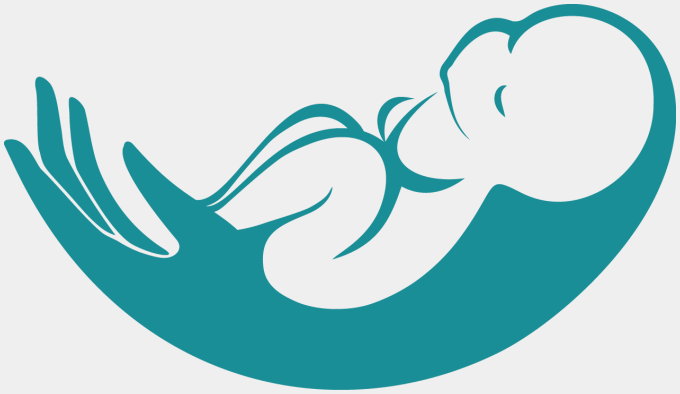


435 PEDIATRICS

Chromosomal & Genetic Disorders

Presented by: Dr. Malak Alghamdi | **Done by:** Lamya Alsaghan

Main References:

"You can use the slides for reference, there is a lot of extra material"

* Doctor's slides + notes (original slides here)

Extras:

"if you would like further reading"

* **Nelson Essentials of Paediatrics** 7th ed, sec 9 p. 146-163 (section here)
* **Illustrated Textbook of Paediatrics** 4th ed, ch 8 p.115-132 (chapter here)
* **Kaplan Lecture Notes** 2017 Pediatrics, ch 2 p. 19-27 (chapter here)

Objectives:

- Understand the basics of chromosomal structural & numerical abnormalities (including microdeletion).
- Recognize the pattern of mendelian inheritance.
- Understand the consequences of uniparental inheritance of chromosomes.
- Understand the concept of recurrence risk and its numerical assessment.

Table of contents:

Don't be deceived by the number of pages! It is just to be more organized!
Do NOT freak out! Take it step by step! Editing file (here)

Color index: [important | notes | extra | skipped]

Section 1

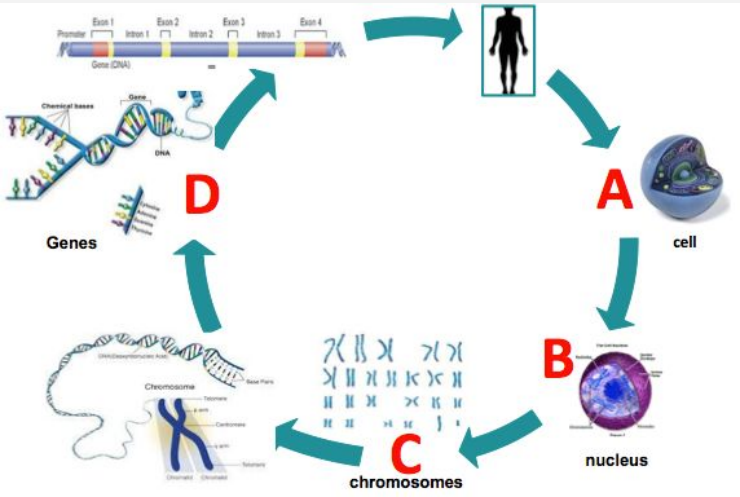
Basic Genetics

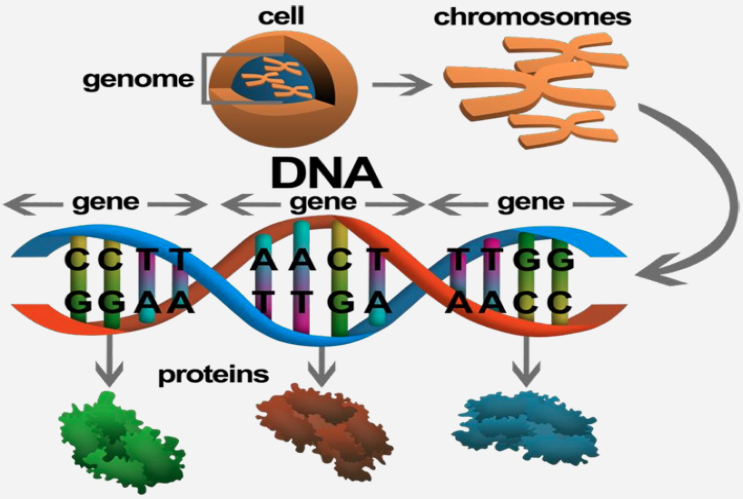
- ❇ Cell Biology & Structure.
- ❇ Mosaicism.
- ❇ Genomic Imprinting.
- ❇ X-Inactivation.
- ❇ Penetrance.
- ❇ Expressivity.
- ❇ Basis of Disease.
- ❇ Molecular Cytogenetics Techniques.

هذه الجزئية مجرد تمهيد للمحاضرة الأساسية, على كلام الدكتورة ما راح نُسأل عنها في الاختبار!
هي مجرد معلومات ومفاهيم أساسية لابد تكونون فاهمينها عشان تفهمون القادم!

Cell Biology & Structure

Stroll down memory lane: back to basics!





Inside the human body there are numerous cells, let's take one single cell **(A)** let's get deeper inside where we can see the nucleus **(B)** Even deeper where we can see the chromosomes [they are shaped and arranged randomly this is just at the karyotype level]; **(C)** Let's open one of the chromosomes in which we can take a closer look at the genes which encode the DNA. Genes have **exons** [coding material] and **introns** [regulatory function without coding material] **(D)**. **Genetic defects can be:**
- **Chromosomal** which occur at **(C)** level: chromosomes aneuploidy (different number) or different structures.
- **Monogenic** which occur at **(D)** level: different sequence, mutation [intronic or exonic], deletion, duplication.

You can see in the picture:
Genome within the cell (DNA) → nucleotide → protein production → protein function.

This is why one way of testing genes is to assess the protein function of that specific gene.

Side note: remember that karyotyping is just a picture of chromosomes it does not provide information about function.

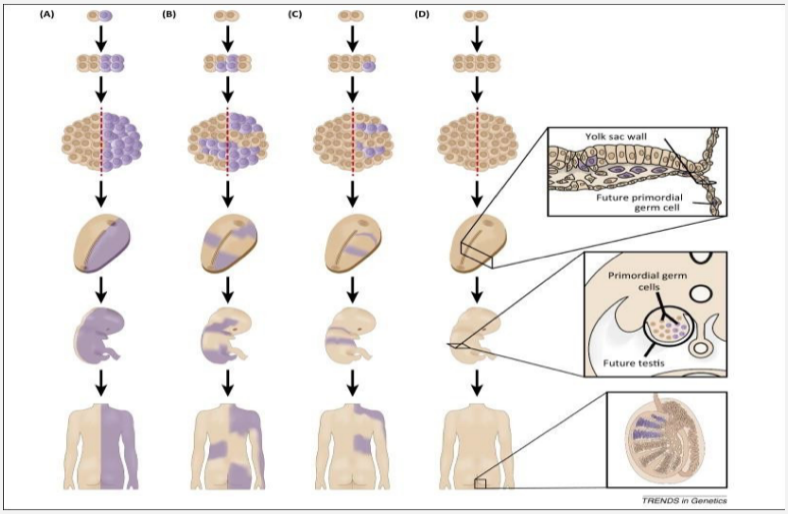
Mosaicism

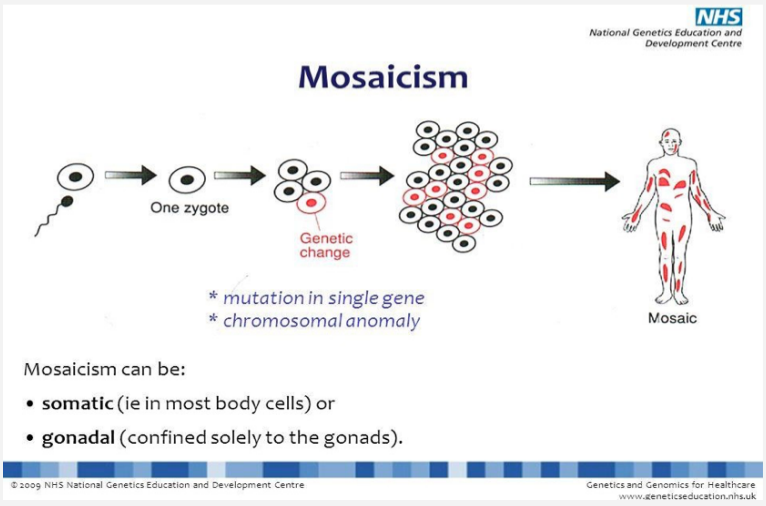
✻ Definition:

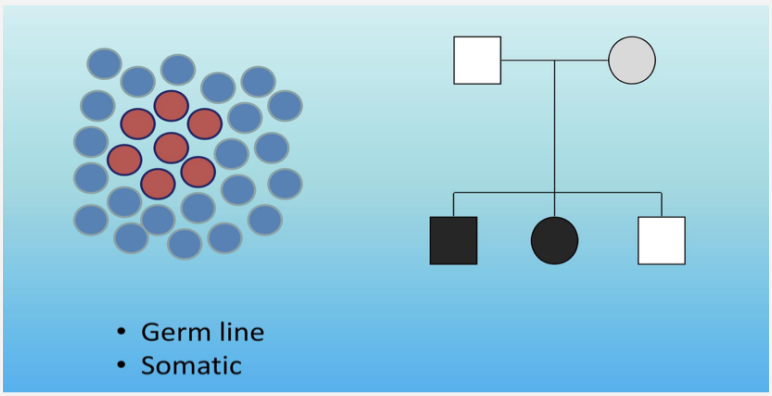
- Is the presence in an individual or a tissue of at least two cell lineages that differ genetically but are derived from a single zygote. Simply, a mixture of more than one line. During the division stage of one single zygote, one of the cells will be deviated (it will have abnormal mutations). After that, all subsequent cell lines (columns) will be abnormal. **For example:** when you get a biopsy from the affected and normal part of the skin, you can see two different cell lines or more. It can be segmental, involving half of the body, germ cell only, or other types like X-inactivation. (if it starts early it will affect a big portion of the body)

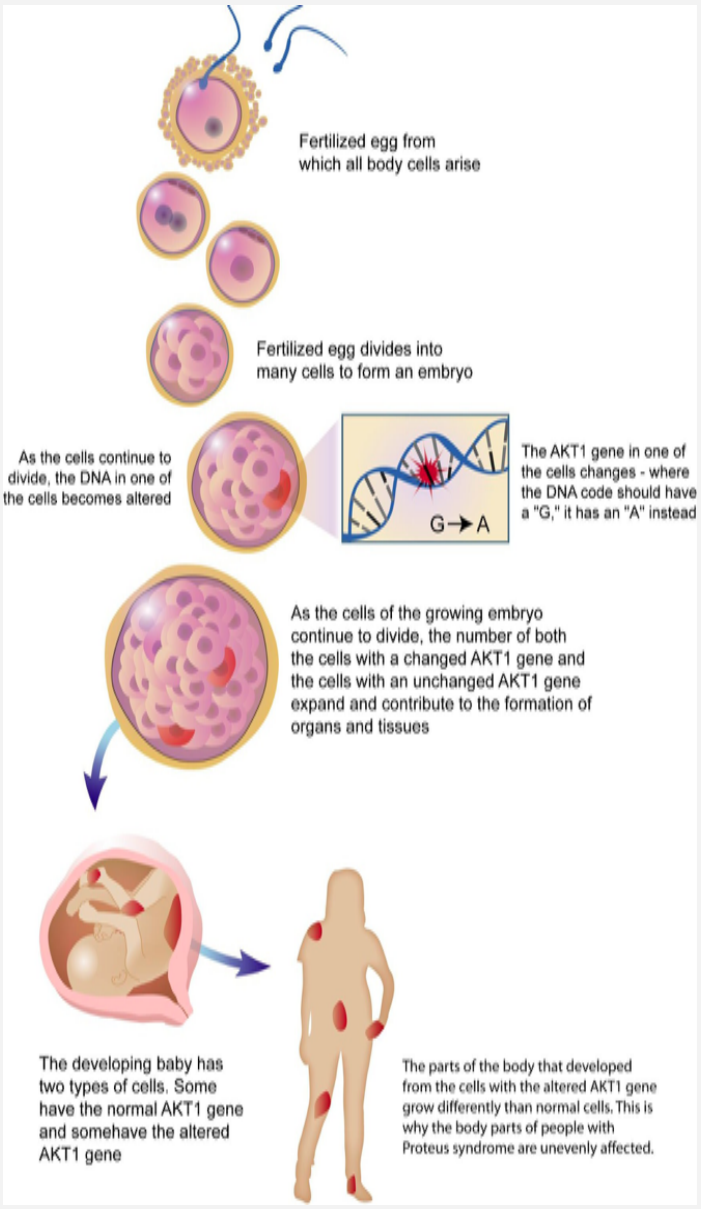
✻ Types: (not really types, those are just examples)

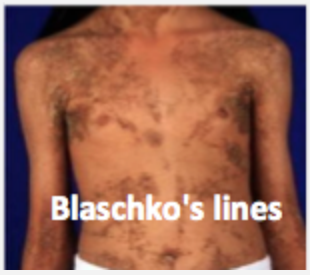
- **Pure confined placental mosaicism.** Placenta if abnormal BUT embryo is normal.
- **Pure somatic (segmental) mosaicism** (NO gonads). Ex. cancer, lines of Blaschko, Down syndrome: **mosaic down syndrome:** initially the genotype is normal (one normal set from each parent). However, mutation occurs [post-zygotically] It is a rare type and less severe than other forms of down syndrome.
- **Pure germline mosaicism.** Ex: osteogenesis imperfecta II (OI II), Turner syndrome, Duchenne muscular dystrophy (DMD) ex. If two siblings are affected by OI II (dominant disease) -which is very atypical- and both parents tested normal. It is most likely a defect (or mutation) in the gonads (sperms or eggs) [pre-zygotically].
- **Gonosomal mosaicism** (a mixture of gonadal and somatic). Ex. Neurofibromatosis type 2 (NF 2)

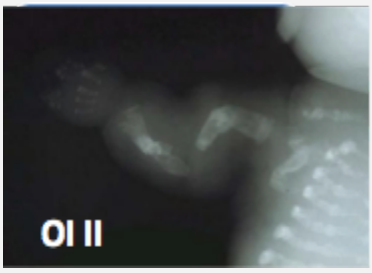

(A)
(B)
(C)
(D)
Yolk sac wall
Future primordial germ cell
Primordial germ cells
Future testis
TRENDS in Genetics


NHS
National Genetics Education and Development Centre
Mosaicism
One zygote
Genetic change
* mutation in single gene
* chromosomal anomaly
Mosaic
Mosaicism can be:
• somatic (ie in most body cells) or
• gonadal (confined solely to the gonads).
© 2009 NHS National Genetics Education and Development Centre
Genetics and Genomics for Healthcare
www.geneticseducation.nhs.uk

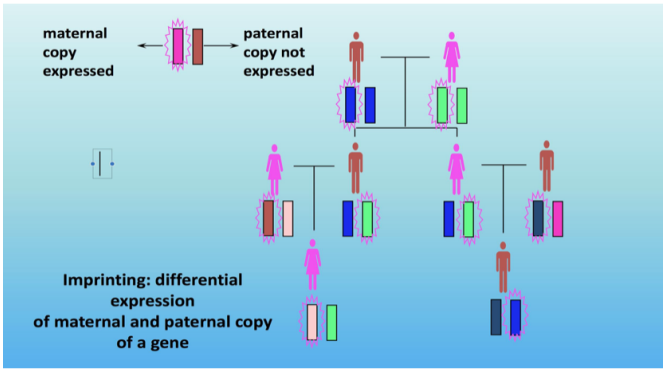

• Germ line
• Somatic

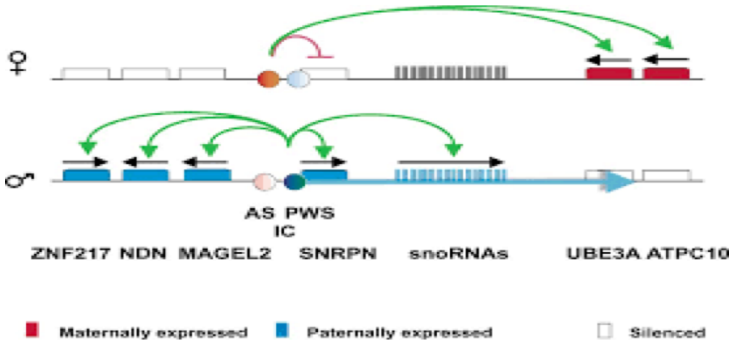

Fertilized egg from which all body cells arise
Fertilized egg divides into many cells to form an embryo
As the cells continue to divide, the DNA in one of the cells becomes altered
G→A
The AKT1 gene in one of the cells changes - where the DNA code should have a "G," it has an "A" instead
As the cells of the growing embryo continue to divide, the number of both the cells with a changed AKT1 gene and the cells with an unchanged AKT1 gene expand and contribute to the formation of organs and tissues
The developing baby has two types of cells. Some have the normal AKT1 gene and somehave the altered AKT1 gene
The parts of the body that developed from the cells with the altered AKT1 gene grow differently than normal cells. This is why the body parts of people with Proteus syndrome are unevenly affected.


Blaschko's lines


OI II

Genomic Imprinting



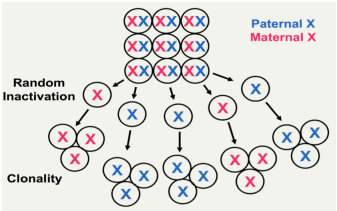


Which gene will be expressed? "Parents of origin difference"; some genes will be expressed from the mother and some from the father. For example, inactivated genes inherited from the mother but activated from the father. If the father's copy is lost; the patient will have the disease or show different phenotype. If the mother's copy is lost, we do not care because it was inactivated from the beginning.
Examples: Prader-Willi and Angelman syndrome.

- **Brief Overview:** (one set of the gene will be activated, the other methylated or silenced -not working at all-)
  - The expression of imprinted genes may be tissue and stage specific with one of the parental alleles being differentially expressed only at a certain developmental stage or in certain cells.
  - Imprinted genes show expression from only one member of the gene pair (allele) and their expression are determined by the parent during production of the gametes.
  - Imprinted genes represent a small subset of mammalian genes that are present but not imprinted in other vertebrates.
  - Genomic imprints are erased in both germlines and reset accordingly; thus, reversible depending on the parent of origin and leads to differential expression in the course of development.
  - **Uniparental disomy (UPD):** the patient will inherit both copies of the chromosome from one parent (not 50/50). So the patient will have the full set, shape, material and dose (balanced and normal). The problem arise when one of the genes get imprinted, meaning you need a copy from the mother because the other is not expressed.

X-Inactivation

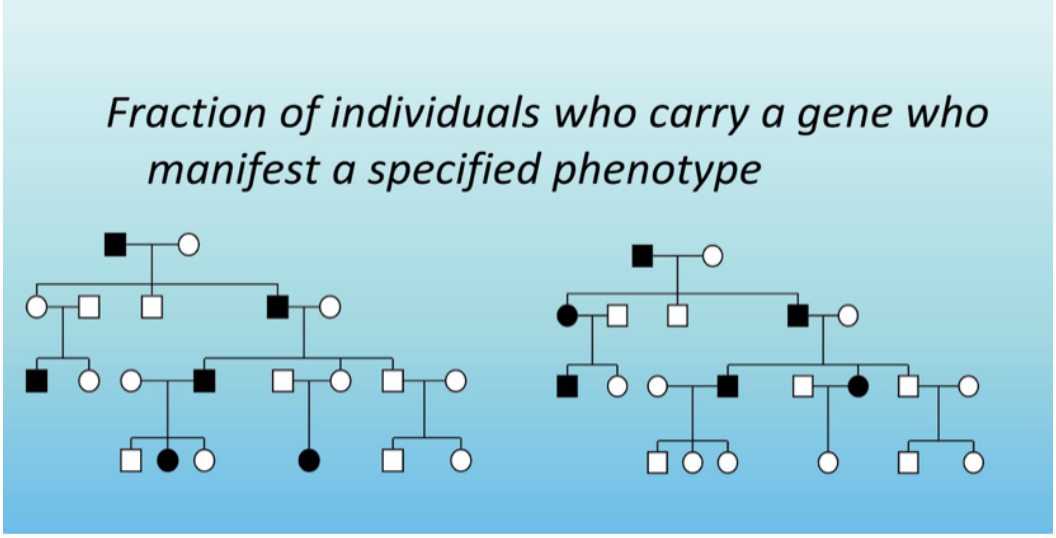
- **Definition:**
  - There are many important genes on the X chromosome. So, how can *males*, with only <u>one</u> X chromosome, and *females* with <u>two</u> chromosomes, not differ in the products encoded by most of these genes?! **Explained by X-inactivation resulting in dosage compensation.**



- **Lyon hypothesis:**
  - **X-inactivation occurs *early* in embryonic life:** ~2 weeks after fertilization, at several hundred cell stages. Note that the inactive X must become reactivated in the female's germ line so that each egg can receive an active X chromosome.
  - **X-inactivation is *random*:** The inactive X may be either the paternal or the maternal X; with a mix of cells, females are mosaics for the X chromosome.
  - **X-inactivation is clonal:** After one X chromosome has become inactivated in a cell, all of that cell's descendants have the same inactive X. same as mosaicism

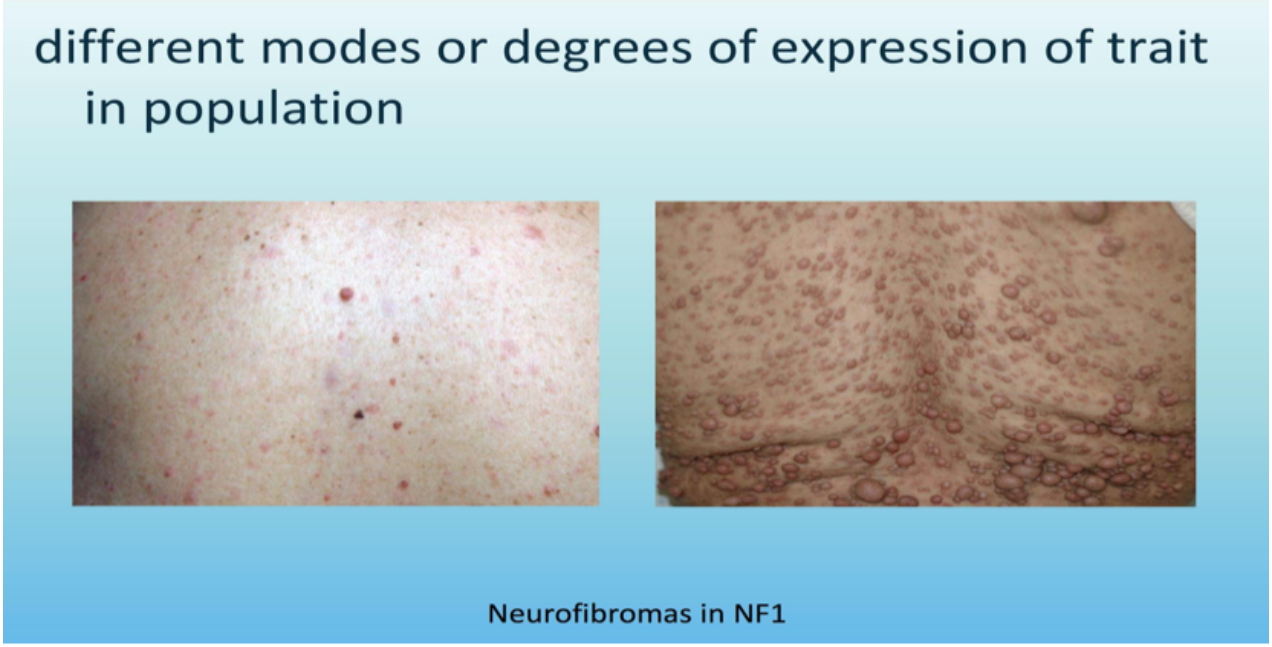
As females; we have one set of our X chromosome working and the other set is not working. Which is working and which is silenced? This is a random process, even within the tissue (some cells have the activated X chromosomes from the father, others are from the mother.) Bear in mind that not all genes of the inactivated X are silenced (about 15-20% are active genes.) If we have one abnormal X (trans-located for example), X-inactivation comes into play by silencing the abnormal and expressing the other normal set. This is a protective mechanism against X-linked diseases (patients will have no disease or mild phenotype) but it will be passed down to their offspring and their sons might get affected.
Side note: normally as females we inherit one set of chromosomes from our mother and the other from our father. Which one will be passed to our offspring? Early reprogramming during zygote developmental occurs so that both maternal copies are passed down to the next generation (it can be active or inactive copies) and the paternal copies will come from the male partner.

Penetrance



If one of the parents is a carrier and the patient is not showing the phenotype = **reduced penetrance**
When you test one of the parents you'll find they are a carrier (for NF as an example) but the patient is not expressing the phenotype.
It shows most with dominant diseases!

Expressivity



Basis of Disease

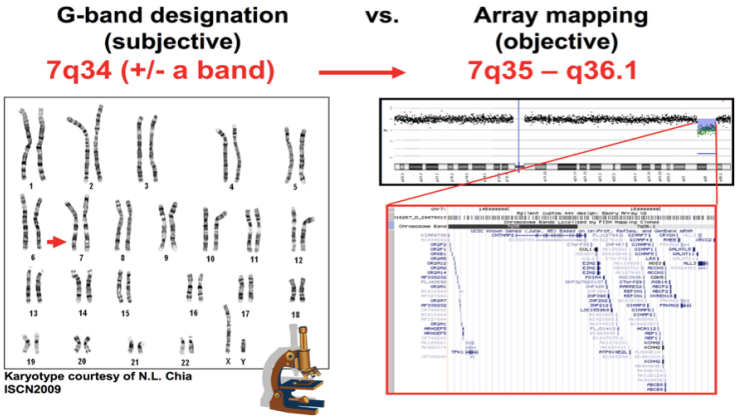
✻ Basis of disease:

- Chromosomal mutation;
  - Numerical.
  - Structural.
- Sub-chromosomal mutation (imbalance); segmental deletion, duplications. can be considered structural
- Single gene including dynamic mutation. missense, nonsense or frameshift mutations GO BACK TO BASICS!
- Imprinting disorders.
- Complex genetic. impossible to anticipate the cause of the disease (multifactorial; genetics play a role only.

With translocated genes, most of the time patients are normal because they have the full genomic material. Problems might arise during reproduction when the missing part of the translocated gene is passed to their offspring. For example part of the short arm of chromosome 14 went to the short arm of chromosome 21. During reproduction the missing or deficient gene from chromosome 14 will be passed down and disease might occur. (most men with transactions are infertile. Women will have recurrent abortions, abnormal babies with different phenotypes or anamolies)

Numerical chromosomal changes	Structural chromosomal changes	Chromosomal imbalances	Imprinting disorders	Monogenic disorders	Complex diseases
- Trisomy (3 sets of one chromosome) - Monosomies. - Triploidy (All chromosomes are of 3 sets) incompatible with life	**- Translocations** **- Inversions** (balanced or unbalanced.)	- Wolf-Hirschhorn. - Williams. - Cri-du-Chat. - Beckwith Wiedemann. - Smith-Magenis. - DiGeorge/VCFS.	- Angelman syndrome. - Prader willi syndrome. Mostly endocrine or neurological.	Mendelian diseases: AD/AR/X-LINKED	- Cancer. - DM. - Psychiatric illnesses. Ex. schizophrenia

Molecular Cytogenetics Techniques



Picture 1 (on your left): shows karyotyping (with Giemsa stain banding) of a male (46, XY) in wich there is a missing band in the long arm of chromosome 7 (7q34.) It is indicated to look for numerical & structural changes (like translocations) especially in patients with recurrent abortions, infertility and unexplained fetal or neonatal death (IUFD).

Picture 2 (on your right): shows chromosome microarray (a higher resolution of karyotyping). It will provide the exact dosage of a chromosome and at what point exactly. It is indicated in small (submicroscopic) deletions or duplications.

Other modalities: whole exome sequencing (WES), next generation sequencing (NGS), fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), quantitative real-time RT-PCR (RQ-PCR; qRTPCR).

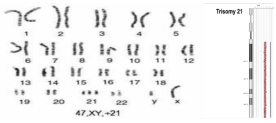
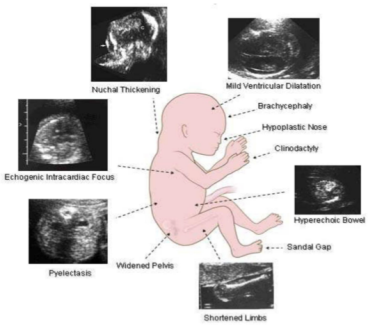
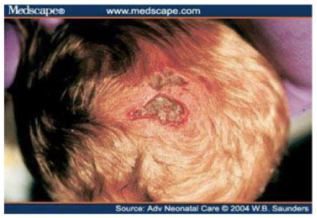
Section 2

Chromosomal Disorders

- **Trisomies:**
  Trisomy 21, Trisomy 18, Trisomy 13
- **X-Chromosome Abnormalities:**
  Turner Syndrome, Klinefelter Syndrome.
- **Microdeletions/Microduplications syndromes:**
  DiGeorge syndrome/VCFS, Cri Du Chat, Wolf-Hirschhorn syndrome.
- **Recurrent Genomic Disorders.**

Defects can occur in: autosomes, X chromosome or just an imbalance.

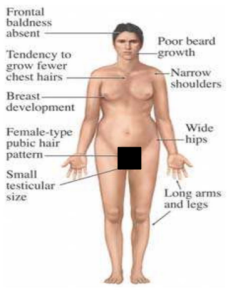
Trisomies

	Trisomy 21 (Down)	Trisomy 18 (Edwards)	Trisomy 13 (Patau)
Inheritance	**95% de novo**, 5% due to Robertsonian translocation or isochromosome 21	Less than 1% due to a **translocation**.	20% due to a translocation
Cytogenetic locus	(21.22.1-22.2) been called the critical region though there have been cases of duplication outside of this region.		
Disease mechanism	**Types:** nondisjunction; commonest, 90% due to **(MCQ) maternal meiosis at stage one** (¾ MI error, ¼ MII error). translocation and mosaic, post-zygotic.	Maternal nondisjunction (90%), mosaicism (10%).	75% (maternal nondisjunction), 20% (translocation) & 5% (mosaicism.) Defect in fusion of the midline prechordial mesoderm in the first three weeks of gestation cause the major midline dysmorphic features.
Clinical features & diagnostic criteria	Mild-mod intellectual disability (ID), hypotonia, growth delay, strabismus, adult cataracts, myopia, conductive HL, macroglossia, hypodontia, joint hyperflexibility, hypogenitalism, congenital heart defect, duodenal atresia, hirschsprung, thyroid disease, early onset Alzheimer's, transient myeloproliferation, ALL.	Clenched hand, fingers 2/5 overlap 3/4, IUGR, rocker bottom feet, micrognathia, prominent occiput, microphthalmia, VSD, ASD, PDA, generalized muscle spasm, renal anomalies, ID. Mosaic Tri 18 has variable but usually somewhat milder expression. Worst system affected is **cardiac**!	The least common of the live born trisomy disorders. Holoprosencephaly, polydactyly, seizures, HL, microcephaly, midline CL/P, omphalocele, cardiac and renal anomalies, ID. Mosaic Tri 13: very broad phenotype from typical features of full trisomy to more mild ID and physical features and longer survival. Worst system affected is **CNS**!
Clinical testing SCREENING "Non- invasive"	Prenatal US abnormalities detected in 50%, maternal serum screen: high beta HCG, low PAPP-A, estradiol, inhibin.	Echo, abdominal US. Maternal serum screen: low AFP, hCG, and UE3.	Brain MRI, EEG, audiogram, echo, renal US. some might not have structural changes but the function is abnormal.
Molecular tests SCREENING "Non- invasive" -read about it- & DIAGNOSTIC 1/200 ≠ amniocentesis	Maternal fetal free DNA testing (after 9 weeks of gestation), karyotype is the only diagnostic. If the risk is < 1/200 (b/c of risk of fetal loss estimated by US & biomarkers)→ go for amniocentesis or villous sampling. + PCR, CGH, FISH (cheap & quick)	Maternal fetal free DNA testing for screening. Karyotype is diagnostic. + Microarray + FISH	Karyotype is diagnostic.
Treatment prognosis	Supportive care, overall life expectancy is reduced.	50% die in the first week, 90% die by one year. This is why we can give the option of terminating the pregnancy!	44% die in the 1st month, >70% die in one year. Severe ID in all survivors.
Pictures	  Soft markers are seen (zoom in). Look for nuchal thickening (translucency) at 12w & anatomical US at 18-21w of gestation.	Overlapping digits or fisting  Rocker bottom 	 **Cutis Aplasia**  Celfting

X-Chromosome Abnormalities

✻ **Sex Chromosome abnormalities:** according to the doctor, the commonest are Turner & trisomy X

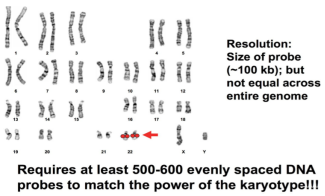
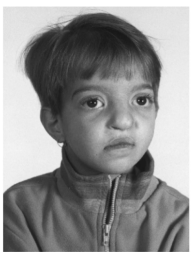
Karyotype	Incidence	Name
45, XO	1 / 3,000	Turner syndrome: short stature, infertility, webbed neck, shield chest, cardiac abnormalities, IQ is normal.
47, XXX	1 / 1,000	Trisomy X: subnormal IQ, tall & obese.
47, XXY	1 / 1,000	Klinefelter syndrome: tall, hypogonadism, subnormal IQ, infertility, gynecomastia, cholesterol defects & cancer.
47, XYY	1 / 1,500	47, XYY syndrome

	Turner syndrome (45, X)	Klinefelter syndrome (47, XXY)
Responsible gene & Proteins	X genes that escape inactivation, SHOX *SHOX: Short stature homeobox protein	
Cytogenetic locus	SHOX: Xpter-p22.32	
Inheritance	Sporadic	
Disease mechanism	SHOX: thought to act as a transcription regulator with many down-stream targets that modify growth and stature. SHOX protein has been id'ed in the growth plate from 12 weeks GA to late childhood.	1st or 2nd meiotic division nondisjunction of either parent. Maternal>paternal origin. +AMA effect
Clinical features & diagnostic criteria	Congenital lymphedema, growth failure), normal intelligence (10% sig delays), coarctation of the aorta, bicuspid aortic valve, HLHS, hyperlipidemia, gonadal dysgenesis (10% 45,X go into puberty), hypothyroidism, diabetes, strabismus, recurrent OM, SNHL, Crohns, renal malformation, osteoporosis. Some only suffer from infertility only. Mostly are completely independant and working in minor jobs.	Tall stature, slightly delayed motor and language skills, inc learning probs, testosterone plateaus age 14, small fibrosed testes, azoospermia and infertility, gynecomastia, inc cholesterol, slightly inc risk of autoimmune disorders and mediastinal germ cell tumors (1% risk)
Clinical testing	Echo, renal US, TFTs, GH testing.	
Molecular tests	Karyotype (monosomy X) + FISH SRY	At least one extra chromosome to a 46,XY karyotype.
Treatment prognosis	GH, HRT, gonadectomy if Y chromosome mosaicism (risk for gonadoblastoma). Need lifelong cardiac follow-up, at risk for aortic dilation and dissection with bicuspid aortic valve.	Testosterone in mid-late adolescence for bone density, secondary sex characteristic development, muscle mass, cholesterol, increase libido, improved energy. Can do testicular biopsy and use any retrieved sperm for ICSI (inc risk sex chrom abnormality so follow with PGD)
Pictures		

Side notes: any patient with extra set of chromosomes are at an increased risk of developing cancer!
The expected phenotype of a mosaic type of monosomy X (mixture of 45,X + 46, XY) is ambiguous genitalia. The patient will have the full male & female genital tract which needs to be corrected ASAP because it puts them at a higher risk for developing cancer!

Microdeletion/Microduplication Syndromes

- **Microdeletion/microduplication syndromes:** just read them in general: definition, how to test, common syndromes.
  - Complex phenotypes due to dosage imbalance of multiple, unrelated genes which happen to be contiguous on chromosome. In some cases, clinical syndrome defined before genetic basis known. You cannot give a specific defect. They have multiple anomalies!
  - Contiguous gene syndromes. Like set of adjacent genes deleted.
  - Segmental aneusomy syndromes. Abnormal number of the segment of chromosomes.
  - Genomic Disorders (subset mediated by segmental duplications – seg dup)
  - Mechanisms include: deletion, duplication, and uniparental disomy UPD = any deviation from normal, biparental inheritance. It is considered a chromosomal defect because it might be deleted or duplicated (missing the gene that should be activated)
  - You need to know how to counsel the patient's parents; explain the phenotype, pathophysiology, IQ and risk of recurrence.

	DiGeorge syndrome/ VCFS	Cri Du Chat	Wolf-Hirschhorn syndrome
Cytogenetic locus Responsible gene	del(22) (q11.2) q one one (band one one)	del(5) (p15.2) / 5p- /monosomy 5p RPS14?, microRNA 145 and 146a?	del(4p)
Inheritance	1 / 4,000 most common microdeletion syndrome.	12% due to unequal segregation of a translocation or recombination involving a pericentric inversion in one of the parents, 85% sporadic de novo deletions (80% are on the paternal chromosome). Most de novo, ~15% from balanced carrier parent	Most de novo, 10-15% from balanced carrier parents.
Disease mechanism		A study of 50 patients with deletions ranging from 5p15.2 to 5p13 and found no correlation with the size of deletion and degree of mental impairment.	
Clinical features & diagnostic criteria	Thymus hypo/aplasia → cellular immunodeficiency, parathyroid hypo/aplasia → hypocalcaemia, DD, ID, cardiovascular (conotruncal heart defects, aortic arch defects), **dysmorphic features** (micrognathia, ear anomalies cleft palate, short palpebral fissures, short upper lip) + IUGR	Microcephaly, Cat-like-cry (abnormal laryngeal development), slow growth, IUGR, microcephaly, ID, hypotonia, strabismus, heart defects, transverse palmer creases, characteristic facial features (round face, hypertelorism, micrognathia, epicanthal folds, down slanting palpebral fissures, low set ears). Cat-like cry only when deletion limited to band 5p 15.32	IUGR, hypotonia, microcephaly, severe ID, **dysmorphic features** (high forehead with prominent glabella, ocular hypertelorism, epicanthus, highly arched eyebrows, short philtrum and upper lip, downturned mouth, micrognathia, poorly formed ears with pits/tags, cleft lip/palate), scalp defect, hypospadias, heart defect, seizures, preauricular pit.
Molecular tests	It is a sub-chromosomal deletion. Not all will be detected with karyotyping → if normal go to microarray you'll find it.	Most are visible, a few are submicroscopic and diagnosed by FISH for the critical region or microarray.	Same.
Treatment prognosis		Supportive.	
Picture	 Requires at least 500-600 evenly spaced DNA probes to match the power of the karyotype!!!		 Don't skip the findings in the picture (zoom in)

Section 3

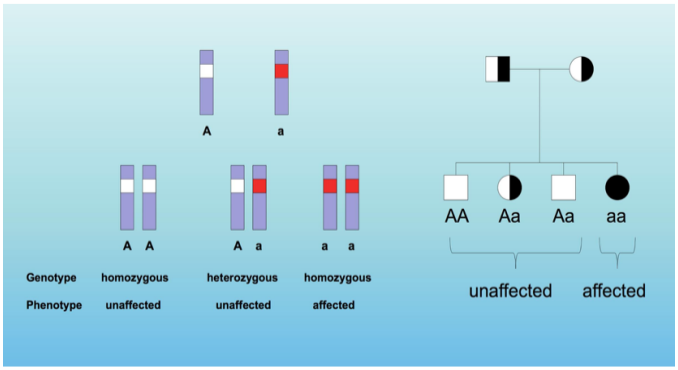
Monogenic Disorders

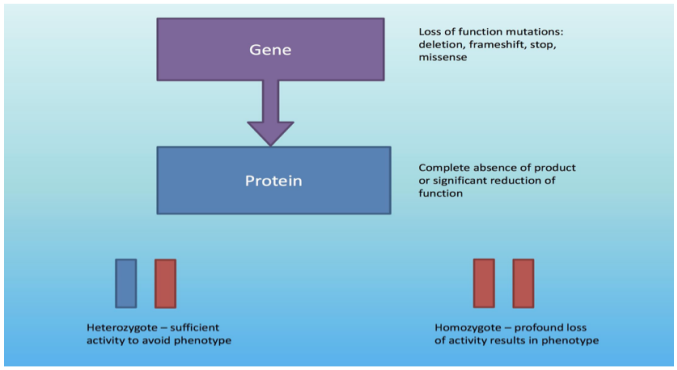
- Recognize patterns of Mendelian transmission
- Describe deviations from classical Mendelian transmission.
- Common examples of mendelian disorders.
  Autosomal recessive: Tay–Sachs disease
  Autosomal dominant: Neurofibromatosis type 1 (NF 1)
  X-linked recessive: Duchene & Becker muscular dystrophy.
  X-linked dominant: lethal in males
  Maternal inheritance: Leber hereditary optic neuropathy
- **Dynamic mutation:** Fragile X syndrome
- Genetic counseling & Consanguinity.

*Most of the questions will come from developmental and monogenic disorders.

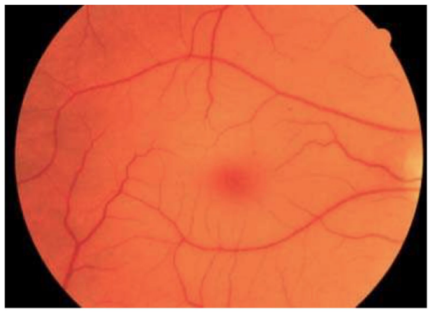
Monogenic disorders are also known as: single gene disorders or mendelian disease.

Autosomal Recessive

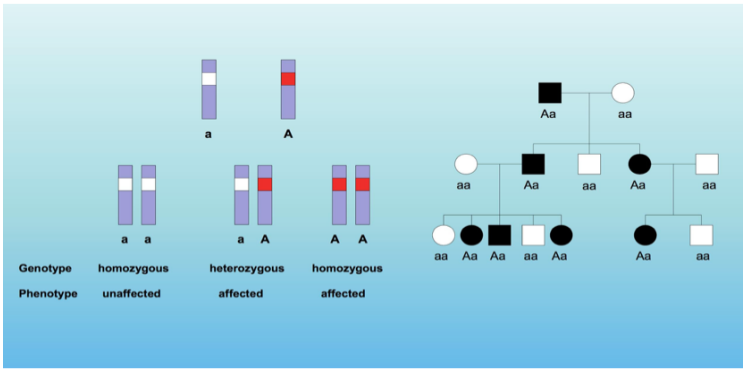


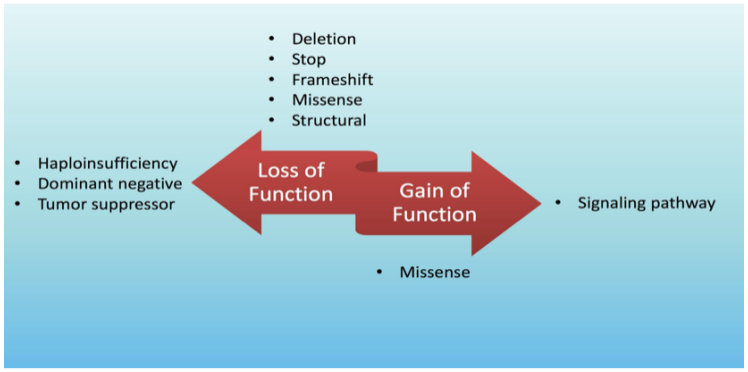


Risk: 25% affected. 25% normal. 50% carrier.
(both parents are carriers)

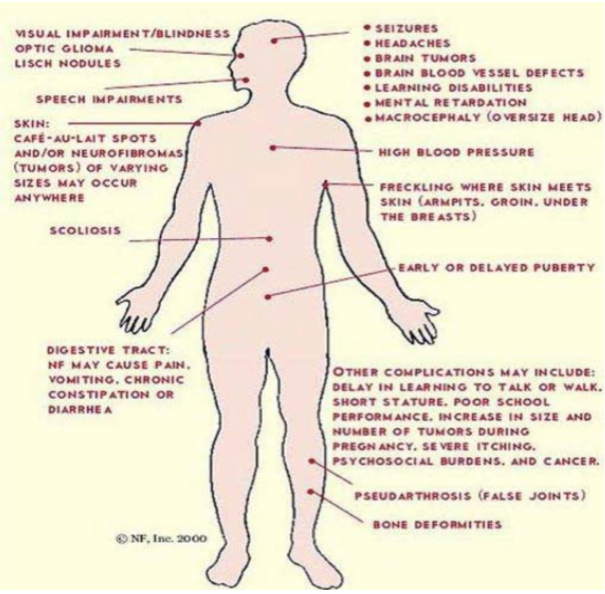
	Tay–Sachs disease
Responsible gene **Protein** **Cytogenetic locus**	HEXA Hexosaminidase A 15q23-q24
Inheritance	Autosomal recessive.
Disease mechanism	Accumulation of GM2 gangliosides in the brain.
Clinical features & diagnostic criteria	Infantile weakness starts at 6 mo, exaggerated startle, seizures and vision loss by the end of the first year, neurodegeneration continues-deaf, cannot swallow, weakening of muscles, and eventual paralysis, death in toddler years. Juvenile muscle coordination problems, seizures, and vision problems starting as young children. Chronic and adult onset start later, progress more slowly, more rare.
Clinical tests	HEXA enzyme activity, cherry red spot on eye exam. "Enzymatic defect or inborn error of metabolism"
Molecular tests	Follow enzyme testing with DNA testing (some with a positive enzyme assay have a pseudodeficiency allele that does not cause Tay Sachs). HEXA 6 common mutation panel: 92% of Ashkenazi Jewish
Treatment prognosis	Supportive only.
Picture	 **Cherry red spot of the macula** http://themedicalbiochemistrypage.org/images/cherryredspot.jpg

Autosomal Dominant

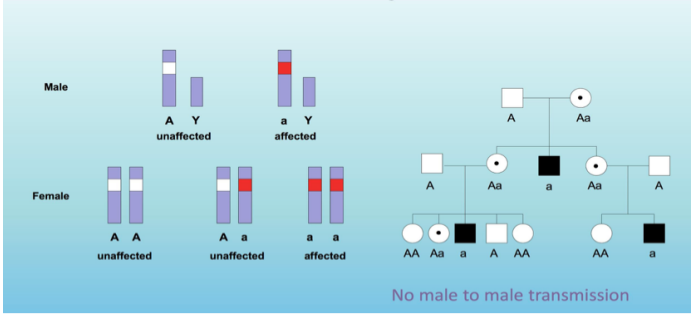
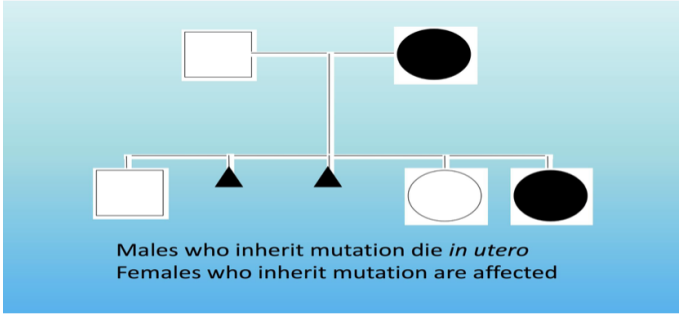


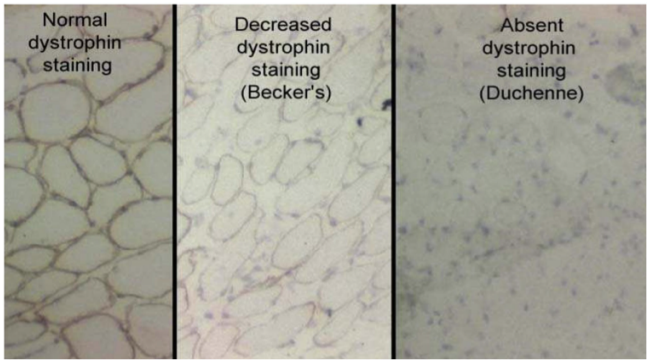


1 mutant allele is enough to express the phenotype

	Neurofibromatosis 1
Responsible gene **Protein** **Cytogenetic locus**	NF 1 Neurofibromin 17q11
Inheritance	Autosomal dominant.
Disease mechanism	Loss of function mutations impair ras GTPase mediated cellular proliferation and tumor suppression.
Clinical features & diagnostic criteria	2 or more of: 6x5mm (prepubertal) or 6x15mm (postpubertal) café au lait, 2 or more neurofibromas, one plexiform neurofibroma, axillary or inguinal freckling, optic glioma, 2 or more Lisch nodules, sphenoid dysplasia or thinned long bone cortex, 1st degree relative with NF-1.
Clinical tests	x-ray, eye exam, brain MRI.
Molecular tests	>500 mutations reported, usually unique to a particular family.
Treatment prognosis	The majority live normal lifespan. Surgery for bone malformations or painful or disfiguring tumors.
Picture	

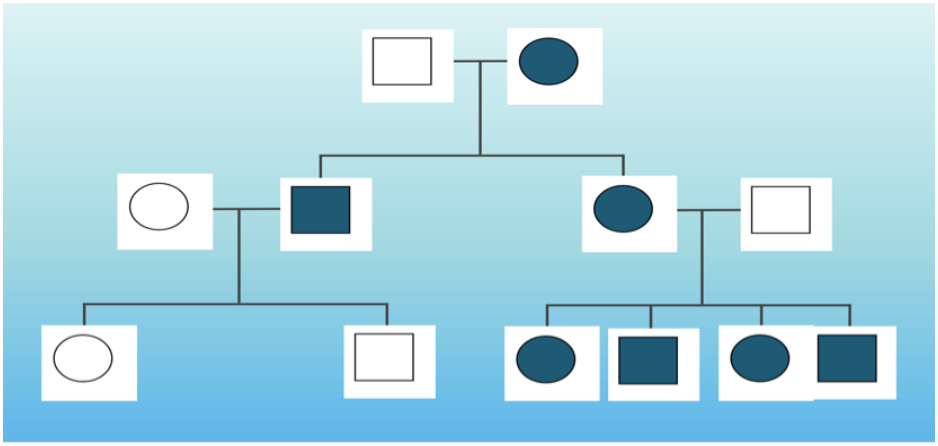
X-linked Inheritance

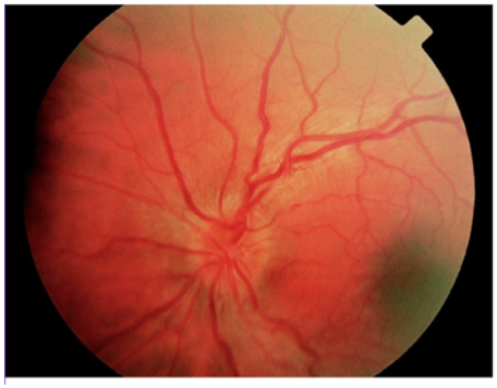
X-linked recessive	X-linked dominant
	

	Duchene and Becker muscular dystrophy (DMD, BMD)
Responsible gene Protein Cytogenetic locus	DMD Dystrophin Xp21.2
Inheritance	**X-linked recessive (XLR)**
Disease mechanism	Dystrophin binds actin and other membrane proteins. Mutations that lead to lack of dystrophin expression: DMD, those that lead to abnormal quality or quantity of dystrophin: BMD.
Clinical features & diagnostic criteria	**DMD:** Symptoms present before age 5, progressive symmetrical muscular weakness, proximal>distal, calf hypertrophy, dilated cardiomyopathy (DCM). **BMD**: Later onset, less severe, weakness of quadriceps may be only sign, activity induced cramping. Preservation of neck flexor muscles (unlike DMD). DCM can occur in isolation.
Clinical tests	CK 10x nl in DMD, 5x nl in BMD. Unreliable test for carrier females, tends to decrease with age.
Molecular tests	Multiplex PCR: DMD gene deletion (65% DMD, 85% BMD). Southern or quantitative PCR for gene duplication (6% DMD), DMD sequencing for small del/ins or point mutations (30% DMD).
Treatment prognosis	Supportive therapy, steroids may prolong walking 2-3 yrs. DMD: wheelchair dependent by age 13, ventilator by age 20, survival into 20's. BMiDs: Wheelchair after age 16 (if at all), survival 40-50's. Carrier females at risk for DCM.
Picture	

Females are protected because of lyonization phenomenon (or X-inactivation). However their offsprings might get affected with 50% of the males having the disease and 50% of the females being carriers! (Not all are expressed in males, and some females might be affected but with a milder phenotype)

Maternal Inheritance



	Leber hereditary optic neuropathy
Responsible gene Protein Cytogenetic locus	MTND1, MTND4, MTND5, MTNDO Complex I subunits of the mitochondrial respiratory chain Mitochondrial
Inheritance	Mitochondrial (maternal inheritance, sons and daughters will be affected but variable due to heteroplasmy (depending on the load of mutation phenotype might be shown)
Disease mechanism	Focal degeneration of the retinal ganglion cell layer and optic nerve.
Clinical features & diagnostic criteria	Blurred or clouded vision progressing to degeneration of the retinal nerve and then optic atrophy. Fundus: vascular tortuosity of central retinal vessels, circumpapillary telangiectatic macroangiopathy, and swelling of the retinal nerve fibers.
Clinical tests	Visual field assessments, ERG, VEP.
Molecular tests	Targeted mutation analysis: G11778A (70% cases), G3460A, T14484C (15%).
Treatment prognosis	No treatment available, worsened by smoking or EtOH.
Picture	 **Acute fundal appearance in Leber hereditary optic neuropathy showing disc hyperaemia, swelling of the parapapillary retinal nerve fibre layer and retinal vascular tortuosity.**

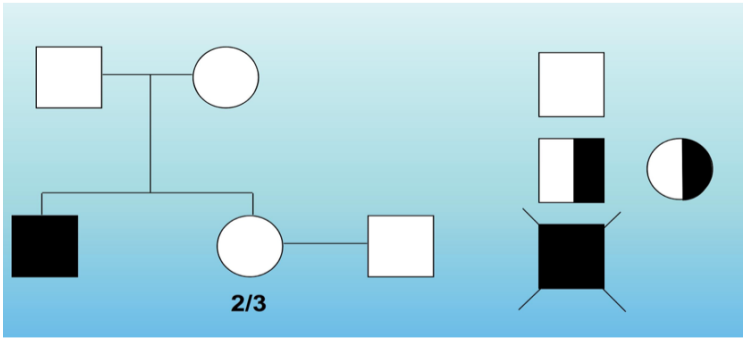
Dynamic Mutation

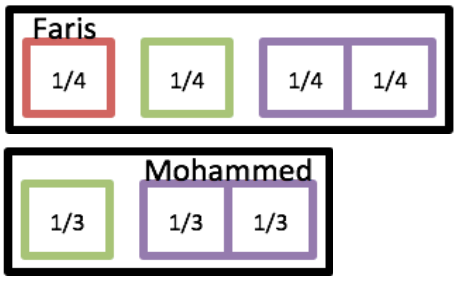
✻ Dynamic mutation (unstable repeat expansion):

- Dynamic mutation: that change from generation to generation.
- The expansion beyond the normal can alter gene expression and function.
- **Parental transmission bias:** anticipation occurs in the mutant allele transmitted through the affected father or mother. Like with X-lined expansion will happen from the mother while huntington disease expansion will be from the father.
- The expansion of premutation alleles occurs primarily in the female germline in FGXS but largest expansion causing juvenile onset HD in male germline.

	Fragile X syndrome
Responsible gene **Protein** **Cytogenetic locus**	FMR-1 FMRP (Fragile X Mental Retardation Protein) Xq27.3
Inheritance	X-linked triplet repeat
Disease mechanism	>200 repeats leads to silencing by methylation. POF and ataxia thought to be due to toxic gain of function.
Clinical features & diagnostic criteria	Delayed motor and verbal development, ID (mod-severe in boys, milder in girls), prominent jaw and forehead, long face and ears, high activity, autistic features. Carrier females: anxiety, OCD, depression, 20% have POF. Carrier Males: (>30% of males >50y), progressive intention tremor, ataxia, parkinsonism, and autonomic dysfunction. Two other loci: FraXE: only ID, FraXF: no phenotype.
Clinical tests	None.
Molecular tests	CGG triplet repeat detection. Southern Blot: good for small or large expansions, doesn't give repeat #. PCR: Better quantification of repeat number, subject to allele dropout with large expansions. NL: 5-44 repeats, Intermediate: 45-58 repeats (gray zone), Pre-mutation: 59-200 repeats, Mutation: >200 repeats.
Treatment prognosis	No specific treatment.
Picture	 **Facial Features:** **Long face,** **Prominent forehead** **Large ears** **Prominent jaw** (suzannebalvanz.blogspot.com/2007_07_01_archive.html)

Genetic Counseling



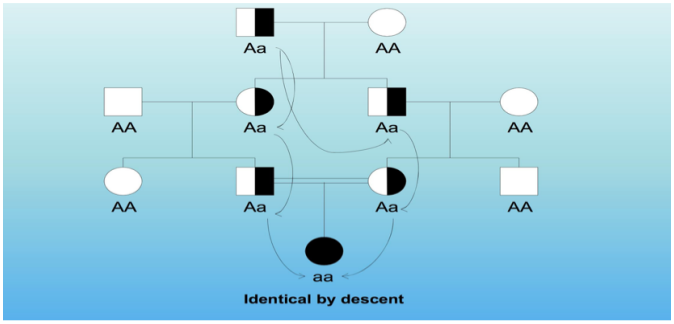


[**red**=affected. **green**=healthy. **carrier**=purple]

(MCQ): Mother of a son (Faris) with Tay–Sachs disease (or cystic fibrosis) asks you what is the risk of her other healthy son (Mohammed) of being a carrier because she is concerned about his future children? -both parents are carriers because it is a recessive disease-
Answer: 2/3. If she is asking about the chances of him being healthy (other question) it is 1/3.
What will you tell the mother about Mohammed? To not marry someone who is a carrier (or to avoid consanguinity) because there is a big chance he might be a carrier and their child will be affected.
When counseling about the affected child, you have to also address the recurrence of the disease, pathophysiology, cognitive outcome and independency (most concerns of the parents)

(MCQ): If both parents are normal, not affected with achondroplasia (or tuberous sclerosis, NF) which is a dominant disease, and their child is affected what will be your explanation? It might be de novo mutation or germ cell mutation. When counseling parents who test normal and their first child is affected most likely you do not have to do anything because the risk of recurrence if very rare (de novo). Unless there is germ cell mutation. However, when their second child get affected too this is not de novo, if you retest the parents you'll find that one of them is a carrier but with reduced penetrance or variable expressivity (very mild phenotype or even normal). [the doctor mentioned a real case scenario where a normal pregnant lady's baby was found to have an intracardiac mass (showing a phenotype) when they examined her further they found multiple kidney masses. She was later found to have tuberous sclerosis but with a very mild phenotype]

Consanguinity



Usual genotype of consanguinity is recessive, which is of two types:

1. **Compound heterozygosity:** AB (A= maternal, B= paternal): usually seen in western population with no consanguinity. A represents a mutation & B represents a different mutation but from the same gene.
2. **Homozygosity:** AA (A= maternal, B= maternal): usually seen in our population with consanguinity. A represents a mutation & the other A represents the same mutation (or variant) from the same gene.

Section 4

Developmental Genetics

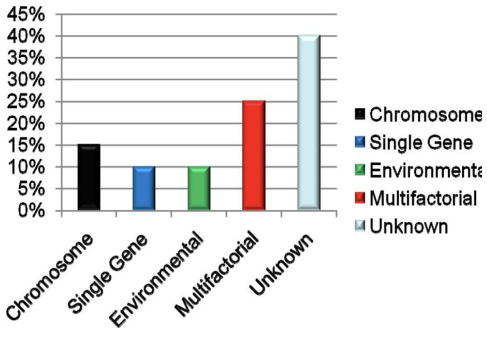
- **Dysmorphology & Congenital anomalies:**
  Deformation
  Disruption
  Malformation
  Dysplasia
- **Pleiotropy:**
  Syndromes: fetal alcohol syndrome.
  Sequences: Pierre Robin sequence
- **Imprinting disorders:**
  Prader Willi syndrome.
  Angelman syndrome.

*Most of the questions will come from developmental & monogenic disorders.

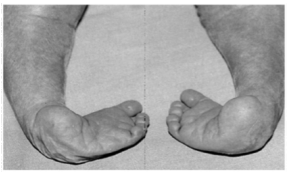
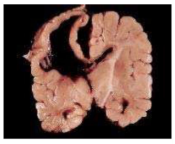
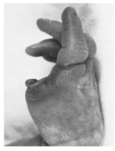
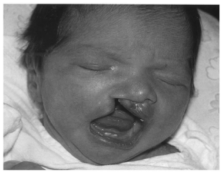
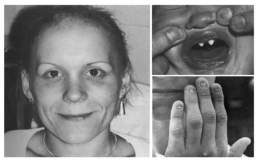
Congenital Anomalies

✻ Epidemiology DO NOT MEMORIZE IT

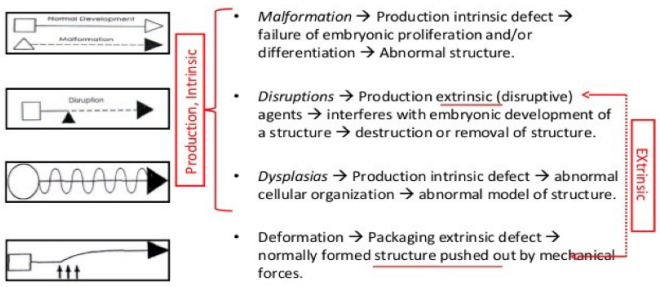
- 3% of all newborns Leading cause of neonatal morbidity and mortality 20% of infant deaths 10% NICU admissions, 25 35% of deaths Pediatrics admissions 25% to 30% have major birth defects.



Isolated Anomaly	Incidence per live births	Isolated Anomaly	Incidence per live births
Undescended testes	1:30	Hypospadias	1:1500
Heart defect	1:150	Polydactyly	1:1500
Club foot	1:300	Cleft palate	1:2000
Neural tube defects	1:1500	Craniosynostosis	1:2000
Cleft lip ± cleft palate	1:1000	Syndactyly	1:2000

	Deformation	Disruption	Malformation	Dysplasia
Developmental Process	Normal. Pregnancy is normal.	Normal, but interrupted Genes are normal	Morphological defect from an intrinsically abnormal developmental.	
Definition	Mechanical force alters structure**,** extrinsic factors impinging physical on the fetus during development usually second trimester. Most of them are reversible.	Destruction of irreplaceable normal fetal tissue → actual loss of tissue. (Vascular insufficiency , trauma, or teratogen.)	Malformation in one part is often but not always associated with malformation elsewhere. (irreversible) From beginning.	Abnormal tissue organization, microscopic structure.
Examples	- Maternal or fetal force - Oligohydramnios - Breech presentation - Bicornuate uterus	- Amniotic band sequence. - Fetal Cocaine exposure.	- Holoprosencephaly. - Congenital heart disease. - Neural tube defect. - Polydactyly.	- Skeletal or connective tissue dysplasia. - Ectodermal dysplasia.
Picture	 Clubbed feet • spina bifida	 Porencephaly  Amniotic Band	 Unilateral Cleft Lip and Palate	 Ectodermal Dysplasia

Diagramatic Sketch

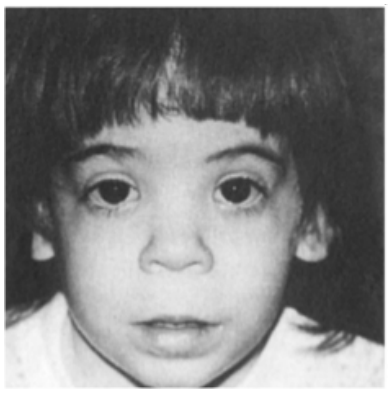
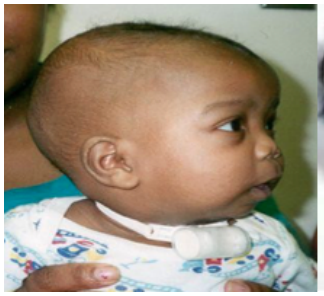
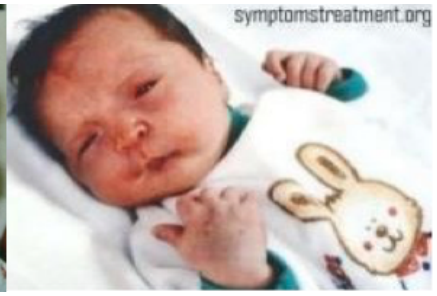


Malformation vs Disruption

Malformation → oligohydramnios → fetal deformation
Some can overlap; like urogenital *malformations* (abnormal bladder, posterior urethral valve) → oligohydramnios → *deformation*.

Vascular malformation → vascular insufficiency → disruption of distal structure

Pleiotropy: Syndrome & Sequence

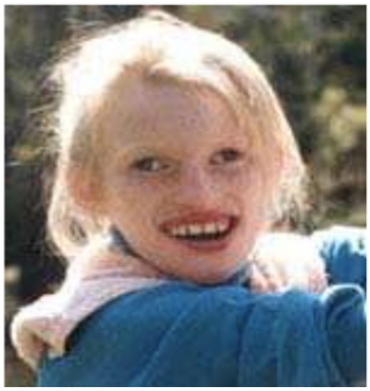
Syndrome	Sequence
- A birth defect resulting from a single underlying causative agent may result in abnormalities of more than one organ system in different parts of the embryo or in multiple structures that arise at different times during development. - Causative agents could be a gene or teratogen. Due to single agent. - When a causative agent causes multiple abnormalities in parallel.	Stepwise, something happened followed by another. - A recognizable pattern of anomalies presumed to be causally related. - Genetic: chromosomal, single gene. - Environmental: alcohol, retinoic acid. - Complex: more than one genetic and/or environmental factor. - Causative agent affects only a single organ at one point of time which then causes the rest of constellation of pleiotropic defect, secondary effect.
Single agent + different times	Multiple agents + single organ at one point in time
Fetal alcohol syndrome	**Pierre Robin sequence**
Growth retardation, mental retardation, Dysmorphic features: microcephaly, short palpebral fissures, short nose, smooth philtrum, thin upper lip, small distal phalanges, hypoplastic fingernails, cardiac defects.	Constellation of three, in sequence: 1. **Micrognathia**: (small jaw, U-shaped) primary anomaly. Maldevelopment or underdevelopment. 2. **Glossoptosis**: displacement of tongue in superior direction (protruding tongue due to inadequate room) 3. **Cleft palate.** * 50% syndromic: stickler (50%), del22q11 (25%), Treacher Collins Rib gap...
	 

You have to differentiate between syndrome, sequence and association!

Imprinting Disorders

SKIPPED

Disorder	Effect	Imprinted genes suspected or known to be affected	Expressed gene copy
Intrauterine growth			
Beckwith-Wiedemann syndrome	Fetal and postnatal overgrowth: excessively large organs; predisposition to tumours	- IGF2 (encoding a growth factor) - CDKN1C (encoding a cell-division regulator)	Paternal Maternal
Silver-Russell syndrome	Severe intrauterine growth restriction	Maternal uniparental disomy and duplications of chromosome 7	
Pre-eclampsia	Pregnancy-associated hypertension, often accompanied by intrauterine growth restriction	Linkage studies suggest involvement of maternally expressed imprinted genes in some families	
Behaviour & brain			
Prader-Willi syndrome	Moderate mental retardation; severe obesity; short stature; poor muscle tone.	Numerous imprinted genes on chromosome 15.	Paternal
Angelman syndrome	Severe motor and mental retardation; paroxysms of laughter, autistic-like behaviour.	UBE3A (encoding a protein-degradation regulator)	Maternal
Turner syndrome (monosomy X)	Affects females only: associated with a characteristic neurocognitive profile, short stature and Ovarian failure.	Enhanced social cognitive skills in patients inheriting the paternal, rather than maternal, X chromosome may indicate imprinting.	
Schizophrenia	Perceived distortions of reality; disturbance of thought and language; withdrawal from social contact.	Some forms of schizophrenia show a lower age of onset after paternal inheritance.	
Maternal behaviour defects (in mice)	Lack of maternal postnatal care of offspring.	- Peg3 (encodes a DNA-binding protein) - Peg1 (encodes an enzyme of the ab-hydrolase family)	Paternal Paternal
Hormones & metabolism			
Albright hereditary osteodystrophy	Short stature; round face; obesity; mental retardation: subcutaneous calcification.	GNAS (encodes a G-protein subunit)	Maternal (tissue specific)
Pseudohypoparathyro-idism 1A	As above, accompanied by resistance to parathyroid hormone and other hormones.	Occurs only on maternal transmission of inactivating GNAS mutations.	Maternal (tissue specific)
Transient neonatal diabetes mellitus	Pancreatic insufficiency and low secretion of insulin during fetal life; intrauterine growth restriction.	PLAGL1 (encodes a DNA-binding protein).	Paternal

	Prader Willi syndrome	Angelman syndrome
Responsible gene & Proteins	Paternally expressed genes (SNURF-SNRPN, MKRN3, MAGEL2, and NDN)	UBE3A Ubiquitin protein ligase E3A
Cytogenetic locus	15q11-13	15q11-q13
Inheritance	Autosomal, expressed from **paternal**. **MCQ: reasons of PWS:** - Deletion of the imprinting center. - Deletion of the whole paternal copy. - Maternal UPD.	Loss of the **maternally** imprinted contribution.
Disease mechanism	Unknown	Disruption of EGAP ultimately causes an abnormality in the ubiquitin protein degradation pathway, but no clear AScausing target protein yet identified.
Clinical features & diagnostic criteria	Hypothalamic insufficiency, neonatal hypotonia, developmental delay, hyperphagia leading to obesity, short stature, small hands and feet, hypogonadism, ID.	Severe developmental delay or ID, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability, microcephaly and seizures
Clinical testing		Acquired microcephaly by age two years, Seizures before age three, abnl EEG: large amp. slow-spike waves.
Molecular tests	3-5 Mb deletion of 15q11.2-q13 (~70%), matUPD (15%), PWS imprinting center defect (1-2%)	4-6 Mb del (65-75%), UBE3A mutation (11%), imprinting defect (2.5%), unbal chromosome transloc (<1%), Pat UPD 15 (<1%), del of imprinting center (0.5%)
Treatment & prognosis	Monitor for feeding problems in infancy, obesity, OCD, psychosis, scoliosis, obstructive sleep apnea, diabetes, osteopenia.	Typical care for medical issues, PT, OT, ST, and individualized education and behavior program.
Pictures		**Facial features:** **Protruding tongue** **Prognathia** **Wide mouth** **Widely spaced teeth** **Strabismus** **Light hair and eye color** 

Section 5

MCQs

1. **The Following are true about Turner's syndrome, EXCEPT:**
    A. Adult height < 150 cm.
    B. Coarctation of aorta.
    C. Cubitus varus of elbow.
    D. Horseshoe kidney.

Answer: C

- Turner's syndrome is due to functional monosomy of 'p'arm of X-chromosome.
- Clinical features:
    - Short stature (<150cms).
    - Sexual infantilism.
    - Bicuspid aortic valve CoA (Coarctation of Aorta).
    - Low hairline, webbed neck, widely placed nipples.
    - Horseshoe kidney
    - Cubitus **valgus** of the elbow.

2. **All are true regarding Trisomy 21, EXCEPT:**
    A. Chromosomal non-disjunction during maternal meiosis responsible for 80-90% of cases.
    B. Brush-field spots on iris.
    C. Epicanthal fold.
    D. Hypertonic at birth.

Answer: D

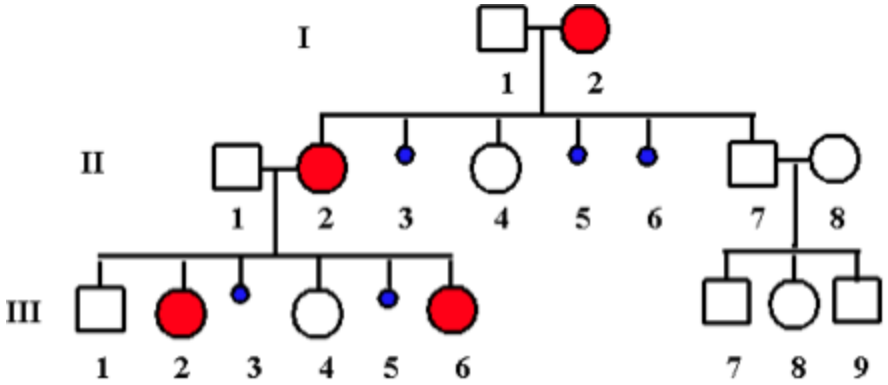
- 92% of Down's syndrome have trisomy with an extra 21 chromosome in all body cells. Chromosomal non-dysjunction during maternal meiosis is responsible for 90% of cases.
- Clinical features:
    - Mental retardation.
    - Epicanthal fold.
    - Upturned nose.
    - Brushfield iris.
    - **Hypotonia** at birth.

3. **In 1991, it was discovered that the fragile X syndrome was caused by a mutation in the fragile X mental retardation-1 (FMR-1) gene. An area of CGG trinucleotide repeats just upstream of the coding area was found to be variable in size. All the following statements regarding the FMR1 gene are true, EXCEPT:**
    A. "Pre-mutations" may expand to full mutations in future generations.
    B. Offspring of male carriers inherit a permutation.
    C. Offspring of female carriers may inherit a pre-mutation or a full mutation.
    D. Individuals with premutation are likely to have mental retardation.

Answer: D

- Several disorders have recently been found to be the result of expanding series of triplet repeats. **These include: the fragile X syndrome, myotonic dystrophy, and Huntington's disease.**
- Although the length of the region is variable in normal individuals, unaffected female carriers, and non-penetrant, transmitting males have "pre-mutations" which are generally 50 to 230 repeats in length.
- Individuals with pre-mutations are, therefore, phenotypically unaffected. Non-penetrant males transmit only unstable pre-mutations; female carriers may transmit either pre-mutations or full mutations, which are associated with mental retardation and the other phenotypic features of the syndrome.

4. **The pedigree described below is an example of what pattern of inheritance?**



Solid figure = Affected individuals | Open figure = Unaffected individuals

A. X-linked recessive inheritance.
B. X-linked dominant inheritance.
C. Autosomal recessive inheritance.
D. Autosomal dominant inheritance.

Answer: B

- The X-linked dominant inheritance pattern is characterized by having affected females in the heterozygous state.
- Affected females are twice as common as affected males, and the affected males are hemizygotes.
- In vitamin D-resistant rickets, both sexes are affected. However, the serum phosphate level is less depressed; hence, the rickets is less severe in the heterozygous female than in the hemizygous male.

5. **Chromosomal imbalance is most frequent during which of the following stages of human development?**

A. Embryonic.
B. Fetal.
C. Childhood.
D. Adult.

Answer: A

- Chromosomal aberrations occur in approximately 1 in 200 live born infants.
- Although the exact frequency of chromosomal anomalies in human embryos (i.e., <8 weeks' gestation) is unknown, the numbers above indicate a substantial frequency of at least 7.5 percent.

6. **Match the following:**

1. Heterozygote.	a. Two locus for different allele.	A. **1**→b, **2**→a, **3**→d.
2. Compound heterozygote.	b. One locus, one allele.	B. **1**→c, **2**→a, **3**→d.
3. Double heterozygote.	c. One locus, one normal, one mutant allele.	C. **1**→c, **2**→d, **3**→a.
	d. One locus, two different, mutant allele.	D. **1**→b, **2**→c, **3**→d.

Answer: C

- A heterozygote, or in the case of an autosomal recessive disorder, a carrier, has one normal allele and one mutant allele at a given locus.
- A compound heterozygote has two different mutant alleles at the same locus.
- A double heterozygote has one mutant allele at each of two different loci.

7. **On physical examination, the patient is noted to have some facial dysmorphism, including a long face, a prominent nose, and flattening in the malar region. In addition, the patient's speech has an unusual quality. Which description best explains the patient's condition?**
    A. Sequence.
    B. Syndrome.
    C. Disruption.
    D. Deformation.

Answer: B

- ❇ The child described in the question has multiple independent anomalies that are characteristic of a syndrome. Although they are likely to be causally related, they do not appear to be sequential.
- ❇ These problems do not appear to be caused by the breakdown of an originally normal developmental process as in a disruption, nor do they appear to be related to a non-disruptive mechanical force as in a deformation.

8. **Fluorescent in situ hybridization (FISH) analysis is useful in all the following situations, EXCEPT:**
    A. Determination of sex in cases of ambiguous genitalia.
    B. Determination of uniparental disomy.
    C. Rapid diagnosis of trisomies.
    D. Identification of submicroscopic deletions.

Answer: B

- ❇ The availability of specific molecular probes allows the use of fluorescent in situ hybridization (FISH) analysis for the evaluation of specific chromosomal regions known to be associated with specific genetic syndromes.
- ❇ Probes specific for the X and Y chromosomes are used in determining sex in cases of ambiguous genitalia.
- ❇ The identification of three signals for specific chromosomes allows for the diagnosis of trisomies much more rapidly than standard karyotypic analysis.
- ❇ Submicroscopic deletions can be detected using FISH probes.
- ❇ Because the parental origin of chromosomes cannot be determined with this technique, uniparental disomy cannot be detected.

9. **A male child presents to your clinic with a history of multiple pulmonary infections. The child's birth was complicated by meconium ileus. The child has had a recurrent cough with thick, difficult to mobilize, viscous sputum. There have been multiple episodes of recurrent pulmonary infections and abnormal chest X-rays. The child is also thin for his stated age and seems to be failing to thrive. Which of the following statements is correct concerning the mode of inheritance of this patient's disease?** -we could mention the diagnosis (CF)-
    A. Most patients will have an affected parent.
    B. Males are more commonly affected than females.
    C. The recurrent risk is 1 in 4 for each subsequent sibling.
    D. The trait is never transmitted directly from father to son.

Answer: C

- ❇ The patient's clinical syndrome is consistent with cystic fibrosis inherited as an autosomal recessive disorder.
- ❇ Characteristically the trait appears only in siblings and not in their parents, offspring, or other relatives.
- ❇ On average, one-fourth of the siblings are affected.
- ❇ In other words, the recurrence rate for each subsequent child is 1 in 4. The parents of the affected child may be consanguineous. Males and females are equally affected.

10. **Indications for genetic counselling include all of the following, EXCEPT:**
    A. Consanguinity.
    B. Family history of cystic fibrosis.
    C. Family history of congenital infection.
    D. Advanced maternal age.

Answer: C

- There are many indications for genetic counselling. **These include advanced maternal age, family history of birth defects or other known or suspected genetic disease, unexplained mental retardation, and consanguinity.**
- Although not technically a genetic problem, **teratogen exposure** is also generally accepted as an indication for genetic counseling.
- Although a history of congenital infection requires that medical information be given to the family, this is not a heritable disorder and, therefore, is not an indication for genetic counselling. However, should a pregnant woman herself contract an infection, such as rubella, which may be teratogenic, genetic counselling should be offered.

11. **A couple is referred to a physician because the first three pregnancies have ended in spontaneous abortion. Chromosomal analysis reveals that the wife has two cell lines in her blood, one with a missing X-chromosome (45, X) and the other normal (46, XX). Her chromosomal constitution can be described as:**
    A. Chimeric.
    B. Monoploid.
    C. Trisomic.
    D. Mosaic.

Answer: D

- The case described in the question represents one of the commoner chromosomal causes of reproductive failure, Turner's mosaicism.
- Turner's syndrome is often associated with a 45,X karyotype (monosomy X) in females, but mosaicism (i.e., two or more cell lines in the same individual with different karyotypes) is common.
- However, chimerism (i.e., two cell lines in an individual arising from different zygotes, such as fraternal twins who do not separate) is extremely rare.
- Trisomy refers to three copies of one chromosome; euploidy, to a normal chromosome number; and monoploidy, to one set of chromosomes (haploid in humans).
- Turner's syndrome represents a pattern of anomalies, including short stature, heart defects, and infertility.

12. **Which of the following are due to micro deletion, EXCEPT?**
    A. Beckwith-Wiedemann syndrome (or trisomy 13)
    B. Retinoblastoma.
    C. Prader-Willi syndrome.
    D. Angelman syndrome.

Answer: A

- Beckwith-Wiedemann syndrome is due to **microduplication on the 'p' arm of chromosome 11.**
- Microdeletion is seen in:
    - WAGR complex (11p13).
    - Retinoblastoma (13q14).
    - Prader-Willi syndrome (15q11).
    - Angelman syndrome (15q11).
    - DiGeorge syndrome (22q11).