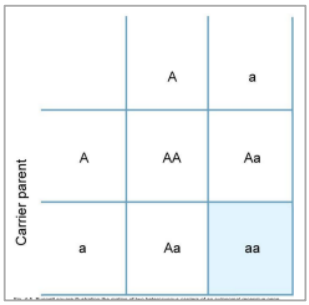
Feature	Description
Prevalence	Rare in populations, requires two carrier parents

Carrier Frequency	Carrier is More common than affected individuals
Affected Individual's Parents	Usually both are carriers
Inheritance Pattern	Horizontal (seen in siblings, not always in parents)
Generational Skipping	Common *imp*
Sex Ratio	Equal in males and females
Consanguinity	Often seen, especially in rare diseases *imp*
Example Diseases	Albinism, cystic fibrosis(common in Caucasians),thalassemia , sickle cell anemia(common in black American&africa)مهم



📊 Punnett Outcomes (Carrier x Carrier)

Outcome	Probability
Normal Homozygote (AA)	25%
Carrier Heterozygote (Aa)	50% (unaffected)
Affected Homozygote (aa)	25%



🧬 RECESSIVE SPECIAL CASES

Mating Type	Outcome
Carrier x Affected	50% affected, 50% carriers (quasi-dominant inheritance)
Affected x Affected	All offspring affected

📄 Comparison Table: Dominant vs Recessive

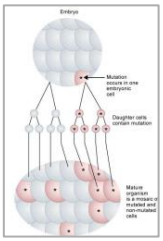
Attribute	Autosomal Dominant	Autosomal Recessive
Recurrence Risk	50%	25% (carrier x carrier)
Transmission Pattern	Vertical	Horizontal (not seen in earlier generations)
Generational Skipping	No	Yes
Sex Ratio	Equal	Equal
Consanguinity	Rare	Common (esp. in rare diseases)

🧪 COMPLICATING FACTORS:

1. New Mutation

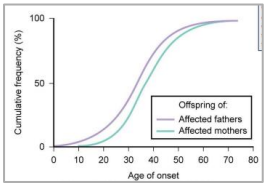
- No family history but affected child → mutation occurred in a parent's gamete
- Recurrence risk for siblings: general population level (not elevated)
- Offspring of affected child: elevated risk
- Example: Achondroplasia (7/8 due to new mutations)

2. Germline Mosaicism



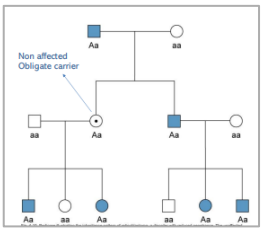
- Mutation in some germline cells, not somatic
- A parent can have multiple affected children despite appearing unaffected
- Seen in: DMD, Hemophilia A, Neurofibromatosis type I, Osteogenesis imperfecta II

3. Delayed Age of Onset



- Symptoms appear in adulthood (e.g Huntington's disease)
- Reduces natural selection, increases its frequency in population

4. Reduced Penetrance



- Individual has disease-causing genotype but no phenotype
- Still can pass disease to offspring
- Example: Retinoblastoma (90% penetrance).. check the pic →

5. Variable Expression

- Severity differs among individuals with the same genotype
- Example: Neurofibromatosis type I
- Causes: environment, modifier genes, mutation type (allelic heterogeneity)

6. Pleiotropy

- One gene affects multiple systems/organs
- Examples: Marfan syndrome(fibrillin mutation), cystic fibrosis, albinism, osteogenesis imperfecta

7. Locus Heterogeneity

- Same disease caused by mutations in different genes/loci
- Examples: APKD (PKD1 on chr 16, PKD2 on chr 4), Osteogenesis imperfecta (collagen chr 7 & 17)

8. Genomic Imprinting

- Phenotype depends on whether mutation is inherited from mother or father (due to differential activation of genes)
- Example: Deletion on chr 15 → Prader-Willi (paternal) or Angelman syndrome (maternal)

9. Anticipation & Repeat Expansion

- Disease appears earlier and more severe in successive generations

- Caused by repeat expansions (e.g myotonic dystrophy)
- 100 to several thousands repeats = severe form “full blown”

Lecture 8 : Sex-linked and Mitochondrial Inheritance

🧬 SEX-LINKED & MITOCHONDRIAL INHERITANCE

Topic	Details
Inheritance types	Sex-linked recessive and dominant (more applicable to females with 2 X chromosomes)
Severity in males	One X only → more severe disease if affected

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🧬 X vs. Y CHROMOSOMES:

X Chromosome	Y Chromosome
Large (group C)	Small (60 Mb)
~5% of nuclear DNA	Only a few dozen genes
≈1100 genes	Some homologous to X (helps in pairing)
-	Contains SRY, male fertility genes

⚡ MITOCHONDRIAL DNA

- More than a dozen diseases are now known to be caused by **mutations in mitochondrial DNA**.

🧠 X-INACTIVATION & LYON HYPOTHESIS

Concept	Details
Dosage imbalance	Female = 2X → more gene product than males, but this don’t really happen! (continue reading to understand)
🦁 **Lyon hypothesis**	One X is inactivated in each female somatic cell
Equalization	Same protein output in males & females = dosage compensation

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🧬 X-INACTIVATION MECHANISM

Process	Notes
Early embryogenesis	Random X inactivation (maternal or paternal)
Inactivation inheritance	Descendant cells (in cell division) keep same inactive X

Mosaicism in females	Females = 2 cell types (paternal-X active, maternal-X active)
Males	No mosaicism → only one X chromosome (always active)

🧪 BARR BODY

What is it?	Notes
Inactivated X chromosome	Appears as dark staining spot in interphase
Cell inheritance	Follows parental X inactivation pattern in all daughter cells *it means all its daughter cells will be also same X inactive*

🐭 ANIMAL & HUMAN EXAMPLES

Species	Phenomenon
Female mice	Heterozygous for X-linked coat color → dappled pattern
Calico cats	Orange & black patches (each = active X)
ocular albinism -Males	No mosaic → one color
Female: ocular albinism	Females show patchy retinal pigmentation

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🧪 BIOCHEMICAL & CYTOGENETIC EVIDENCE

- **G6PD Enzyme:**
  - Encoded on X chromosome
  - Equal expression in males/females due to inactivation
- **Heterozygous females:** express either A or B G6PD (bc she has different alleles)
- **Cytogenetics:** Barr body observed since 1940s

⚙️ MOLECULAR MECHANISM

Point	Details
Transcription	Only from active X in somatic cells
X-inactivation center	1-Mb region on long arm of X
Timing	Starts 7–10 days after fertilization
In placenta	Only paternal X is inactivated in extra-embryonic tissue

In germline	Reactivation needed to transmit both X chromosomes

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BARR BODY COUNT

Karyotype	Barr Bodies
XX (normal female)	1
XY (normal male)	0
XO (Turner)	0
XXY (Klinefelter)	1
XXX	2

Note: Extra X chromosomes ≠ full inactivation; some genes escape.

ESCAPED INACTIVATION

- **Inactivation is incomplete**
- Some regions remain active:
  - Short and long arm tips
  - *Short tip: homologous to Y
- ~15% of X-linked genes escape (for keeping equal dosage in males&females)
- Examples:
  - XG blood group gene
  - Kallmann syndrome gene

XIST GENE & EPIGENETIC MODIFICATIONS

Component	Role
XIST gene	Located at X-inactivation center; transcribed from inactive X
XIST RNA	17 kb, coats inactive X, **not translated**
Epigenetic changes	CG methylation, histone deacetylation

X-LINKED RECESSIVE INHERITANCE:

- Seen in **Hemophilia A, Duchenne muscular dystrophy, red-green color blindness**

- **Females:**
  - Homozygous affected
  - Heterozygous carriers
  - Homozygous normal
- **Males:**
  - normal
  - Affected if carrying mutation

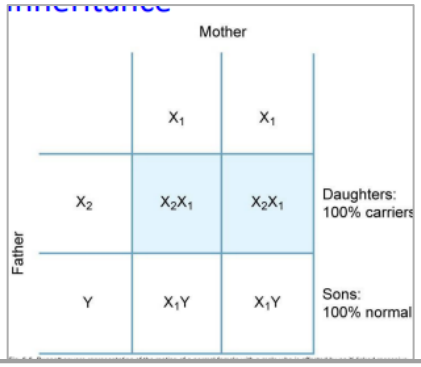
🔢 FREQUENCY & GENETIC RATIOS باختصار احتمالية اصابة الإناث أقل

Assume gene frequency = q
• Males: disease frequency = q
• Females: disease frequency = q^2
Example: Hemophilia A
- Males: 1 in 10,000
- Females: 1 in 100,000,000

👨‍👩‍👧 INHERITANCE PATTERNS

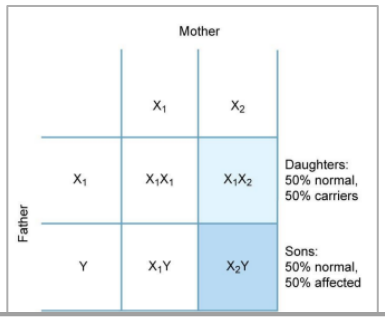
Affected Father (X_2Y) + Normal Mother (X_1X_1)

Offspring	Genotype
All daughters	X_1X_2 (carriers)
All sons	X_1Y (normal)



Carrier Mother (X_1X_2) + Normal Father (X_1Y) *frequent scenario*

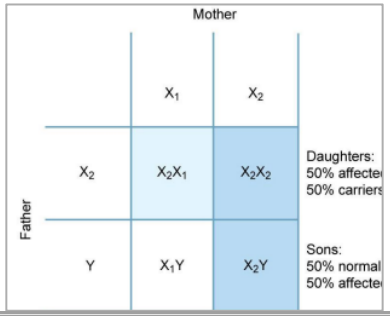
Offspring	Chance
50% sons	X_2Y (affected)
50% daughters	X_1X_2 (carriers)



Carrier Female (X_1X_2) + Affected Father (X_2Y)

Offspring	Outcome
50% daughters	Affected (X_2X_2)

50% daughters	Carrier (X_1X_2)
50% sons	Affected (X_2Y)
50% sons	Normal (X_1Y)



MANIFESTING HETEROZYGOTES

- Some female carriers may **show symptoms**
- Due to random X-inactivation (affected X remains active)
- Example: ~5% of female carriers of **Hemophilia A** show mild symptoms
- Also seen in **Turner syndrome females (X0),** but less commonly

Lecture 9 : X-Linked Dominant Inheritance

X-Linked Dominant Inheritance

• Fewer in number and prevalence than X-linked recessive

• **Hypophosphatemic rickets**: kidneys fail to reabsorb phosphate

• **Incontinentia pigmenti type 1**: skin pigmentation, missing/conical teeth, ocular & neuro abnormalities

→ Seen **only in females** (fatal in males , die after birth)

→ **Heterozygous females** = milder expression (homozygous is rare & more severe)

Rett Syndrome

• Neurodevelopmental disorder, seen in 1/10,000 to 1/15,000 females

• Mutation in **MECP2** gene (binds methylated CG sites near 5' end)

• Protein helps repress transcription of downstream genes

• Mutation → loss of repression → overexpression or misexpression of brain-related genes

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Pedigree & Transmission

• Pedigree appears similar to autosomal dominant

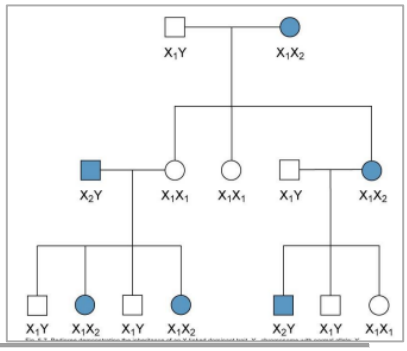
• A single copy of the mutant X causes disease

• **More common in females** (2 X chromosomes)

• Affected mothers → pass disease to sons and daughters

• Affected fathers → pass disease **only to daughters**

• Father affected → 50% chance to have normal male among all kids



📊 Table: X-Linked Dominant vs. X-Linked Recessive

Attribute	X-Linked Dominant	X-Linked Recessive
Heterozygous female × normal male	50% sons affected, 50% daughters affected	50% sons affected, 50% daughters carriers
Affected male × normal female	0% sons affected, 100% daughters affected	0% sons affected, 100% daughters carriers
Transmission pattern	Vertical (seen in every generation)	May skip generations via female carriers
Sex ratio	More females affected (unless lethal in males)	Mostly males; affected females are rare
Male-to-male transmission	Not seen	Not seen
Severity	Less severe in heterozygous females	Carrier females may manifest mild form

🧠 *Doctor emphasized this table: very important, memorize differences.*

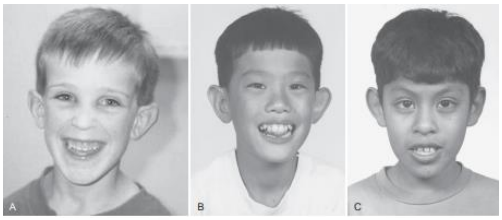
🧠 The Fragile X Story

• Most common inherited mental retardation (40% of X-linked cases)

• **Not Mendelian** inheritance: repeat expansion disorder

• Milder in females, more severe in males (~25% more severe)

• Features: long face, large ears, macroorchidism, hypermobile joints



• Seen in all ethnicities (European, Asian, Latin)

📸 Microscopy

• Fragile site on X becomes visible in folate-deficient media

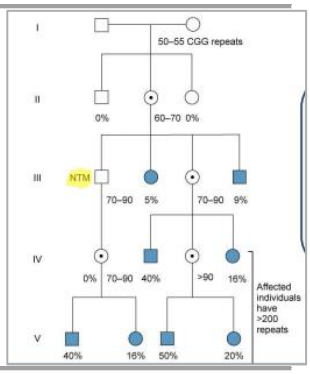
• Cytogenetic prep: culture lymphocytes, arrest at metaphase

• Fragile X = broken appearance near long arm tip

Fragile X Molecular Genetics

Feature	Details
Gene	FMR1 (Located on X chromosome, with CGG repeat in 5' untranslated region)
Normal Range	6–50 CGG repeats
Premutation	~50–230 repeats → "normal transmitting males" (unaffected)
Full Mutation	230–1000+ repeats → No FMR1 mRNA, severe disorder
Mutation Mechanism	Hypermethylation of CGG island → gene silencing
Effect	No production of FMRP protein (needed for neural development)

Transmission Pattern

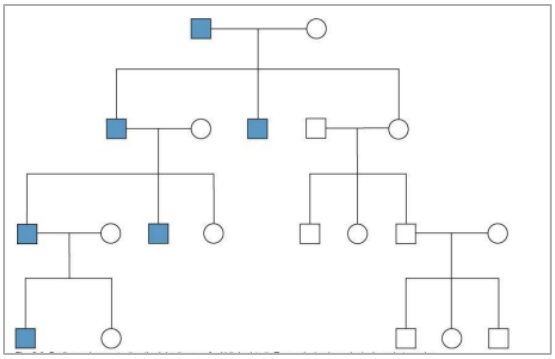


- Males with premutation = "normal transmitting males" (unaffected)
- Expansion occurs via **females,** leading to earlier onset (anticipation)
- **Degree of methylation** correlates with **severity** of the disorder

FRAXE (Secondary Fragile Site)

Feature	Details
Gene	FMR2
CGG Expansion	Occurs in the 5' region
Effect of Expansion	Hypermethylation leads to mental retardation
Inheritance Pattern	Repeat can expand from both **males and females**

Y-Linked Inheritance (Holandric)



- Y chromosome = smallest (≈60 Mb), few genes
- Contains:
  - **SRY** gene (sex determination)
  - **Azoospermia factors** (spermatogenesis)

- **HY antigen**

- Housekeeping genes (also present on X, escape inactivation)

• Inheritance is **strictly father to son**

Sex-Limited vs. Sex-Influenced Traits

Trait Type
Sex-Limited: Expressed in only one sex
E.g. uterine or testicular defects
Sex-Influenced: Present in both sexes, but varies
E.g **male-pattern baldness** (Autosomal , not X-linked)
- Autosomal dominant in males
- Autosomal recessive in females
- Female heterozygotes = carriers only (unless homozygous)

Mitochondrial Inheritance - Overview

• Mitochondria = oxidative phosphorylation → ATP

• Each cell = hundreds of mitochondria

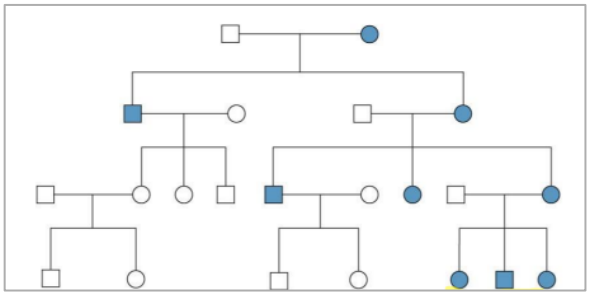
• mtDNA: 16,569 bp, **circular**, **no introns**, transcribed in mitochondria

• Encodes: 13 polypeptides + 2 rRNAs + 22 tRNAs

• Most proteins (~90) come from nuclear DNA

• mtDNA inherited **only maternally** (sperm mitochondria don't enter egg)

Mitochondrial Mutations & Heteroplasmy



Mutation Features

• mtDNA has 10× mutation rate
(no repair mechanism)

• Oxidative stress adds to mutation load

• **Heteroplasmy** = mixture of normal & mutant mtDNA in one cell

Mutation Features

• Disease severity = % of mutant mtDNA

• As cells divide, proportions shift due to:

- **Chance**

- **Selective replication advantage** (e.g. smaller mutated mtDNA replicates faster)

🧠 Organs Most Affected + Examples

• Tissues needing more ATP → affected more

• CNS consumes 20% of body ATP

• mtDNA mutation = CNS often hit first

🧬 Mitochondrial Disorders

Disease	Mutation Type	Features
LHON (Leber's Hereditary Optic Neuropathy)	Missense mutation	Vision loss (irreversible, age ~30s)
MERRF (Myoclonic epilepsy with ragged-red fibers)	tRNA mutation (single base mutation)	Epilepsy, ataxia, myopathy, highly variable (bc it's heteroplasmic)
MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)	tRNA mutation (single base mutation)	May cause deafness in 1–2%
Kearns-Sayre	Duplication&Deletions	Muscle weakness, cerebellar damage, heart failure
Pearson Syndrome	Duplication&Deletions	Pancreatic insufficiency, anemia, lactic acidosis
CPEO	Duplication&Deletions	(Chronic Progressive External Ophthalmoplegia)
Other suspected associations	—	Diabetes, Alzheimer's, aging

Lecture 10 : X-Linked Dominant Inheritance

🧬 Hemophilia A:

Section	Content
Overview	• X-linked recessive disorder • Most common severe bleeding disorder • Affects ~1 in 5,000 to 10,000 males
Cause	• Deficient/defective Factor VIII

Effect	• Impaired fibrin formation • Prolonged bleeding • Joint and muscle hemorrhage
Severity	• <1% = Severe • 1–5% = Moderate • 5–40% = Mild • ≥40% = Functionally normal
Genetics	• Gene on Xq arm • 186 kb, 26 exons • 9 kb mRNA → 2,332 amino acid protein
Mutations	• 45% severe = Inversion • 5% = Deletion • Nonsense = severe • Missense = mild
Treatment History	• 1960s: Plasma-derived Factor VIII • Risk: HIV, Hep B/C infections
Function of Factor VIII	1. Binds Factor IXa → activates Factor X 2. Factor X → converts prothrombin → thrombin 3. Thrombin → converts fibrinogen → fibrin
Interaction with vWF	• In plasma, Factor VIII binds vWF • Upon activation: detaches, becomes active two-chain form

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Hemophilia B (Christmas Disease)

Section	Content
Overview	• X-linked recessive • Less severe & less common than Hemophilia A (1/5th as frequent)
Cause	• Deficiency of Factor IX
Gene Info	• 34 kb, 8 exons • Gene cloned
Treatment	• Donor-derived Factor IX
Pedigree Example	• Queen Victoria = first documented carrier • Pattern: female carriers → affected sons

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Von Willebrand Disease

Section	Content

Type	• Autosomal dominant • Variable expression
Gene Location	• Chromosome 12
Protein Function	• Binds & stabilizes Factor VIII • Promotes platelet adhesion to damaged vessels
Mutation Impact	• Instability of Factor VIII • Half-life reduced to 8–12 hours • Hemophilia A–like symptoms

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Clinical Cytogenetics Overview

Section	Content
Definition	Study of chromosomes at cellular level
Abnormalities	• Numerical (e.g triploidy, tetraploidy) • Structural: deletion, duplication, inversion, translocation
Impact	• Major cause of pregnancy loss & intellectual disability • 50% of 1st trimester miscarriages • 20% of 2nd trimester miscarriages

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Cytogenetic Techniques

Step	Detail
1. Spindle Poisons	• Colchicine/colcemid stop cells in metaphase • Chromosomes visible & countable
2. Hypotonic Solution	• Cells swell → nucleus rupture → clear chromosome spread
3. Staining	• Differential banding (dark/light regions) • Unique for each chromosome
4. Karyotyping Process	1. Tissue collection (blood) 2. Culture (2–3 days) 3. Arrest (colchicine) 4. Hypotonic treatment 5. Fix/drop 6. Stain 7. Photograph/analyze

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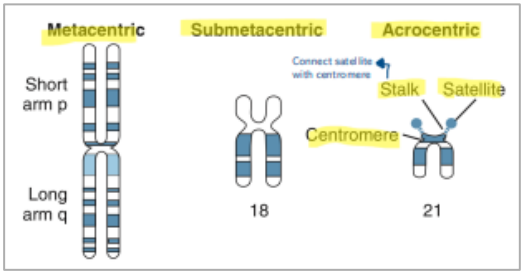
Karyotyping

Feature	Details
Manual	Cut/paste printed photos Pair chromosomes by size

Digital	Software arranges based on length/banding Results = Karyotype
Classification	• By size • Centromere position: (metacentric, submetacentric, acrocentric) → • Banding pattern
Notations	Example: 14q32.3 → Chr.14, long arm, region 3, band 2, sub-band 3



Banding Techniques

Method	Details
G-Banding	• Most common • Trypsin + Giemsa stain • Dark = AT-rich (additional info)
Q-Banding	• Fluorescent • Requires UV microscope
R-Banding	• Reverse of G-band • Dark = GC-rich (additional info)
C-Banding	• Stains centromeric heterochromatin
NOR Staining	• Nuclear organizer region, stains satellites
High-Resolution Banding	• Detects >800 bands • Early pro-metaphase chromosomes

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FISH – Fluorescence in Situ Hybridization

Step	Detail
1. Denaturation	Heat → ssDNA
2. Probe Hybridization	Complementary probe binds to specific region
3. Visualization	Fluorescence microscope shows binding site
Uses	• Detect deletions (e.g Prader-Willi, Smith-Magenis, Williiams) • Detect extra copies • Detect translocations
Advantages	• Doesn't require cell division • High resolution (~1Mb) • Used in IVF, prenatal, cancer diagnosis

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CGH – Comparative Genomic Hybridization

Step	Detail
1. Label DNA	Test = red, Control = green
2. Hybridize	Mix onto 1.metaphase chromosomes or 2.microarray
3. Analyze	• Yellow = normal • Red = duplication • Green = deletion
Resolution	• Metaphase CGH: 5–10 Mb • Array CGH: 50–100 kb
Limitation	Cannot detect **balanced rearrangements** (e.g. inversions, translocations), but SKY can do.

Chromosome Number Abnormalities

Type	Description
Euploidy	Normal multiples of 23 chromosomes (46 chromosmes)
Triploidy	69 chromosomes: caused by dispermy, fusion with polar body, meiotic failure
Tetraploidy	92 chromosomes: caused by mitotic failure or zygote fusion
Effect	• Excess gene dosage → severe CNS/heart malformations • Usually lethal, miscarriage or early neonatal death

Lecture 11 : Clinical cytogenetics

Aneuploidy Overview

Concept	Details
Aneuploidy	Abnormal number of individual chromosomes (45, 47...)
Monosomy	One copy of a chromosome (e.g. Monosomy X)
Trisomy	Extra copy of a chromosome (e.g. Trisomy 13, 18, 21)
Tolerance	Body tolerates excess material better than deletions مهم
Mechanism	Due to nondisjunction (failure of chromosomes to separate)

Trisomy 21 – Down Syndrome

Section	Points

Basics	• Trisomy 21 (47,XY,+21 or 47,XX,+21) • Named after John Langdon Down (1866) • Genetic basis discovered 1959
Facial Features	• Low nasal root , Upward slanting palpebral fissures • Small, overfolded ears, Flat forehead • Brachycephaly(short skull)
Other Signs	• Simian crease (50%) • Hypotonia
Epidemiology	• 1:800–1000 live births • Most common viable aneuploidy • Risk ↑ with maternal age >36 or <20
Medical Complications	1. Duodenal or esophageal atresia 2. ↑ Leukemia risk (15–20×) 3. 40% have AV canal heart defect • IQ 25–60 (10% of all mental retardation cases)
Survival & Fertility	• ↓ Survival due to heart defects • Males usually sterile • 40% of females fail to ovulate • 50% risk of transmitting 2 copies of Chr 21 in eggs
Causes	• 95% nondisjunction (75% in meiosis I) • 5% translocation • 90–95% maternal in origin
Mosaicism	• 2–4% of cases • Example: 47,XY,+21[10]/46,XY[10]
Dx	• Analyze 20 metaphase cells (to check Mosaicism) • Use FISH

Trisomy 18 – Edwards Syndrome

Section	Points
Karyotype	• Trisomy 18 (47,XY,+18)
Prevalence	• 1 in 6,000 live births • Most common chromosomal abnormality in stillbirths
Features	• Small ears • Short sternum • Short big toes • Facial abnormalities • Heart defects • Reduced birth weight
Mortality	• 50% die within weeks • Marked disabilities; most cannot walk
Cause	• >95% = full trisomy • 90% = maternal nondisjunction

Trisomy 13 – Patau Syndrome

Section	Points
Karyotype	• Trisomy 13 (47,XY,+13)
Incidence	• 1 in 10,000
Features	• Cleft lip/palate • Broad nose • Small eyes • Polydactyly
Prognosis	• 95% die within 1 year • Delayed development, some communication ability
Cause	• 80% full trisomy • Many due to translocation • Risk ↑ with maternal age • 95% spontaneously lost during pregnancy

Trisomies, Nondisjunction & Maternal Age

Topic	Details
Risk by Age	• <30y = <1/1000 • 35y = 1/400 • 40y = 1/100 • 45y = 1/25
Patterns	• Other trisomies ↑ with age • Older women less likely to abort trisomic fetus
Oocyte Age	• Oocyte is same age as mother • Risk accumulates with aging eggs
Key Note	• ¾ of Down syndrome births = mothers <35y • Bc most births are in this age group
Paternal Age	• Minimal effect (sperm renewed constantly)

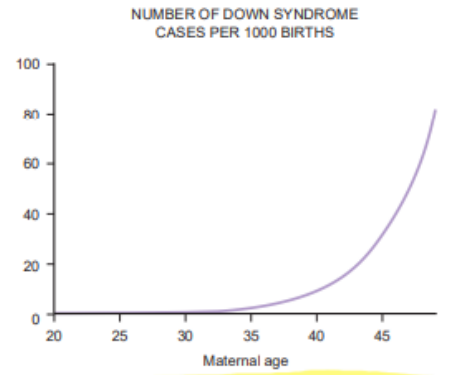

FIG 6-11 The prevalence of Down syndrome among live births in relation to age of the mother. The prevalence increases with maternal age and becomes especially notable after the age of 35 years. (Data from Hook EB, Chambers

Monosomy X – Turner Syndrome

Karyotype	(45,X) or (45,XO)
Features	1. Short stature 2. Ovarian dysgenesis (most are infertile) 3. Triangle face, webbed neck, shield chest • Heart & kidney defects • Normal intelligence
Growth	• ↓ Height by 20 cm • No adolescent growth spurt
Fertility	• Streak ovaries • Infertile • Require estrogen for secondary sex traits & bone health

Karyotype Stats	• 50% = 45,X • 30–40% = mosaic (45,X/46,XX or 45,X/46,XY أقل شيوعًا) • 10–20% = structural abnormalities in X chromosome
Origin	• 60–80% missing paternal X • >99% of 45,X pregnancies lost pre-natally

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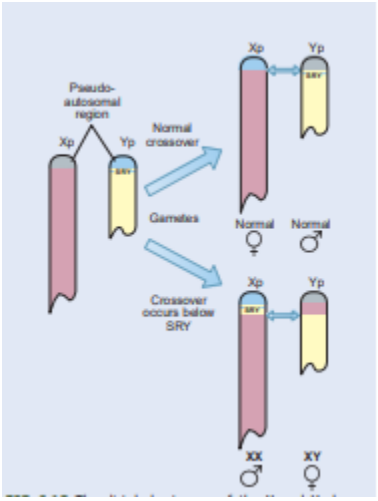
XX Male Syndrome



Section	Points
Karyotype	46,XX (phenotypically male)
Cause	• Translocation of SRY gene from Y to X during paternal meiosis
Features	• Normal male appearance • Small testes • Gynecomastia • Azoospermia • Normal testosterone levels • Absence of Müllerian structures
Note	• Not inherited (de novo event)

XY Female (Swyer Syndrome)

Karyotype	46,XY (phenotypically female)
Cause	• Deletion/mutation of SRY gene or genes downstream
Features	• Female phenotype • No secondary sexual characteristics • Streak gonads • Risk of gonadoblastoma
Note	• Often de novo mutation • Can be X-linked recessive if downstream of SRY

Klinefelter Syndrome (47,XXY)

Prevalence	1/500 – 1/1,000 males
Features	• Tall, long limbs • Sterile (small testes) • Gynecomastia (⅓) • ↓ Body hair, ↓ muscle mass • Slight ↓ IQ (10–15 points)
Inheritance	• 50% maternal origin • Risk ↑ with maternal age • 50% of conceptions spontaneously aborted • Viable sperm in mosaicism (15%)
Variants	• 48,XXXY / 49,XXXXY = More severe defects

Treatment	• Testosterone for secondary traits, ↓ osteoporosis risk

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Trisomy X (47,XXX)

Prevalence	**1/1,000 females**
Features	• Mostly benign • Sometimes: sterility, menstrual irregularity, mild MR • Fertility usually normal
Mechanism	• Due to maternal nondisjunction (90%) • Extra Xs → ↑ MR & physical defects

اللهم يا مهيء الظروف، خالق الأسباب، لك أمورنا كلها، فمكّنا مما نريد، وما نَحلم، وما نطمح، اللهم اكفنا شرّ الدنيا، شرّ الفقد، شرّ الفاجعة، شرّ أنفسنا، اللهم جمّل حالنا واجعله حالاً يرضيك ثم يرضينا، ربي أنت الميسّر وأنت المُسهّل سهّل أمرنا وحقق مطالبنا يارب يا كريم.

47,XYY Syndrome

Karyotype	**47,XYY**
Features	• Tall stature • ↓ IQ (10–15 points) • ↑ incidence in prison population (1/30) • Behavioral: ADHD, learning issues

Lecture 12 | Last Lec :) - Clinical cytogenetics:

Chromosome Structure Abnormalities

Type	Details
Unbalanced	• Deletion or duplication • Net gain/loss of genetic material • Usually results in severe genetic diseases
Balanced	• Exchange between two chromosomes • No net gain/loss • Carriers are usually unaffected
Causes	• Misalignment during meiosis • Chromosome breakage during mitosis/meiosis
Clastogens	• Ionizing radiation • Viral infections • Chemicals
Types	• Deletion • Duplication • Inversion • Translocation

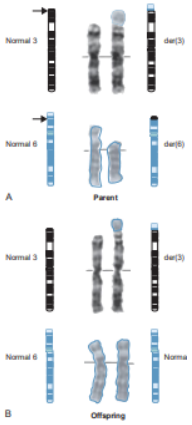
Translocations

Concept	**Points**

Definition	• Exchange of material between **nonhomologous chromosomes**
Prevalence	• Balanced: 1/500 to 1/1000 individuals
Types	• Reciprocal • Robertsonian

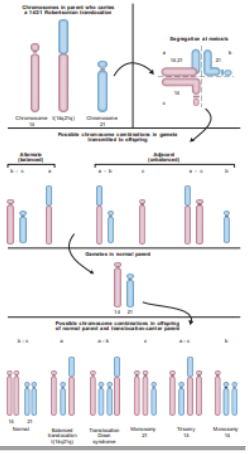
Reciprocal Translocations

Concept	Details
Mechanism	• Two chromosome breaks → mutual exchange • Resulting in **derivative chromosomes**
Phenotype	• Carriers are usually unaffected
Offspring Outcomes	1. **Normal karyotype** 2. **Balanced translocation carrier** 3. **Unbalanced translocation** → duplication/deletion → clinical effects



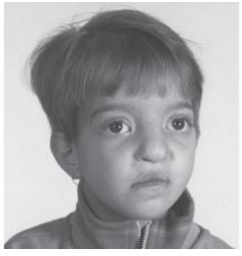
Robertsonian Translocations *more common than Reciprocal*

Concept	Details
Mechanism	• Fusion of long arms of acrocentric chromosomes (13, 14, 15, 21, 22) • Short arms lost (non-essential)
Phenotype	• 45 chromosomes • Complete genetic material → phenotypically normal
Example	• t(14;21)(q10;q10) Robertsonian Down syndrome
Outcomes **check the pic**	• Alternate segregation → normal or balanced carrier • Adjacent segregation → trisomy/monosomy (e.g translocation Down syndrome)



Deletions

Types	Details
Terminal	• Single break at chromosome end → Loss of distal part
Interstitial	• Two breaks within chromosome → Internal loss (interstitial)
Mechanism	• Smaller fragment lost • Visible under microscope
Clinical Impact	• Severe outcomes



This is a female patient diagnosed with Wolf-Hirschhorn syndrome, which is caused by a deletion on the short arm (p arm) of chromosome 4. Clinically, she presents with widely spaced eyes (hypertelorism) and abnormalities of the upper lip, (cleft lip).

Microdeletion Syndromes :

Microdeletions are caused by the presence of multiple repeated sequences, termed low-copy repeats (LCRs), at the deletion boundaries. These repeated sequences, even though present in low numbers, increase susceptibility to microdeletions.

These sequences promote unequal crossing over, which:

- **Produces duplications and**
- **Deletions of the region bounded by the repeat elements.**

Williams syndrome is given as an example of this mechanism.

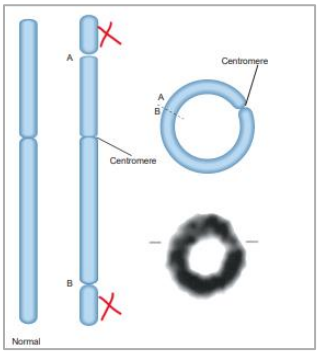
Syndrome	Deletion Region	Features
Cri-du-chat	5p deletion	Loss of part of short arm of chromosome 5 chromosome 5 (5p-) • Cat-like cry in infants • Microcephaly , mental retardaiton
Wolf–Hirschhorn	**Deletion on short arm of chromosome 4 (4p-)**	
Prader–Willi	15q11-13 (paternal)	Obesity, short stature, hypotonia, small feet, intellectual disability
Angelman	15q11-13 (maternal)	Intellectual disability, ataxia, seizures, laughter
Langer–Giedion	8q24	Sparse hair, exostoses
Miller–Dieker	17p13.3	Lissencephaly, cognitive disability
VCF/DiGeorge	22q11	Cleft palate, heart defects, thymus hypoplasia
Smith–Magenis	17p11.2	Self-injury, dysmorphic features
Williams	7q11	Aortic stenosis, development disability

Duplications

Concept	Details
Definition	• Partial trisomy: duplicated region
Causes	• Unequal crossover • Reciprocal Translocation parents' offspring
Example	• Charcot-Marie-Tooth: duplication in PMP22 gene
Clinical Impact	• Usually milder than deletions

Ring Chromosomes

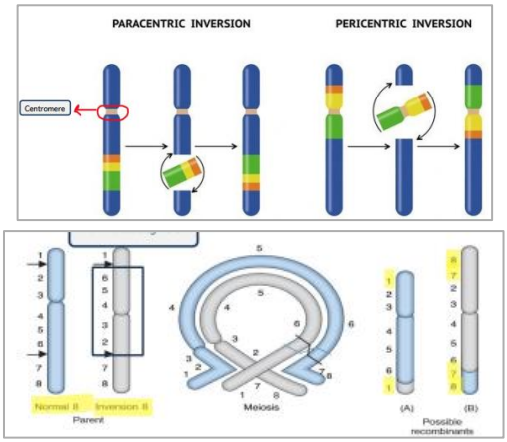
Mechanism	Details
Formation	• Terminal deletions (both tips) → sticky ends fuse
Example	• 46,X,r(X) female



Effects	• Loss → monosomy in some cells • Centromere presence = viability • Without centromere = instability

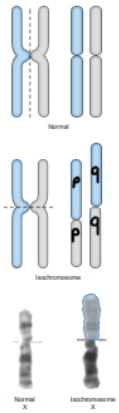
Inversions

Type	Details
Pericentric	• Includes centromere • Breaks on both arms
Paracentric	• Only one arm involved
Mechanism	• Segment flips and reinserts
Outcome	• Carriers = normal • Offspring may have duplication/deletion due to mispairing loop



Isochromosomes

Concept	Details
Mechanism	• Abnormal perpendicular division → 2 p-arms or 2 q-arms
Effects	• Most autosomes are lethal • Xq iso = Turner syndrome features • i(18q) = Edwards syndrome
Cancer Link	• Isochromosomes common in cancer



Cancer Cytogenetics

Concept	Details
Cause	• Somatic chromosomal rearrangements (not inherited)
Examples	1. **CML**: t(9;22) → BCR-ABL (Philadelphia chromosome) 2. **Burkitt lymphoma**: t(8;14) → MYC activation
Methods	• Spectral karyotyping • FISH • Chromosome analysis
Clinical Relevance	• Helps in dx , therapy choice, prognosis

Cancer-Linked Rearrangements

Cancer	Cytogenetic Change
CML	t(9;22)(q34;q11) Philadelphia
AML	t(8;21)(q22;q22)
Acute promyelocytic leukemia	t(15;17)(q22;q11–12)

ALL	t(12;21)(p13;q22)
Burkitt lymphoma	t(8;14)(q24;q32) – MYC oncogene
Neuroblastoma	N-MYC amplification
Breast cancer	HER2/NEU amplification

Chromosome Instability Syndromes

Syndrome	Details
Fanconi anemia	• High breakage with alkylating agents
Bloom syndrome	• ↑ Sister chromatid exchange
Ataxia telangiectasia	• Breakage under lab conditions
Xeroderma pigmentosum	• UV sensitivity
Shared Feature	• All are autosomal recessive • High cancer risk • Faulty DNA repair/replication

اللّٰهُمَّ إِنَّكَ عَفُوٌّ كَرِيمٌ تُحِبُّ الْعَفْوَ فَاعْفُ عَنَّا

The End