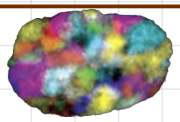
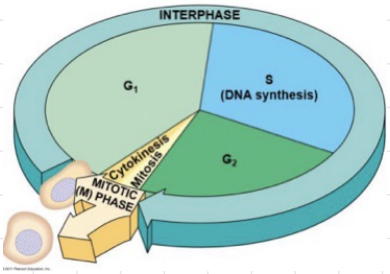
★Topic 1-1

- DNA molecule (double-stranded DNA)
  - Formation of chromosome :- DNA molecule is wrapped around histones (proteins).
    → Nucleosomes → arranged together → chromatin (thread like) → arranged in scaffold → chromatids → chromosome (2 identical chromatids).
    - DNA molecule + Histones → nucleosomes → chromatin → chromatids → chromosome.

- Interphase
  - S :- DNA replication, DNA polymerase + DNA to form daughter strands. form 2 sister chromatids
    - DNA Accessible :- Loose 3D structure & available for attachment. it's important for gene expression & protein synthesis (Transcription & Translation).
  - G :- Growth phase, ↑protein & ↑organelles, ↑size
    - (no clear shapes of chromosomes)

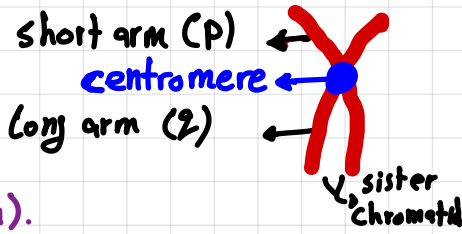
Before s phase 46 chromosome with 1 DNA molecule (ds) → 46 chromosome (2ds)





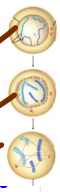
- M phase :- no Replicating, no expressing genes, form 2 daughter cells is the purpose. (normal shape)

- Nomenclature of chromosomes
  - chromosome shape
    - Metacentric :- centromere in the center II.
    - Submetacentric :- centromere is displaced from the center II.
    - Acrocentric :- centromere near the end II (Barely a p arm).
    - Telocentric :- pathological in humans II.
  - Autosomes :- 22 diploid
  - sex chromosomes :- 1 diploid



- each chromosome has 2 copies → Maternal (mother), paternal (father) → Homologous chromosomes.

- Mitosis :- produce identical daughter cells (46, identical sequence of DNA).
  - happens in :- fetus, newborn, Tissue repair, wound healing, proliferation of immune cells.



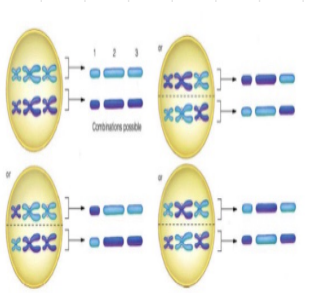
1. Prophase
   - Early prophase :- fragmentsy & disapperiy of nuclear envelope.
   - Late prophase :- two pairs of centrioles will migrate to opposite pole.
   - Transition to metaphase :- mitotic spindles comes out & hold onto every chromosome.
2. Metaphase :- chromosomes align individually on the plate, chromosome + spindle
3. Anaphase :- sister chromatids distain (opposite pole), 1 chromatid = chromosome
4. Telophase :- cytokinesis (cytoplasm cleavage) → 2 daughter nuclei appear

- Meiosis :- only in testes & ovaries to produce eggs & sperms (diffrent sequence of DNA, 23).
  - Meiosis I (reductional division) :- Homologus separation, ↓chromosomes number.
    - prophase I :- condense, nuclear envelope disappear, crossing over occurs, spindle fibers appear.
    - Metaphase I :- Homologus chromosomes align in pairs at the plate, attached to spindle fibers.
    - Anaphase I :- Homologus chromosomes will migrate to the opposite site of the cell (2 chromatid)
    - Telophase I :- cytokinesis → 2 daughter cells (carrying ½ number of chromosomes).
  - Meiosis II (equational division) :- sister chromatids separate.
    - prophase II :- chromosome + spindle fibers from opposite side.
    - Metaphase II :- chromosomes align individually along the plate.
    - Anaphase II :- sister chromatatids separate from each other.
    - Telophase II :- cytokinesis.
  - There is no interphase between meiosis I & II (Telophase I → prophase II).

- **Homologous chromosomes:-** 2 copies of each chromosome, one from each parent (maternal & paternal)
  - crossing over (recombination):- exchange of genetic material between non-sister chromatids of a pair of homologous chromosomes (prophase I).

- **Prophase I**
  - Leptotene:- initiation of chromatin condensation & Replicated chromosomes align.
  - Zygotene:- synapse → chiasma.
  - pachytene:- crossed over → Tetrads (4 chromatid / 2 homologus chromosome (non-sister)
  - Diplotene:- crossing over is done, Homolgus separate but remain close & bound to chiasma.
  - Diakinesis:- chromosome condensation occurs. (prepare to metaphase.

- **Genetic consequences of meiosis**
  - ↓ of chromosome number.
  - Diploid to haploid (essential for gametes).
  - Random assortment of maternal & paternal chromosomes.
  - Segregation of alleles.
  - Recombination/crossing-over



- **Gregor mendel rules**
  - Law of segregation (1):- on meiosis, the homologous chromosomes → gametes → diffrent cell. same genes, but not necessarily identical (Allele is diffrent)
  - Law of independent (2):- in meiosis 1, the chromosomes align in form of pairs (indepedently)
    - 2^n, n = 23 = 8.4 million spermatogenesis & 8.4 million oogenesis combinations.

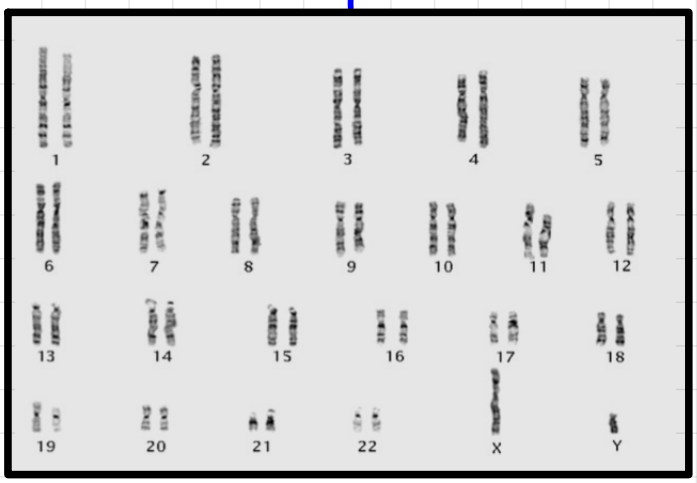
★Topic 1-2

- **We study cytogenetic:-** Because there are many clinical abnormalities happen due to chromosomes abnormalities, noted in
  - individuals having sex reversal or pubertal anomalies
  - spontaneous miscarriages.
  - couples having a history of multiple miscarriage.
  - the majority of cells from Leukemia samples or solid tumors.

- **Research uses for cytogenetic evaluation**
  - Localization of DNA onto a chromosome(s)
  - Determination of genomic complement.
  - characterization of genetic change(s).
  - Recognition of chromosomal changes following treatment(s) or in vitro culturing.

- **Tissue for chromosome studies:-** Depends on the type of the disease.
  - peripheral Blood (Lymphocytes):- Down.
  - Bone marrow:- Leukemia.
  - chorionic villi biopsy.
  - Amniotic fliud cells:- fetus.
  - skin or organ biopsy.

- **Karyogram:-** An ordered arrangment of the chromosomes from a cell placed in standard segencence (generally by length). as homologus pairs (1 maternally, 1 paternally), normal diploid chromosomes for humans are 46 (46xx, 46xy). visible at M phase (chromosomes are loose or decondenced in interphase), each chromoseme is made of 2 sister chromatids.

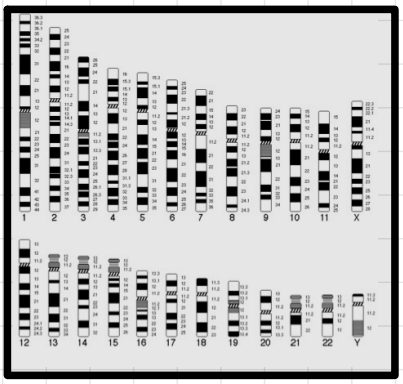


- **ideogram:-** is a diagrammatic representation of the Karyotype, (patterns of chromosome).
  - Types of Banding → G-banding (Giemsa)
    - R-banding (Reverse)
    - others:- C & Q & T & silver staining

1 G-Banding:- thymine – Adenine has 2 hydrogen Bounds while guanine-cytosine Has 3 3 hydrogen Bounds.

Standert

- Giemsa stain will Bound to AT rich areas (not GC rich)
  - AT rich:- Has Giemsa → Dark Bands (poor gene). (heterochromatic).
  - GC rich:- No Giemsa → Light Bands (Rich gene). (euchromatic).
- The method will normally produce 300-400 Bands.
- Firstly treated by trypsin (dijest some potein → relaxiy to chromatin → Giemsa dye access).



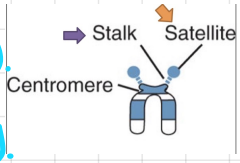
2 R-Banding:- Reverse of G-Banding
- AT rich:- Light Band (Heterochromatic).
- GC rich:- Dark Band (euchrocromatic).

- chromosomes are heated Before adding giemsa stain → AT:- weaker, stop binding with the stain.
  - GC:- Loosen up, Bind with the stain.

- **primary steps for culture establishment & harvest of specimens:-** (cells that proliferate in culture, T-Lymphocyt
  1) if cell is arrested it will be in G_0 phase (mostly) → we need it in M phase (metaphase).
  2) put the sample on a flask or petri dish in a specific media + Mitogen (phytrohemaglutenin or PHA) to induce the cell cycle. ($G_1 \rightarrow S \rightarrow G_2 \rightarrow M$).
  3) After 1-2 days we add colchicine which block spindle fibers (no chromosome pulling).
  4) certrifuged at low speed + hypotonic solution → swollen & frayile cells (Ready to Lyse).
  5) Cell are droped onto slides & chromosome will appear. (+ Giemsa).

every arm have 3 regions (1,2,3)
Numbers are incressing as we go from the centromere → Telomere.

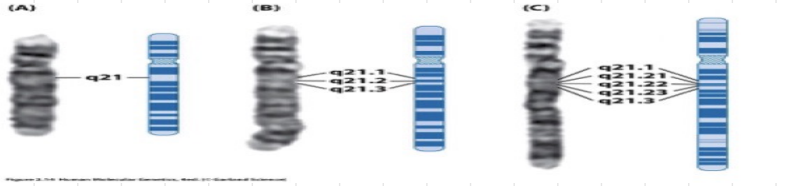
- **Chromosome shape:-** Q arm usually downward & P upward.
  - Metacentric:- centromere in the middle. (P & Q same Lenght)
  - Submetacentric:- Centromere is displaced from the center. (centromere is shorter than telomere)
  - Acrocentric:- centromere near the end (centromere is significatly shorter than telomere).
    - Chromosomes 13, 14, 15, 21, 22
    - P arm of acrocentric chromosomes → Stalk:- to make r-RNA (euchromatin).
      - Satellite:- repepetitive region does not encode proteins (heterochromatin).



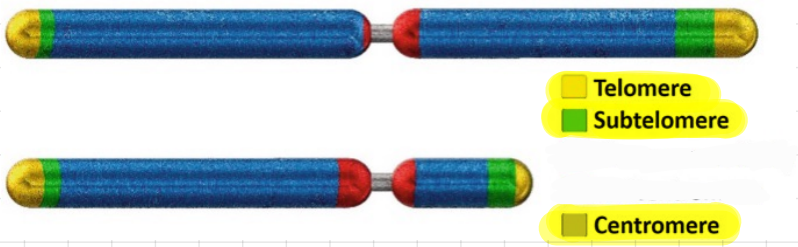
- the deletion in P arm of a single chromosome (eg 14) → no clincal outcome Because All 5 acrocentric chromosomes have the same DNA (Ribosomal) → r-RNA.

- Heterochromatin:- condensed regions, can't be expressed.
- euchromatin:- Decondensed regions (>chromatin), protein coding gene.

- **High resolution Banding:-** it's easier to detect the abnormalities in Less condensed chromosomes. Band increases from 300-450 to 800 per haploid set.



- **Components of the chromosome**
  - Centromere (Heterochromatin):- sequence of DNA with proteins (doesn't encode for gene).
    - The main purpose is to +spindle fibers (microtubules).
    - Tandem repeats:- 171 nucleotides are repeated
      - repeats on alpha → alpha satellite for centromere:- chromosomal segregation (anaphase)
  - Telomere (TTAGGG):- A specelized structure at the ends of eukaryotic chromosomes. Maintain chromosomal integrity by preventing end-to-end fusion of chromosome.
    - repetition of TTAGGG, no genes, Helps DNA polymerase to replicate
    - in zygote ↑mitosis → shorter tolemerase, adulthood → weak tolemerase activity, aging → eroded
    - Benifit:- cell trying to be cancerous cell → ↑mitosis → shortness of tolemerase → cell will die.
    - cancerous cell → Returns the activity of tolemerase → ↑mitosis (immortal cells).
    - All chromosomes (46) have the same sequence of Tolemerase (TTAGGG).
  - Sub-telomere:- Region Between centromere & tolomere that don't have sequence (not universal it can be common but not identical among all chromosomes).



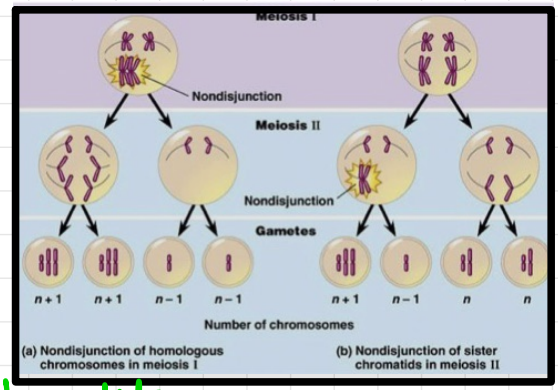
★Topic 1-3

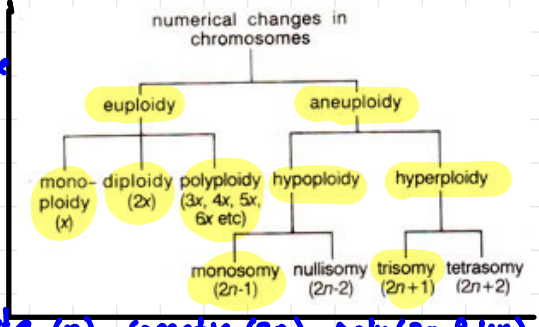
·An:- not, Eu:- normal, ploid - number of chromosomes.

- **Aneuploid:-** Any chromosome number that is not the exact multiple of the haploid number (n).
  - Trisomy:- presence of an extra chromosome (n+1), Common.
  - Monosomy:- Absence of single chromosome (n-1).

(n=23) chromosomes → cells:- 46. → gametes:- 23.

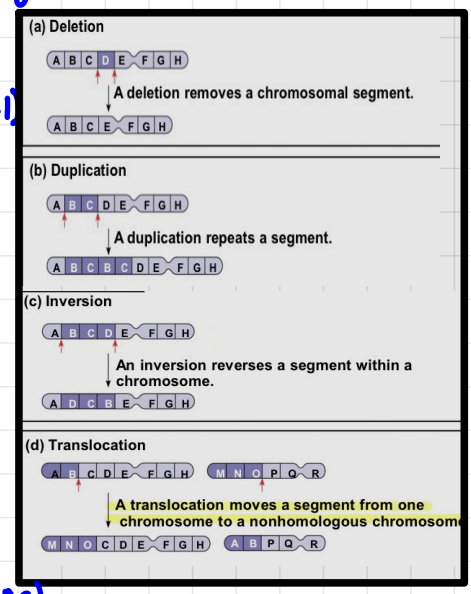
- **Nondisjunction:-** causes Aneuploid
  - Meiosis I:- Faliure of disjoin of homologus chromosomes
    - → Both chromosomes go to one end & do not separate
    - → 1 cell carrying 3 chromosomes & other carrying 1
    - → can't recognize that error was made → meiosis 2
    - → each single chromosome will align individually → sister chromatids will be seperated → cytokinesis
      - Results:- 50% (n+1 = 24), 50% (n-1 = 22)
  - Meiosis 2 or mitosis:- Faliure of disjoin of of sister chromatids
    - Results:- 50% (n=23), 25% (n+1=24), 25% (n-1 = 22).
    - The same mechanism → in normal human abnormal cell divide may occur.





- **Polyploidy**:- more than two complete sets of chromosome (more then 2n)
  - Triploidy (3n):- three sets of chromosome
    - it may happen if 2 sperms fertilize one egg.
  - Tetraploidy (4n):- four sets of chromosome
  - → Abnormal
  - Common in plants, more normal than aneuploids.
- **Euploid**:- exact multiple of the chromosomes normal haploid gemete (n)., somatic (2n), poly (3n & 4n).

- **Alteration of chromosome structure**:- normal n but some damge of chromosome occurs.
  - Deletion:- Remove a chromosomal segment.
  - Duplication:- repeats a segment
  - inversion:- reverses orientation of the segment (1,2,3→3,2,1)
  - Translocation:- moves a segment from one chromosome to another (non-homologus chromosomes).
    - Recombination:- exchange segments between non-sister chromatids of homologus chromosomes.



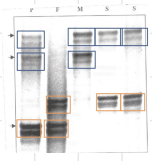
✱Human Disorders due to chromosomal Alteration (Aneuploidy)

1 Down syndrome (Trisomy 21)

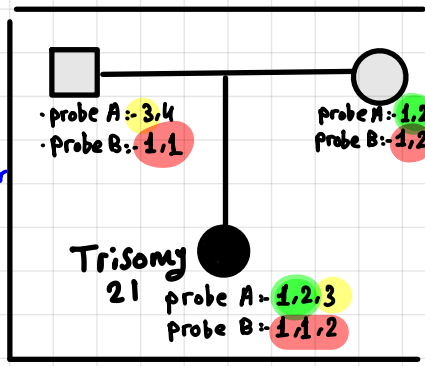
- Risk factor:- increase maternal age, M>F
- clinical features:- mental retardation, Low nasal brisde, hypotonia, up slanting palpebral fissure (eye shape). small Low-set ears, Consenital heart disease (VSD, AV), Epicanthic folds (eye), protruding tounsue, intestinal problems, Gap Between 1st & 2nd toes, x15 Leukemia, Simian Line.
- causes:- nonjunction in meiosis I or II
  - Maternal Errors (94%):- MI (64%), MII (19%), interminate (11%)
  - paternal Errors (4.5%):- MI (1%), MII (3.5%)
  - unknown (1.5%)

Extra information (theory): As woman age, the eggs in their ovaries also age, and the chances of chromosomal abnormalities occurring in the eggs increases. This is because the eggs have been exposed to environmental factors and DNA damage over time, which can lead to errors in the process of cell division. In a particular the risk of Down syndrome increases significantly after the age of 35.

- **Evaluate the origin of the Extra chromosome**
  - polymorphic markers:- Regions do not encode for proteins or RNA (no transcription or transulation), This regions are repetitive, The number of Repeats is diffrent (individually).
    - probe B:- not an informative region.
    - probe A:- 1,2 from mother, 3 from father
  - Gel electrophoresis.



- P = patient
- M = Mother
- f = father
- s = standart.



- **Partial Trisomy (46,21q+)**:- normal Karyotype (46), no extra chromosome 21.
  - Acrocentric chromosome → very small p arm (ribosomal DNA & repititive sequences).
  - carrying two fused q arm together (no p arm, we don't care about deletion) → 46,21q+

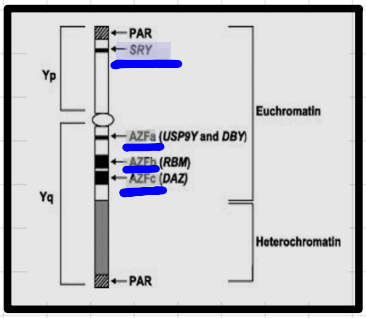
2 Edward syndrome (Trisomy 18):- clinical features:- CHD (Cardiac), faliure to thrive (FTT) mental retardation, Growth retardation, hypertonia, promienent occiput, Low-set & short sternum unusual hand position (clenched fist), Rocker bottom feet.

3 patau syndrome (Trisomy 13):- clinically:- CHD, mental retardation, hyper or hypotonia, Scalp defects, microcephaly, small eyes, Low-set ear, cleft lip/palate, polydectyly & syndactyly polycystic kidney, Rocker-Bottom feet (same as edward).

★ Topic 1-4

- The chromosomal Basis of sex :- Large X & small y (genes (thousands) in X are absent in y (hundreds), 1genes in x).
  - Hemizygous:- only 1 allele for this genes (not homozygous or heterozygous).
  - pseudoautosomal regions:- shared regions between x & y chromosomes (two alleles in samegene).

- y-chromosome
  1) SRY region :- sex deterermining region of y chromosome, if SRY present → Male baby.
     - 46 xy but primary sexual organ is female, this will occur if there is deletion in SRY region.
  2) AZF_a, AZF_b, AZF_c :- formation of sperms.
     - mutation → infertile (↓sperm, azoospermic (zero)).

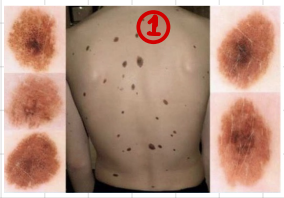


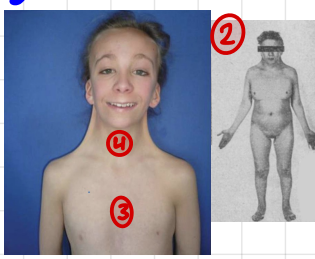
- on the sex chromosomes not all the genes that are carried on the sex chromosomes are necessarily related to sex Triads
  - Hemophilia gene on x.
  - Duchenne muscular dystrophy gene.
  - Red-green color blindness gene.

★ Aneuploidy of sex chromosomes :- Nondisjunction of sex chromosomes.

1 Kleinfelter's syndrome (47,xxy,+x)
- males (SRY) with some development of Breast tissue & hip fat distribution.
- Little Body hair + tall + small testes.
- infertility (abs of sperms) (primary male organs are underdeveloped).
- Evidence of mental retardation may or may not be present.

2 Turner syndrome (45,X)
- female (no SRY)
- nevi:- Brown spots. ①
- ovaries are rudimentary & goonads are under developed → no menstrual cycle → infertile.
- shortened metacarpal IV & small finger nails.
- Abnormal elbow position. ②
- underdeveloped breast & wide distance between niples ③
- webbed neck (extra skin). ④
- 20 cm shorter.

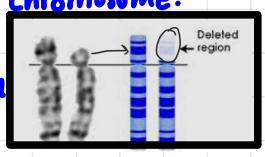




- Monosomy:- not a viable fetus (except turner) → extra genetic material is Less deleterious than missing genetic material.

★ Structurally Altered chromosomes (chromosomal aberration:- when we have 46 chromosome but they are not all complete/normal, something wrong with the structure of the chromosome.

1 cri du chat/cry of the cat (deletion in chromosome 5):- missing part of p arm

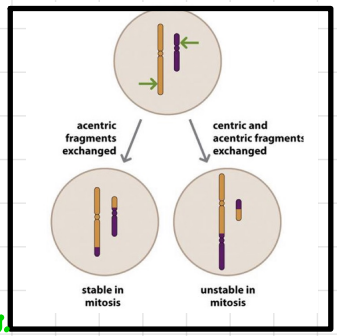


- symptoms
  - shape:- Microcephaly (small head), round face, small chin apart eyes, folds of skin over their eyes, small nose bridge.
  - inside the body:- Heart defects, Mascular/skeletal problems, Hearing or sight problems difficulty walking & Talking, hyperactivity & aggression, mental retardation.
- prognosis:- 75%:- few months, 90%:- Before 1 year. (it's better nowadays).

2 Chronic myelogenous Leukemia (t(9,22)) :- Adults > children.

- hematology reminder:- stem cell → myloid stem cell (These two precesor cells for WBC which CML can develop from them) → myeloid blast → monocyte & granulocyte.
- philadelphia chromosome:- Translocation between chromosome 9 & 22 (nonhomologus chromosomes).
- due to:- the gene that induces the cell cycle ABL is translocated to a Location which is under a stronger promotor BCR, ↑cell cycle → ↑chance for cancer.

- Types of Translocation

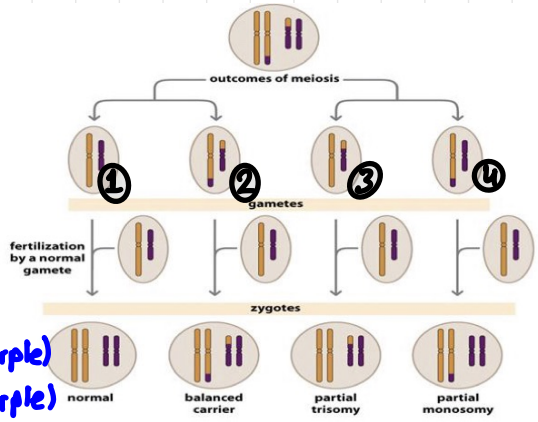


1 Reciprocal:- one single fragment is exchanged for another.

- stable in mitosis:- acentric fragment exchange with acentric
- unstable in mitosis:- centric fragment exchange with acentric → 2 centers.

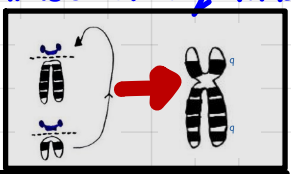
- Balanced carrier:- there is rearrangment of gentic material without gain or loss.
- The problem arises when this individual makes gametes during meiosis → each gamete carries 1 of each homogos

Gametes possibilites
1. totally Brown & purple
2. Translocated Brown & purple.
3. one totally Brown & Translocated purple.
4. Translocated Brown & totally purple.

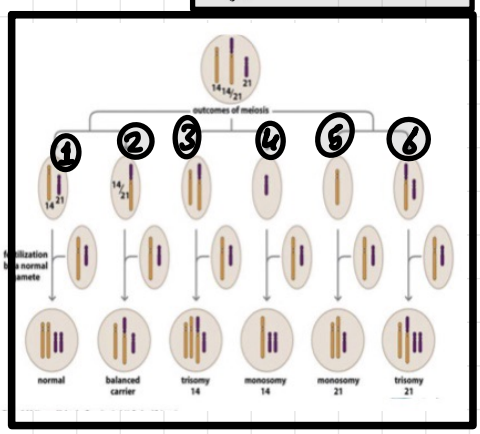


- Results After fertilization.
  1. normal
  2. Balanced carrier (identical to parient).
  3. partial trisomy to Brown, partial monosomy (purple)
  4. partial monosomy to Brown, partial Trisomy (purple)

2 Robertsonian:- specalized type of translocation between acrocentric chromosomes (13,14,15,21 & 22) the q arm of one chromosome will fuse on top of other q arm → chromosome made of 2 q arms from two diffrent acrocentric chromosomes (no p arm).



- example:- 45, xx(or xy), t(21q, 14q)
- Gametes possibilities
  1. chromosome 21 & 14 → normal gamete.
  2. Translocated chromosome 14/21
  3. chromosome 14 & Translocated chromosome 14/21
  4. chromosome 21
  5. chromosome 14
  6. Translocated chromosome 14/21 + chromosome 21.



- Results After fertilization.
  1. normal zygote
  2. Balanced carrier (identical to parient).
  3. full trisomy 14
  4. full monosomy 14 → not viable.
  5. full monosomy 21 → not viable.
  6. full Trisomy 21 (down syndrome)

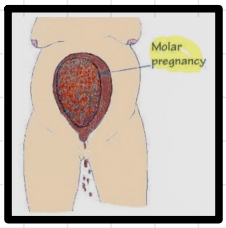
- Viable aneuploids
  - patau syndrome:- Trisomy 13
  - Edwards syndrome:- Trisomy 18
  - Down syndrome:- Trisomy 21
  - Turner syndrome:- only viable monosomy.

*Topic 1-5

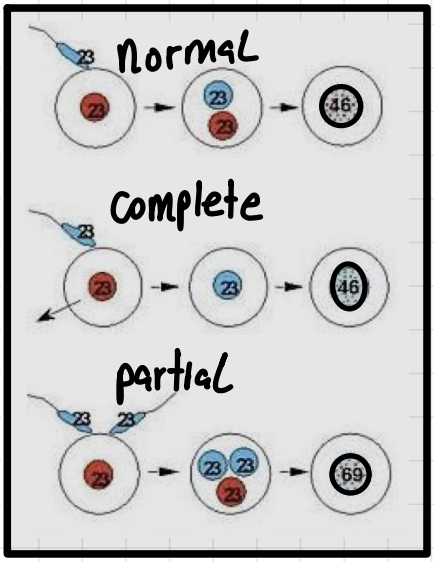
- **Polyploidy** (not viable, Rare).
  - Triploidy (3n)
    - 66% :- 2 sperms accidetly fertilizing one egg. (69,xxy / 69,xxx / 69,xyy).
    - 10% :- one egg mistakenly carrying (2n), The third set (n) by the sperm.
    - 25% :- sperm mistakenly carrying (2n), The third set (n) by the edd.
  - Tetraploidy (4n) :- endomitosis (nucles divided & Replicate DNA, but the cytoplasm don't divide.

- **Clinical outcomes of polyploidy**
  - Findings :- Severe intrauterine growth retardation, Macrocephaly, CNS/heart/renal defects, Low-set ears, foot deformities, Hypertelorism, Abdominal wall defect.
  - Types
    - Maternal triploidy (digynic) :- Macrocephaly, sever intrauterine growth retardation.
    - paternal triploidy (diandric) :- Enlarged or cyst-like placenta, well formed fetus ± Microcephaly.

  - Molar pregnancy :- Lack to embryonic tissues & abnormal benign growth
    - complete molar pregency :- no embryonic tissue at all (grape Like tissue).
  - Hydatidiform mole :- pure triploidy (90%).



- **Genetic status in normal conception & molar pregrency.**
  - normal conception :- 23 egg + 23 sperm = 46 chromosome (normal viable fetus).
  - Complete mole :- Loss of oocyte DNA → egg with only paternal chromosomes (androgentic).
    - Chromosomal rescue :- Replicates it's own DNA (Homozygous).
    - fertilised by 2 sperms (Heterozygous).
  - partial mole :- 2 sperms + 1 egg = Zygote (3n) (69 chromosome).



★Topic 2-1

- The family history is important to understand the past to predict the future.

- **Degrees of Dominance:-**
  - complete dominance:- when pheotype of the Heterozygote & dominant homozygot are identical.
  - incomplete dominance:- The pheotype is hybrids (Between the phenotype of the 2 paternals).
  - codominance:- two dominant alleles affect the phenotype in separate (distingushable way).

- **The Relation Between Dominance & phenotype**
  - A dominant allele does not subdue a recessive allele, they are simply variations in a gene's nucleotide sequence.
  - dominance/recessiveness Relationships depends on the LvL which we examine the phenotype (There is no relationship between the prevalence of a disease & it's dominace, prevelance depends on the disease itself).

- **Tay-sachs:-** recessive metabolic disease by mutation on chromosome 15 in the HEX A gene → Lipid Build-up → damge the cell (lysosomal storage disorder). (↳ q arm, position 23,24)
  - inheritance pattern:- Autosomal recessive. (Heterozygous → Normal clinicaly).
  - physical effects:- First mounth of life (3-6 m) → Nerve cell destroyed → Loss of motor control, atrophy, seizures. → Death (3-4 m)
  - Levels → organismal/phenotype:- recessive (complete dominance).
    - Biochemical LvL:- incomplete dominance (Homozygotic 100%, Heterozygotic 50%).
    - molecular/genatic LvL:- Codominant (RNA polymerase will use use Both DNA alleles).

Tay Sach's features:
TAY SACHS
- Testing recommended
- Autosomal recessive
- Young death (<4 yrs.)
- Spot in macula (cherry red spots)
- Ashkenazi Jews
- CNS degeneration
- Hex A deficiency
- Storage disease

if the question didn't specify which LevEL → answer regarding phenotype

- **Frequency of dominant alleles:-** Dominant alleles are not necessarily more than Recessive alleles.
  - polydactyly (1/400) :- Dominante allele (Less than the recessive allele).

- **Mutiple Alleles:-** Most genes in populations is more than two allelic form (But each individual carries 2 allels for each character gene except of sex gene).
  - ABo blood grooup :- I^A, I^B, i.

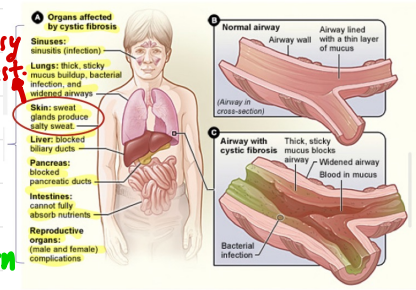
(a) The three alleles for the ABO blood groups and their carbohydrates

Allele	I^A	I^B	i
Carbohydrate	A △	B ○	none

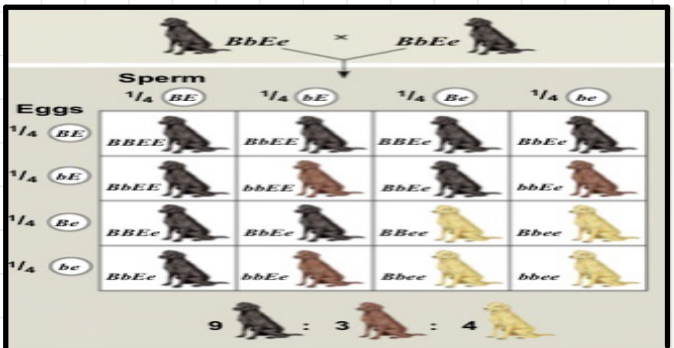
(b) Blood group genotypes and phenotypes

Genotype	I^AI^A or I^Ai	I^BI^B or I^Bi	I^AI^B	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB	O

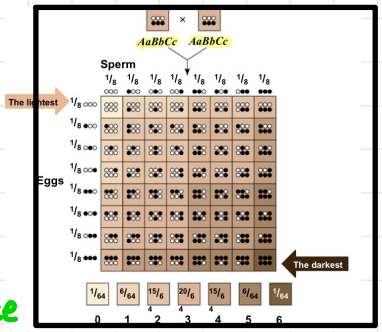
- **pleiotropy:-** multiple phenotypic effect for 1 gene (1 gene = 1 phenotypic effect → not pleotropy).
  - cystic fibrosis:- Autosmal recesive, mutation in (CFTR) → defective membrane protein (cloride ion chennels) → Cl^- accumulate out-side the cells → Bulid mucus in most of the Lumens → Mucus. (easy test)
  - sickle-cell.



- **Epistass:-** gene at one Locus alters the phenotypic expression of a gene at a second Locus (E gene allows B gene to produce the color or not.
  BB = Black, Bb = Black, bb = Brown (B is dominant) ee:- not black or Brown
  Ee/EE:- allows the function of the B gene.



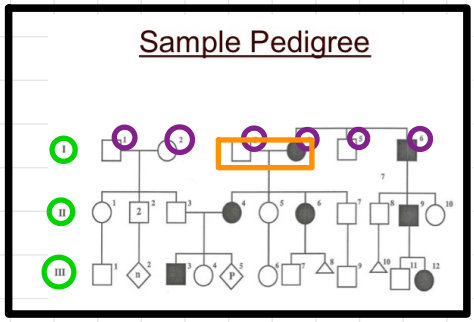
- **Polygenic inheritance** :- Quantitative variation, an additive effect of two or more genes in a single phenotype
  - Cancer, CVS disorders, DM.
  - Skin color :- 3 genes (6 alleles) → Bell-shaped curve not Binomial.



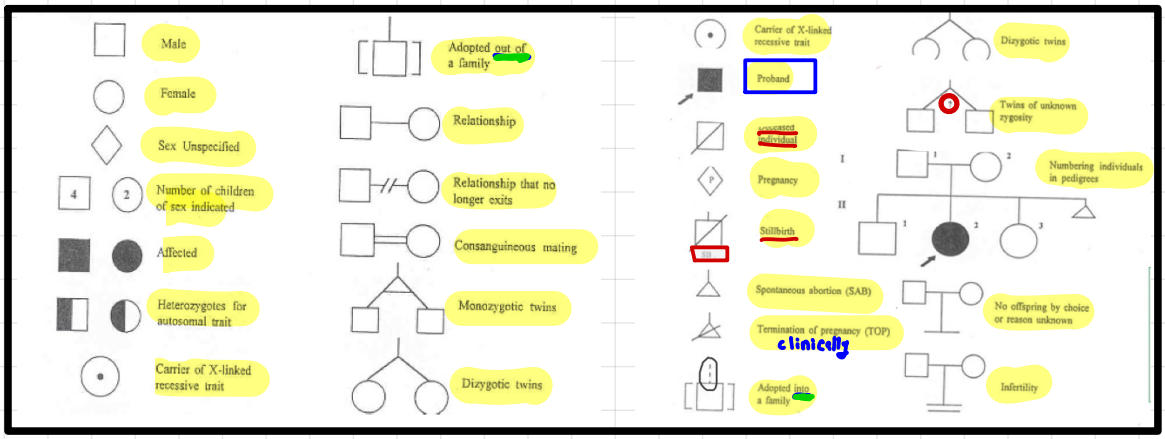
- **Nature & Nuture** :- The Enviromental impact on phenotype.
  - The norm of reaction :- the phenotypic range of a genotype influced by the environment. (for polygenic characters)
  - Mutifactorial :- genetic & enviromental factors collectively influence the phenotype (Alchol addiction, sex orientation, Lung cancer).

★ Topic 2-2

- **Humans are not good subjects for genetic research** :-
  - Generation time is too long.
  - Parents produce relatively few offspring.
  - Breeding experiments are unacceptable.

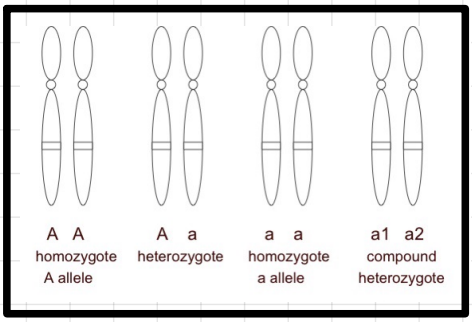


- **Pedigree** :- Family tree that describes the interrelationships of parents & childrens across generations.
  - Analysis
    - trace & describe inheritance patterns.
    - make predictions about future offspring.
    - predict the probality of specific phenotype
  - Designation of generations & individuals
    - Horizantal Line = generation, oldest on top, Roman numbers for generations
    - Arabic numbers for individuals within the generation, oldest → youngest from Lt to Rt.
    - male partner is usually placed to the left of the female partner.
    - Record (name, age, DoB, age of death, race, ethnic origin, Health problems, Cause of Death).



- proband :- individual that Brings the family to clinic.

- **The Gene is the unit of inheritence**
  - Locus :- The Location of a gene on a chromosome.
  - Allels :- Alternative forms of a gene at a particular Locus.
  - Homozygous :- Both alleles are identical at the Locus (AA).
  - Heterozygous :- Allels are differ at the Locus (Aa)
  - Compound Heterozygote :- 2 diffrent mutant alleles.



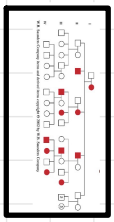
- **Types of Genetic disease**
  - Chromosomal
  - single gene (Mendelian
  - Multifactorial
  - Teratogenic

- **Autosomal dominant:-** traits in which the phenotype of heterozygote & homozygote for the dominant allele are the same (Aa = AA).
  - Examples
    - familial hypercholesterolemia.
    - Huntigon disease.
    - Neurofibromatosis 1 (NF1).
    - Myotonic dystrophy.
    - Marfan syndrome.
    - Achondroplasia.

DISEASE	CLINICAL FEATURES Note: Key aspects of phenotypic expression or inheritance features are bolded
Autosomal Dominant	
HUNTINGTON DISEASE •Basal ganglia	Progressive loss of brain neurons, dementia, loss of motor control Affects 1/20,000 persons of European descent **Late onset, typically between 30-40 years, but may be earlier** (See lecture on unstable trinucleotide repeats.)
MYOTONIC DYSTROPHY •weakness of Muscles	Facial weakness Cataracts Progressive muscular weakness Variable onset (Age) → differ Variable expressivity (How Bad is differ)
NEUROFIBROMATOSIS TYPE I (NF1)	Cafe-au-lait spots (hyperpigmented skin) Lisch nodules (benign growths on the iris) Peripheral nerve tumors **Variable expressivity** (good example) High mutation rate
FAMILIAL HYPERCHOLESTEROLEMIA	Arteriosclerosis, xanthomas **Heterozygotes: Increased LDL coronary heart disease in middle age** (40) **Homozygotes: childhood coronary heart disease**
MARFAN SYNDROME (Connective tissue disorder)	Tall stature with long limbs Narrow facies with high, narrow palate Dislocated lenses & myopia Cardiac manifestations, i.e., aortic aneurysm **Variable expressivity** **Pleiotropy**
ACHONDROPLASIA •most common form of dwarfism	Short-limbed dwarfism Megalocephaly Lordosis & Kyphosis **80% new mutations** Increased mutations with increasing paternal age

•aurotic rupture
• eye → myopia
→ parent are healthy (de novo mutation).

  - if one parent are Heterozygous (Aa) & other is Homozygous (aa) → 50% affected child.
  - Features
    - Vertical trasmition:- 1 from every generation is effected

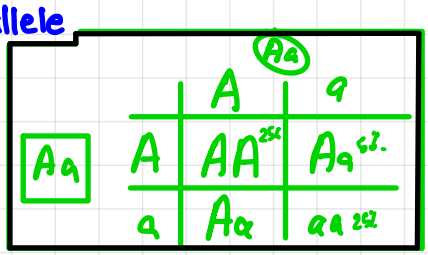


    - Both sexes (1:1) are affected & tramit the triat.
    - Heterozygous (1affect) more common than homozygous (1affect).
    - variable expressivity & age.
    - may be due new mutation.
    - Gene product is usually a structural protein (non-enzymatic).
  - if Both parents are Heterozygous (Aa) → 75% affected child.

- **Autosomal Recessive:-** phenotype is expressed only of Homozygous for the recessive alleles (aa).
  - Examples
    - Cystic fibrosis (2-1)
    - sickle cell anemia
    - Tay-sachs disease (2-1)
    - phenylketonuria.
    - most inborn errors of metabolism.
    - Albinism:- ↓pigmentation of hair & skin (Sun Light → DNA damge).

Autosomal Recessive	
CYSTIC FIBROSIS	Chronic, progressive pulmonary disease Pancreatic endocrine insufficiency Caused by chloride ion channel defect + mucus build up Elevated sweat chloride **Higher frequency in European Caucasians**
TAY-SACHS DISEASE	Progressive neurological abnormalities Retinal cherry-red spot **Higher frequency in the Ashkenazi Jewish and French Canadian populations** Reduced serum hexosaminidase A Due to the mutation of hexosaminidase A Usually fatal in early childhood
SICKLE CELL ANEMIA	Failure to thrive Chronic anemia Vasoocclusive crisis (pain) Increased risk for infection **Higher frequency in those of African descent** Heterozygote advantage

  - carriers:- Heterozygous → phenotypically normal (most individuals).
  - Consanguineous matings:- mating Between close relatives, ↑chance of autosomal recessive disorder by ↑ the chance of mating between 2 carriers of the same rare allele
  - Features
    - Horizontal transmission
    - Both sexes are affected & transmit mutant allele
    - May observe consanguinity
    - Gene product is usually an enzymatic protein.



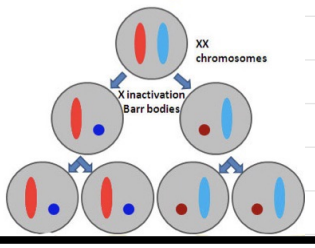
- **phenylketonuria (PKU):-** ↑Lvl of phenylalanine in the blood due to ↓ in phenylanine hydroxlase (PAH):- phenylanine → tyrosine

★Topic 2-3

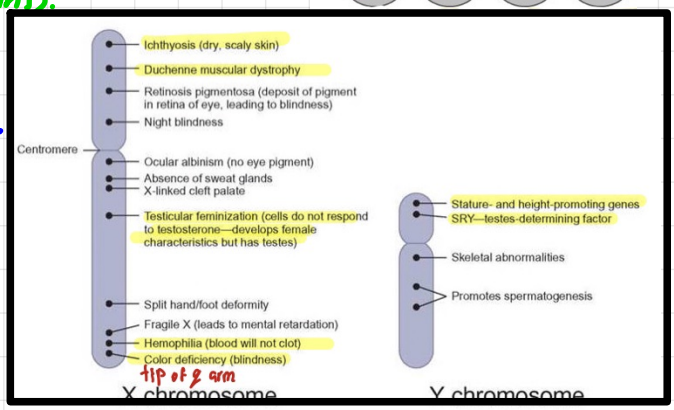
- **Sex Linkage & x-inactivation**
  - Hemizygous :- X^AY
  - Homozygous :- X^aX^a
  - Heterozygous :- X^AX^a

- **Dosage compensation** :- is the process by which organisms equalize the expression of genes between number of different biological sexes (due to x-inactivation).
  - for autosomal :- 2 doses → Normal phenotype , 1 dose or >2 → clinical significance (RNA polymerase will bind to Both alleles of each gene) :- same in Both sexes.
  - for x-linked :- two doses in females & one dose in males → normal phenotype :- in female there will be more expression of these genes, Because each gene on the x chromosome in females made of two alleles , so RNA polymerase bind to first one & second one make RNA from Both alleles , in males there is only one allele that is being transcribed into RNA → ↑RNA in females for genes on x-chromosomes.
    - these genes & proteins , don't function individually (by interaction between each others).

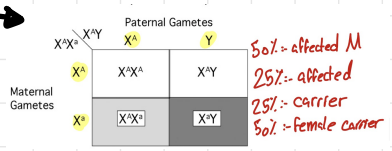
- **X-inactivation (Lyon hypothesis)**
  - Barr body :- inactivated x-chromosome randomly (paternal/maternal) in the early embryonic life (3-7 days). → The same x will be inactive in all descendants of a particular cell).
  - some genes remain active (escape inactivation) :- these include 1) gene in pseudoautosomal region that have matching gene on the y.
    2) genes outside the pseudoautosomal region that have related copies on the y-chromosomes.
  - if a female is heterozygous for a particular gene located on x she will be mosiac for that character (↓symptoms).

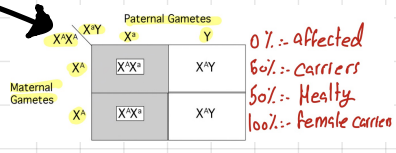


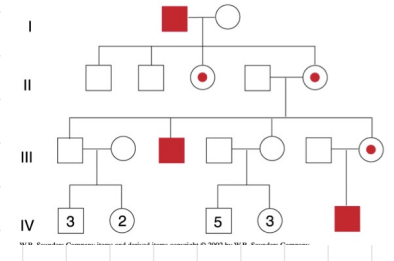
- **inheritance of Sex-Linked genes**
  - sex Linked :- genes is Located on either sex chromos-
  - Y- Linked :- genes on y chromosomes (few)
  - X-linked :- genes on x chromosomes



- **X-Linked recessive** :- Homozygous (f) or Hemizygous are affected , more common on males.
  - features
    - Absent of male-male transmission.
    - Diagonal inheritance :- affected males related through females of the maternal life.
    - Males > females
    - full expression in hemizygous males.
    - No or mild expression in carrier females due to x-inactivation.
  - Transmission probablities
    - A son never inherits the disorder from his father.
    - All Daughters of a male with the disorder are obligate carriers.
    - Sons & Daughters of carrier females have a 50% chance of inheriting the disorder.







- Examples
  - Color blindness (Redgreen).
  - Duchenne muscular dystrophy.
  - Hemophilia

X-Linked Recessive	
HEMOPHILIA A	Coagulation disorder Prolonged bleeding Easy bruising Hemorrhage Various mutations & very heterogeneous
DUCHENNE MUSCULAR DYSTROPHY	Progressive muscle weakness Death typically in 2nd or 3rd decade 30% cases due to new mutation → de novo (spontaneous or) **Allelic heterogeneity (Becker MD)** ↳ lesser

- **X-Linked dominant**
  - Features
    - x2 females as males
    - absent of male-male transmission.
    - Males transmit it to all daughters.
    - females usually have more mild & variable expression due to x-inactivation.
    - few disorders.
  - Transmission probabilites
    - Son never inherits the disorder from his father.
    - All daughters of male with the disorder will have the disorder.
    - Sons & daughters of affected females have a 50% chance.
    - autosomal/x-linked dominant differ at offspring of affected males.
  - Vit D resistance (Rickets)

X-linked Dominant	
VITAMIN D RESISTANT RICKETS	Rickets Short stature Low serum phosphate **Less severe in heterozygous females**

- Affected patient → Heterozygous.