MED439
KING SAUD UNIVERSITY

pediatric
439 Teamwork

Revised by The Academic Leader
Homoud Algadheb

Chromosomal and genetic disorders

objectives:

- Understand the basics of chromosomal structural and numerical abnormalities including microdeletions.
- Recognize the pattern of Mendelian inheritance.
- Understand the consequences of uniparental inheritance of chromosomes.
- Understand the concept of recurrence risk and its numerical assessment.

Disclaimer: I didn't add the basics of genetics due to the shortage of time, so if u want to study them refer to the lecture

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Special thanks to team 437 & Faisal alsaif

Notes

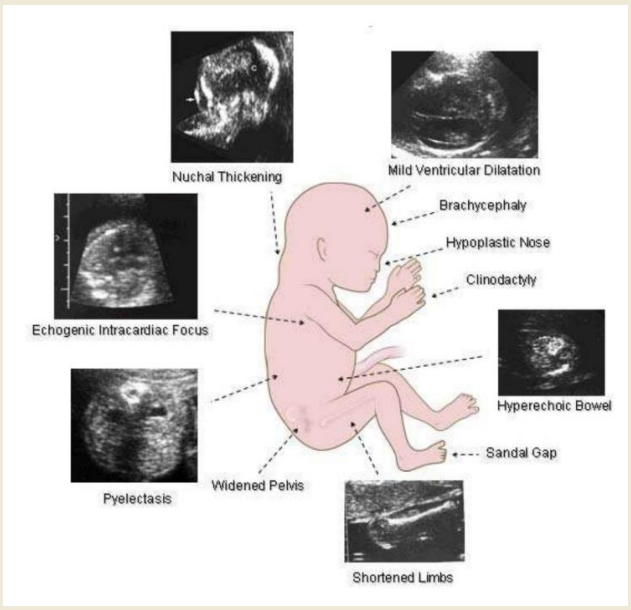
Important

Book

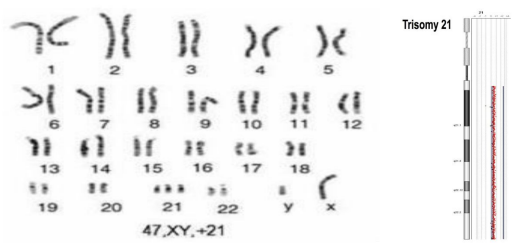
Trisomy

Trisomy 21 (Down Syndrome):

Cytogenetic locus (loci)	(21.22.1-22.2 has been called the DS critical region though there have been cases of duplication outside of this region who manifest DS.
Inheritance	95% de novo, 5% due to Robertsonian translocation Between chromosome 21 and 14 or isochromosome 21.
Clinical Features and Diagnostic Criteria	Most imp here is cardiac, hypotonia and risk of cancer and leukemia in the future , facial features and short obese stature mild-mod ID, hypotonia,growth delay, strabismus, adult cataracts, myopia, conductive HL,macroglossia, hypodontia, joint hyperflexibility, hypogenitalism, congenital heart defect, duodenal atresia, hirschsprung, celiac, thyroid disease, early onset Alzheimer's, transient myeloproliferation, ALL.
Clinical Tests	prenatal US abnormalities detected in 50%, maternal.
serum screen	high free beta HCG, low PAPP-A.
Molecular Tests	maternal fetal free DNA testing, karyotype is diagnostic. Most of the time screening in utero, generally using karyotyping, array and FISH
Disease Mechanism	90% due to maternal meiosis nondisjunction (¾ MI error, ¼ MII error). Associated with increase in maternal age
Treatment/Prognosis	Supportive care, overall life expectancy is reduced.



Trisomy 21 karyotyping vs CMA



The prenatal testing for down s. could be a screening or diagnostic test, invasive or noninvasive, maternal or fetal sample. Based on situation, parents consent and budget we choose the test, if the mother is >35 with high risk of down s. we can give her option to do screening invasive (amniotic fluid sample 14-16 weeks , Chorionic villus sampling 11-13 weeks) or noninvasive (maternal blood sample ”free fetal blood, BHCG, and other biomarkers)

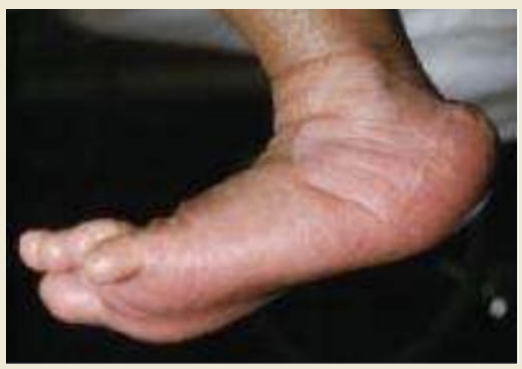
imp message: we shouldn’t take a medicolegal action (termination) based on the noninvasive methods, we should have a detailed diagnostic report

Trisomy

Trisomy 18 (Edward Syndrome):

Inheritance	Less than 1% due to a translocation.
Clinical Features and Diagnostic Criteria	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.
Clinical Tests	Echo, abdominal US. Its imp to do MRI and cardiac testing to these patients
serum screen	low AFP, hCG, and UE3.
Molecular Tests	karytype is diagnostic 2- microarray 3- FISH
Disease Mechanism	Maternal nondysjunction (90%), mosaicism (10%) milder
Treatment/Prognosis	50% die in first week, 90% die by one year. That's why its allowed to terminated before 19 نفخ الروح weeks

Typical digit 2 over 3 and 5 over 4 in Trisomy 18. Overlapping digits (clenched hand)



Typical rocker bottom foot of trisomy 18

	Condition		
Serum test marker	**Down's syndrome (trisomy 21)**	**Edward's syndrome (trisomy 18)**	**Neural tube defect**
AFP	Low	Low	High
HCG	High	Low	NA
Unconjugated oestriol	Low	Low	NA
Dimeric inhibin-A	High	Low	NA

AFP, α-fetoprotein; HCG, human choriogonadotropin.

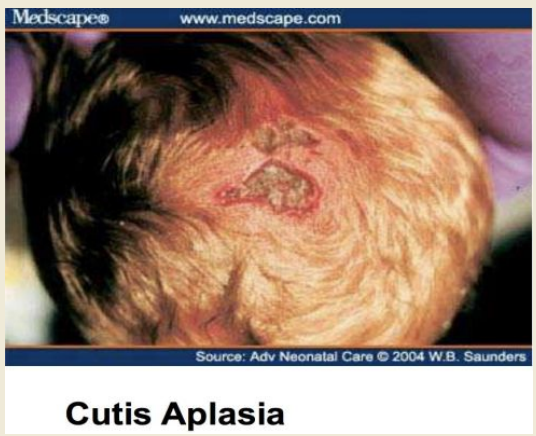
Trisomy 13 (Patau Syndrome):

Inheritance	20% due to a translocation
Clinical Features and Diagnostic Criteria	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.
Clinical Tests	Brain MRI, EEG, audiogram, echo, renal US

Trisomy

Trisomy 13 (Patau Syndrome) cont.:

Molecular Tests	Karyotype is diagnostic
Disease Mechanism	75% are due to maternal nondysjunction, 20% to a translocation, and 5% to mosaicism. Defect in fusion of the midline prechordial mesoderm in the first three weeks of gestation cause the major midline dysmorphic features.
Treatment/Prognosis	44% die in the first month, >70% die within one year. Severe ID exists in all survivors.



Cutis Aplasia

Sex chromosome abnormalities

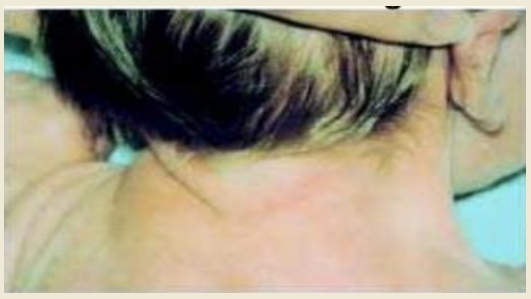
Karyotype	Incidence	Name
45,X	(1/3000)	Turner syndrome
47,XXX	(1/1000)	Trisomy X[1]
47,XXY	(1/1000)	Klinefelter syndrome
47,XYY	(1/1500)	47,XYY syndrome

1- Phenotype: close to normal, obese and tall and subnormal intellectual , with no other problem even no fertility problems, bc the extra X will be inactivated

Sex chromosome abnormalities

Turner syndrome (Monosomy X)

Responsible genes	X genes that escape inactivation, SHOX.
Proteins	Short stature homeobox protein.
Cytogenetic locus (loci)	SHOX: Xpter-p22.32
Inheritance	Sporadic
Clinical Features and 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.
Clinical Tests	echo, renal US, TFTs, GH testing, FISH SRY.
Molecular Tests	Karyotype
Disease Mechanism	SHOX: thought to act as a transcription regulator with many down-stream targets that modify gro and stature. SHOX protein has been id'ed in the growth plate from 12 weeks GA to late childhood.
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.



Low posterior hairline and neck webbing

Hypertelorism and low set eares

this pic will show you that most of the turner patients will not be picked up early in life. maybe in the post Natal with lymphoedema and cardiac issues or if they don't have, they will come later in life with pubertal issues like poor short stature, but they don't have a major distinctive features

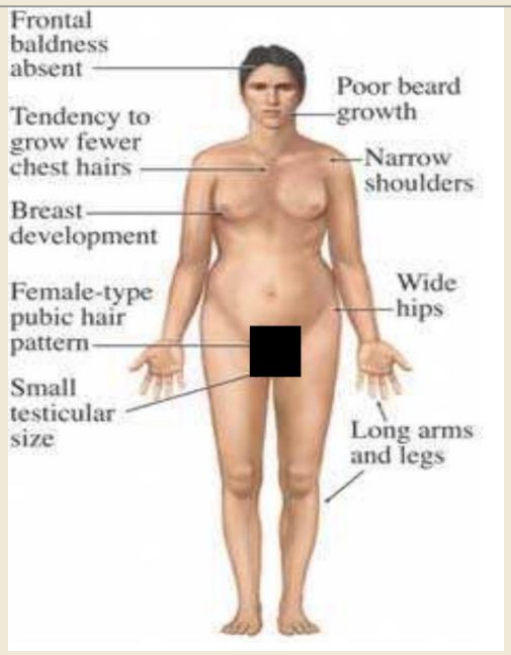
Box 9.4 Clinical features of Turner syndrome

- Lymphoedema of hands and feet in neonate, which may persist
- Spoon-shaped nails
- Short stature – a cardinal feature
- Neck webbing or thick neck
- Wide carrying angle (cubitus valgus)
- Widely spaced nipples
- Congenital heart defects (particularly coarctation of the aorta)
- Delayed puberty
- Ovarian dysgenesis resulting in infertility, although pregnancy may be possible with in vitro fertilization using donated ova
- Hypothyroidism
- Renal anomalies
- Pigmented moles
- Recurrent otitis media
- Normal intellectual function in most cases

Sex chromosome abnormalities

Klinefelter syndrome

Clinical Features and Diagnostic Criteria	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 Tests	echo, renal US, TFTs, GH testing, FISH SRY.
Molecular Tests	karyotype, at least one extra chromosome to a 46,XY Karyotype
Disease Mechanism	• 1st or 2nd meiotic division nondisjunction of either parent. • Maternal>paternal origin. • +AMA effect.
Treatment/Prognosis	• 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)



Microdeletion/microduplication syndromes

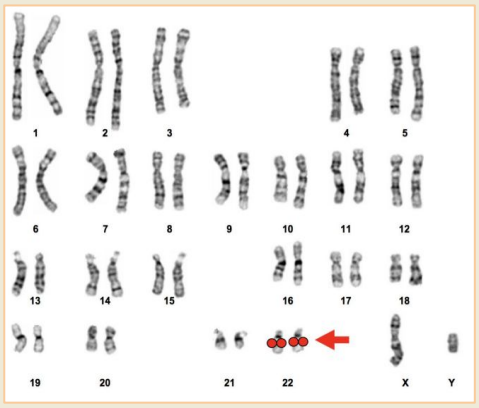
- Its complex bc more than 1 gene are involved, sometimes they're not related to each other, eg. CNS + renal + CVS + skin....with no specific constellation of the phenotype
- Complex phenotypes due to dosage imbalance of multiple, unrelated genes which happen to be contiguous on chromosome. In some cases, clinical syndrome defined before genetic basis known.
- Contiguous gene syndromes
- Segmental aneusomy syndromes Aneusomy means different number
- Genomic Disorders (subset mediated by segmental duplications –seg dup)
- Mechanisms include deletion, duplication, and UPD one chromosome copy from one parent only = any deviation from normal, biparental inheritance

Microdeletion/microduplication syndromes

DiGeorge syndrome/ VCFS/del(22)(q11.2):

~1/4,000 – most common mdel microdeletion syndrome
- Thymus hypo/aplasia → cellular immunodeficiency Absent Thymus in CXR
- Parathyroid hypo/aplasia → hypocalcemia
- DD, ID.
- Cardiovascular: Conotruncal heart defects, aortic arch defects
- Dysmorphic features: Micrognathia, ear anomalies, cleft palate,short palpebral fissures, short upper lip

We can also see the deletion area through karyotyping bc its considered microdeletion, but go with microarray or fish

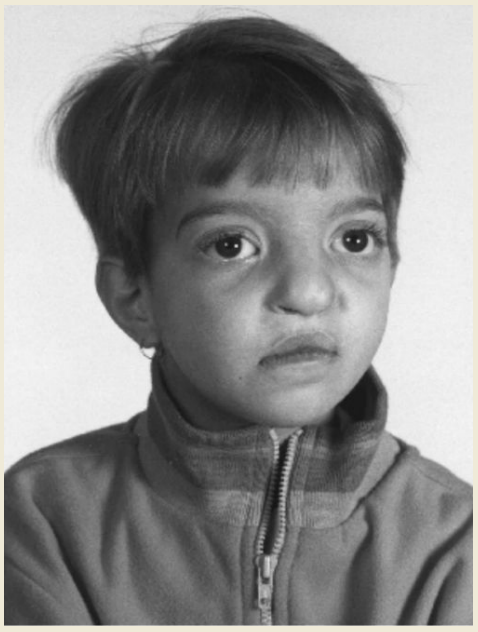


Resolution: Size of prob (100kb), but not equal across entire genome.

Requires at least 500-600 evenly spaced DNA probes to match the power of the karyotype!!!

Wolf-Hirschhorn syndrome /del(4p):

- IUGR, microcephaly, hypotonia, severe ID.
- Dysmorphic facial features: hypertelorism, prominent glabella, arched eyebrows, nose broad or beaked, CL/P, short upper lip.
- Other: scalp defect, hypospadias, heart defect, seizures, preauricular pit.
- Most de novo, 10-15% from balanced carrier parent.



Facial Features:
'Greek warrior helmet appearance' of the nose (the broad bridge of the nose continuing to the forehead)
Microcephaly
High forehead with prominent glabella
Ocular hypertelorism,Epicanthus,Highly arched eyebrows,Short philtrum,Downturned mouth,Micrognathia,Poorly formed ears with pits/tags

Microdeletion/microduplication syndromes

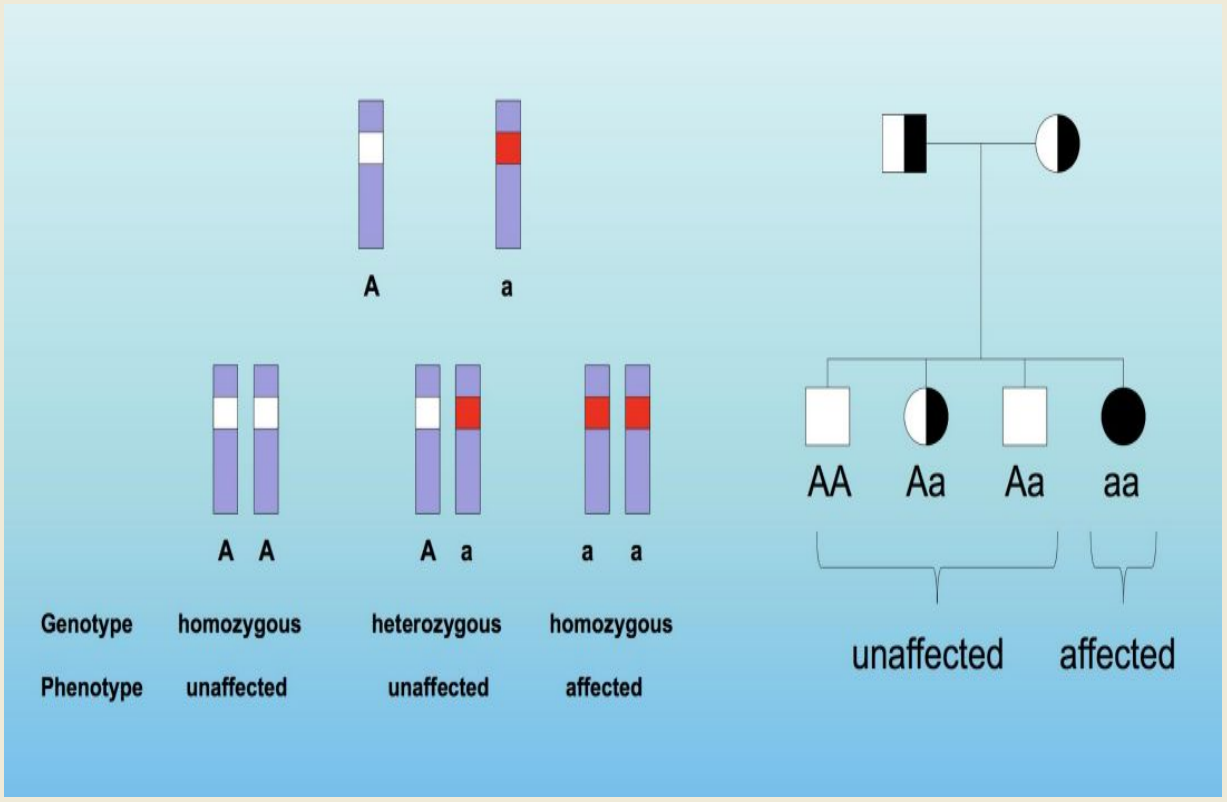
Cri Du Chat del(5p minus syndrome):

Responsible genes	RPS14?, microRNA 145 and 146a?
Proteins	Short stature homeobox protein.
Cytogenetic locus (loci)	5p15.2

Inheritance	12% due to unequal segregation of a translocation or recombination involving a pericentric inversion in one of the parents, 85% sporadic de novo deletions wont effect the offspring (80% are on the paternal chromosome)
Clinical Features and Diagnostic Criteria	Cat-like cry (abnormal laryngeal development), slow growth, IUGR microcephaly, ID, hypotonia, strabismus, characteristic facial features (Hypertelorism, round face, epicanthal folds, down slanting palpebral fissures, strabismus, Micrognathia, Low-set ears) associated with Heart defect and Transverse palmar creases. Cat-like cry only when deletion limited to band 5p15.32
Clinical Tests	echo, renal US, TFTs, GH testing, FISH SRY.
Molecular Tests	Most are visible, a few are submicroscopic and diagnosed by FISH for the critical region.
Disease Mechanism	A study of 50 patients with deletions ranging from 5p15.2 to 5p13 and found no correlation with size of deletion and degree of mental impairment.
Treatment/Prognosis	Supportive care

Single gene disorders

Autosomal recessive



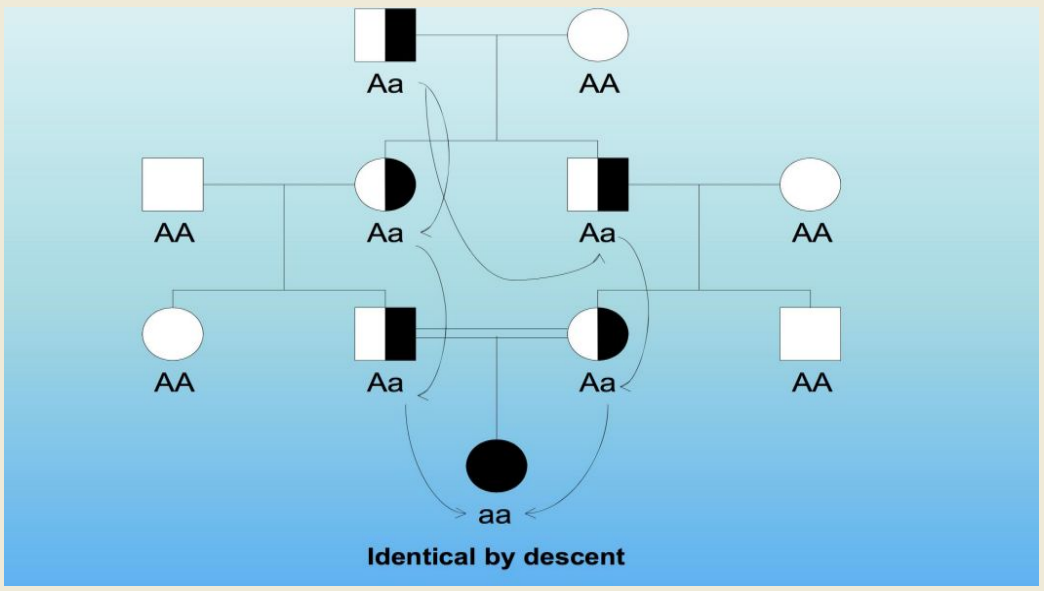
Box 9.7 Examples of autosomal recessive disorders

- Congenital adrenal hyperplasia
- Cystic fibrosis
- Friedreich ataxia
- Galactosaemia
- Glycogen storage diseases
- Hurler syndrome
- Oculocutaneous albinism
- Phenylketonuria
- Sickle cell disease
- Tay–Sachs disease
- Thalassaemia
- Werdnig–Hoffmann disease (SMA1).

- When we counsel, we tell them the chances are 4, 1 chance is homozygous taking both mutant allele (affected) , wild type taking both healthy alleles from parents, and 50% taking a mutant allele either from the mother or father (heterozygous)
- All the offspring of affected individual will carry the conditions. If an affected individual has children with carrier then 50% offspring are affected.

- Scenario: a family with one affected offspring with cystic fibrosis “a recessive disease” both parents are carriers and the mother brought one of her healthy offspring (a sibling) and told you what is the chance of this child to be carrier? First we exclude the affected one and we remain with 3 chances, and the chance of being a carrier will be 2/3. and the chance of having a wild type (healthy) not carrier is 1/3
- AD often affect structural proteins. AR often affect metabolic pathways.

Consanguinity

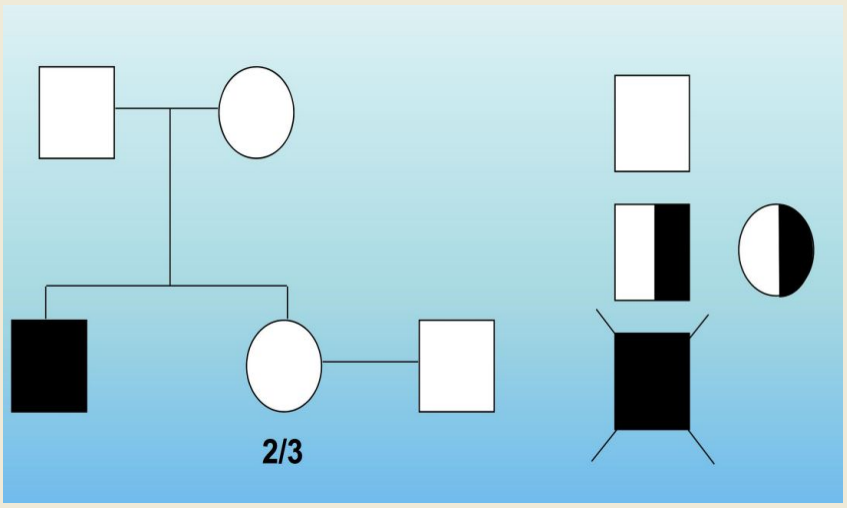


Ex:
- sickle cell disease in african
- Thalassemia in mediterranean and asian
- Tay-sachs disease in Ashkenazi Jew

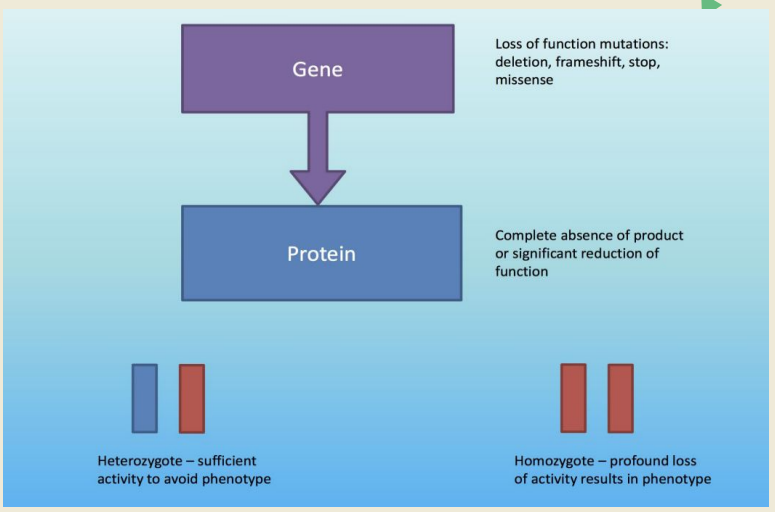
- It increases the risk of recessive disease because they’re identical by descent and carry the same genetic variation

Single gene disorders

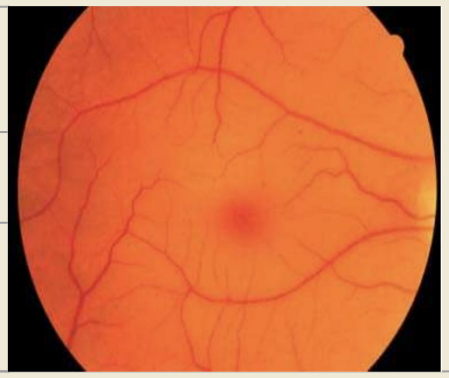
Genetic counselling



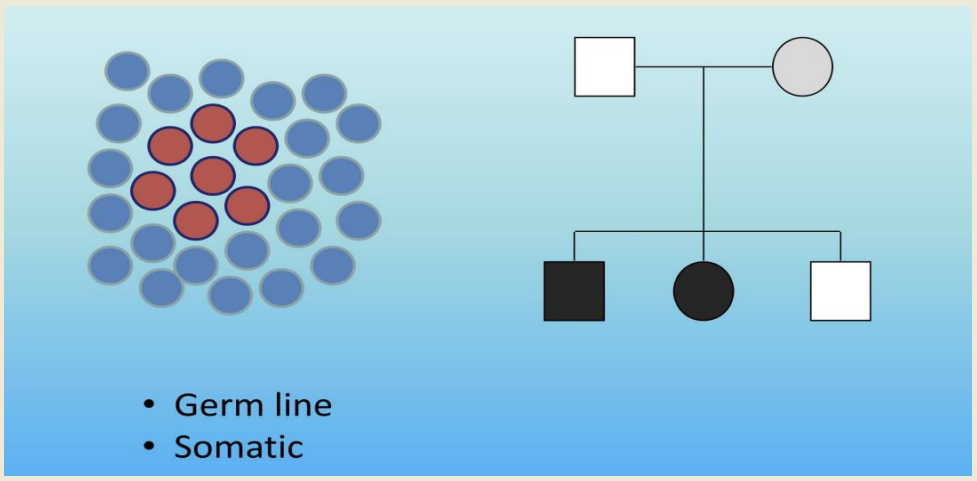
Recessive mechanism



Tay Sachs disease:

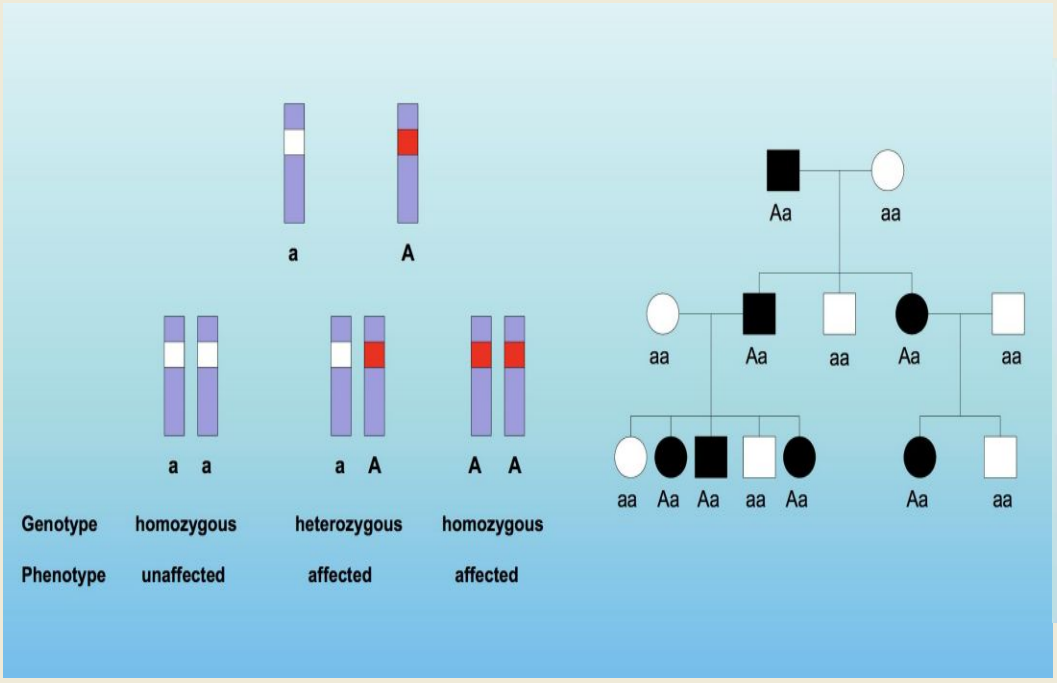
Responsible genes	HEXA	 Cherry red spot of the macula
Proteins	Hexosaminidase A	
Cytogenetic locus & Inheritance	15q23-q24 AR	
Clinical Features and Diagnostic Criteria	Infantile weakness starts at 6 mo, exaggerated startle, seizures and vision loss by the end of the first year, neurodegeneration continues- 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.	
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	
Disease Mechanism & Treatment/Prognosis	Accumulation of GM2 gangliosides in the brain. Supportive care	

Mosaicism



Single gene disorders

Autosomal dominant

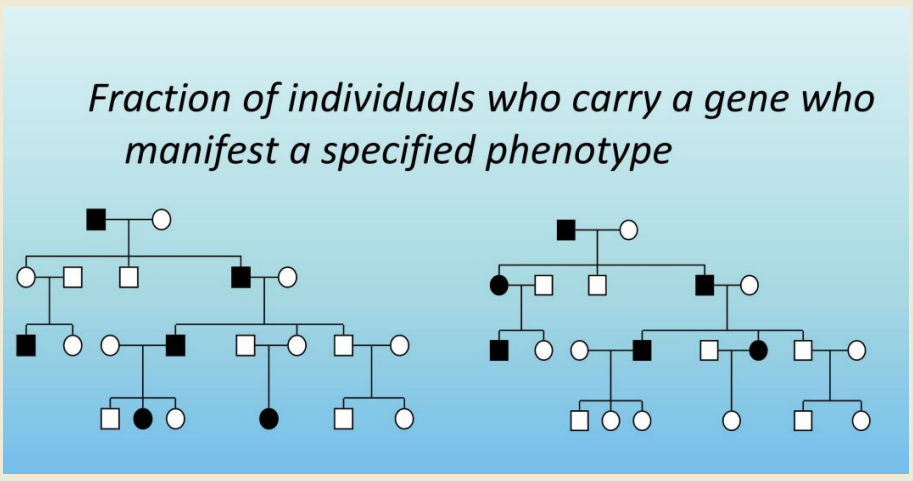


Box 9.6 Examples of autosomal dominant disorders

- Achondroplasia
- Ehlers–Danlos syndrome (this is a family of disorders rather than a single condition)
- Familial hypercholesterolaemia
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy
- Neurofibromatosis
- Noonan syndrome
- Osteogenesis imperfecta
- Otosclerosis
- Polyposis coli
- Tuberous sclerosis

- AD gene are located in chromosome 1-22. Thus, Male and females are equally affected
- Heterozygous is affected in autosomal dominant, one copy of allele is enough with 50% risk

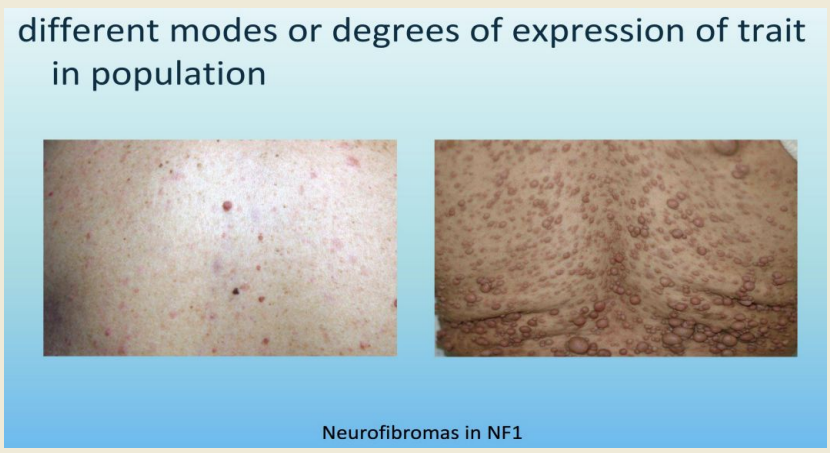
Penetrance



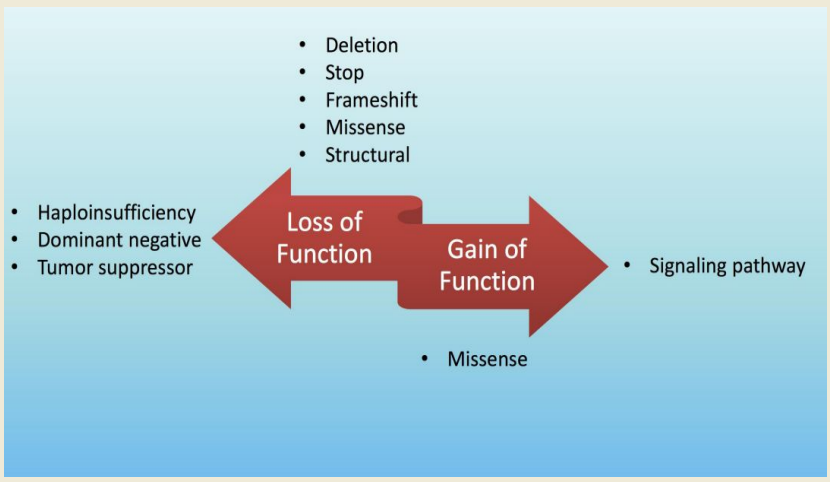
Fraction of individuals who carry a gene who manifest a specified phenotype

- The presentation of the phenotype if you carry the genotype, penetrance is the chance of showing the phenotype
- Reduced penetrance means that it's not always if you carry the genotype, you'll show the phenotype (skipping generations)

Expressivity



- Variable phenotype for ex. Mother has MS with very reduced phenotype and symptoms and her offspring carry the same genotype but show the complete phenotype of MS

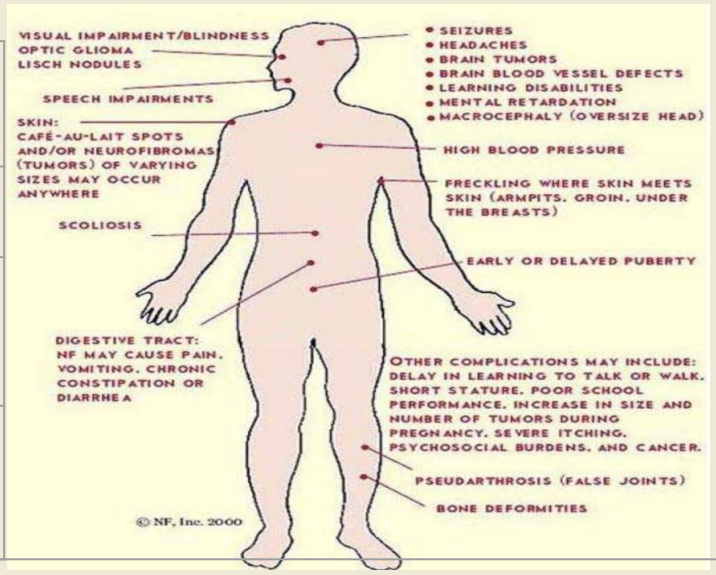


Dominant mechanism

Single gene disorders

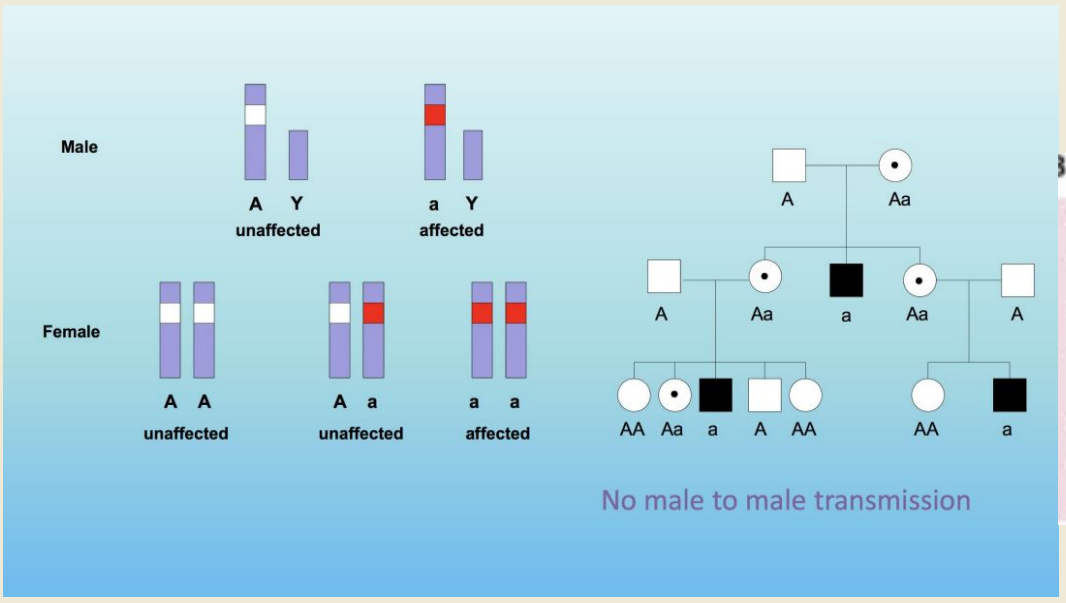
Neurofibromatosis 1:

Responsible genes	NF1
Proteins	Neurofibromin
Cytogenetic locus (loci)	17q11
Inheritance	AD



Clinical Features and 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
Disease Mechanism	Loss of function mutations impair ras GTPase mediated cellular proliferation and tumor suppression
Treatment/Prognosis	The majority live normal lifespan. Surgery for bone malformations or painful or disfiguring tumors

X-linked



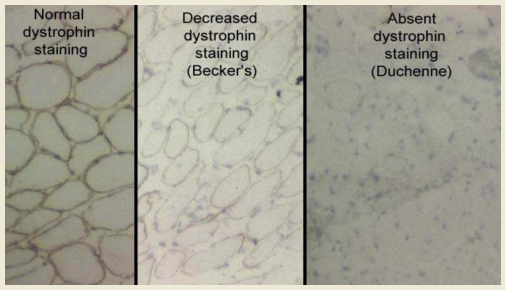
Box 9.8 Examples of X-linked recessive disorders

- Colour blindness (red–green)
- Duchenne and Becker muscular dystrophies
- Fragile X syndrome
- Glucose-6-phosphate dehydrogenase deficiency
- Haemophilia A and B
- Hunter syndrome (mucopolysaccharidosis II)

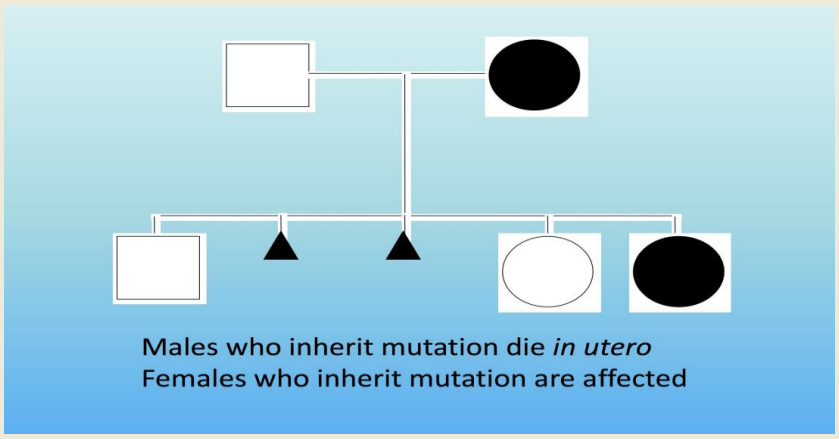
- The phenotype will be expressed in males, females are carrier
- If the mother is a carrier, then the chance of the female offspring is 50% carrier 50% healthy and the male offspring will be 50% affected and 50% healthy

Single gene disorders

Duchenne and Becker muscular dystrophy (DMD/BMD):

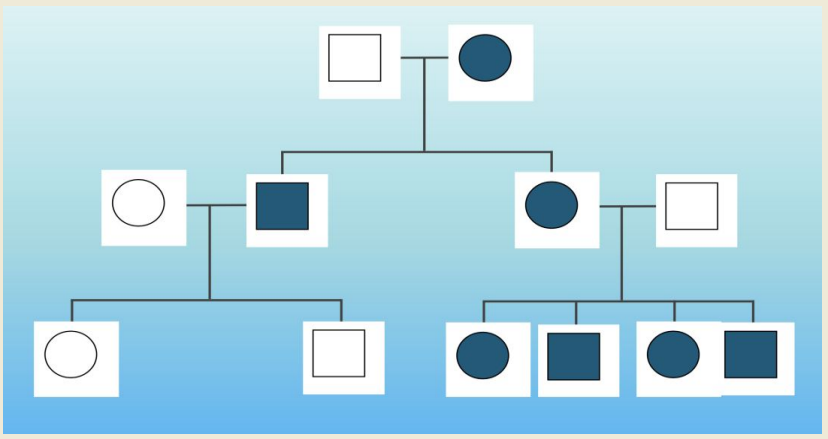
Responsible genes	DMD
Proteins	Dystrophin
Cytogenetic locus (loci)	Xp21.2
Inheritance	XLR
Clinical Features and Diagnostic Criteria	DMD: Symptoms present before age 5, progressive symmetrical muscular weakness, proximal>distal, calf hypertrophy, dilated cardiomyopathy(DCM). BMD: Later onset, less severe, 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).
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.
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.

X-linked dominant lethal in male



Its very rare and dominant in males, it can show in the female but its lethal in males Ex: Rett syndrome and hypophosphatemia (vit d resistant) rickets.

Maternal inheritance

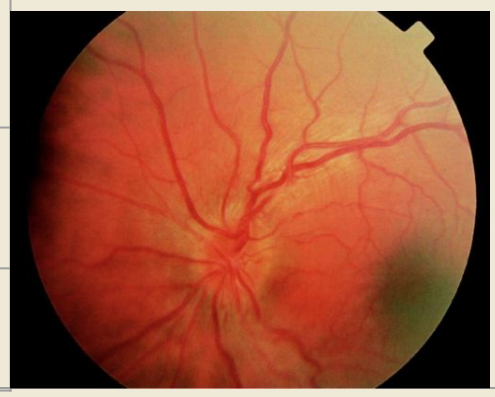


Transmitted both to the male and female from the maternal side, ex. Most mitochondrial disorders

Single gene disorders

Leber hereditary optic neuropathy:

Responsible genes	MTND1, MTND4, MTND5, MTND6
Proteins	Complex I subunits of the mitochondrial respiratory chain
Cytogenetic locus (loci)	Mitochondrial
Inheritance	Mitochondrial maternal inheritance
Clinical Features and 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 microangiopathy, 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%).
Disease Mechanism	Focal degeneration of the retinal ganglion cell layer and optic nerve.
Treatment/Prognosis	No treatment available, worsened by smoking or EtOH



Dynamic mutation (unstable repeat expansion)

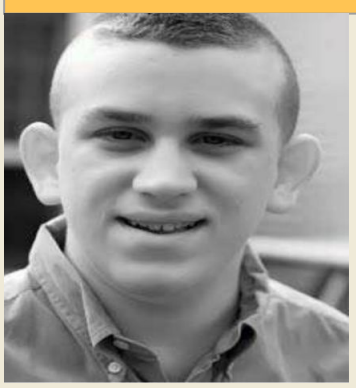
Dynamic mutation: that change from generation to generation.

- The expansion beyond the normal can alter gene expression and function. Becoming more severe
- Parental transmission bias: anticipation occurs the mutant allele transmitted through the affected father or mother. Sometimes it's worse and severe if transmitted through the father and sometimes it gets worse and severe if transmitted through the mother
- The expansion of premutation alleles occurs primarily in the female germline in FGXS but largest expansion causing juvenile onset HD in male germline if the father is a carrier of the permutation it's more likely, it'll cause severe phenotype in his offspring
- If the mother is a carrier of the premutation allele of FGXS she'll more likely transmit to her male offspring
- Most common diseases: Fragile X syndrome, Huntington's disease, Myotonic dystrophy

Dynamic mutation (unstable repeat expansion)

Fragile X syndrome :

Responsible gene	FMR-1
Protein	FMRP (Fragile X Mental Retardation Protein)
Cytogenetic locus (loci)	Xq27.3
Inheritance	X-linked triplet repeat
Clinical Features and Diagnostic Criteria	Delayed motor and verbal development, ID (mod-severe in boys, milder in girls), prominent jaw and forehead, 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.
Disease Mechanism	>200 repeats leads to silencing by methylation. POF and ataxia thought to be due to toxic gain of function.
Treatment/Prognosis	No specific treatment.



Facial features:
Long face
Prominent forehead
Large ears
Prominent jaw

Box 9.9 Clinical findings in males in fragile X syndrome

- Moderate–severe learning difficulty (IQ 20–80, mean 50)
- Macrocephaly
- Macroorchidism – postpubertal
- Characteristic facies – long face, large everted ears, prominent mandible, and broad forehead, most evident in affected adults
- Other features – mitral valve prolapse, joint laxity, scoliosis, autism, hyperactivity

- In the female carriers, they suffer from milder form but with anxiety, ocd , ovarian failure
- In the carrier male (<200 repeats) progressive intention tremor, ataxia, parkinsonism its called fraxF
- One of the commonest mental retardations, it's a repeat expansion mutation
- When the triplet repeat expansion is in the coding One of the commonest mental retardations, it's a repeat expansion mutation sequence, as in Huntington disease. proteins containing an excess of the amino acid, glutamine, are produced. Glutamine can damage the cells in the central nervous system when present in excess, leading to neurodegeneration. When the triplet repeat expansion is in other regions of the gene, reduced quantities of the protein are produced. In these cases, the reduction in the amount of the available protein leads to myotonic dystrophy.

Developmental genetic

Dysmorphology Pleiotropy Congenital anomalies

Congenital anomalies:

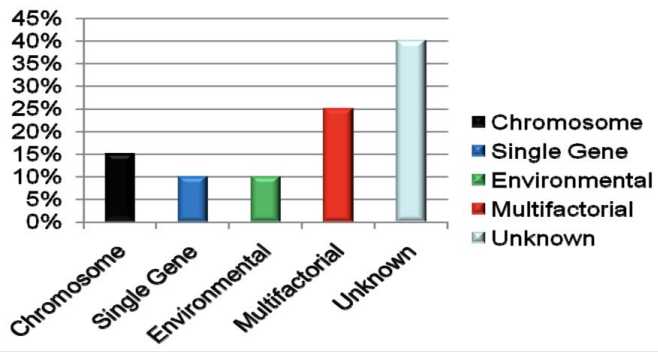
13% of all newborns

20% of infant deaths
10% NICU admissions
25 35% of deaths

Leading cause of neonatal morbidity and mortality

Pediatrics admissions: 25% to 30% have major birth defect

Causes of congenital anomalies



Congenital anomalies

Isolated Anomaly	Incidence per livebirths
Undescended testes	1:30
Heart defect	1:150
Club foot	1:300
Neural tube defects	1:500
Cleft lip ± cleft palate	1:1000
Hypospadias	1:1000
Polydactyly	1:1500
Cleft palate	1:2000
Craniosynostosis	1:2000
Syndactyly	1:2000

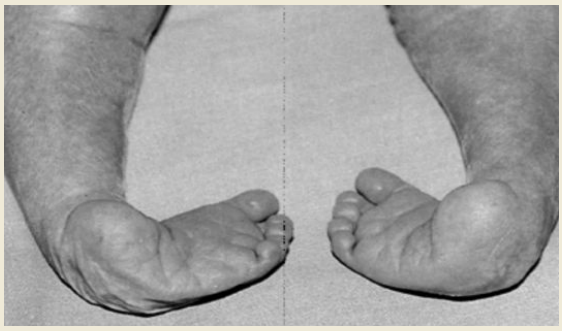
Dysmorphology:

Pathogenic mechanism	Explannition	Examples
Deformation	• Developmental Process is normal. • Mechanical force alters structure , extrinsic factors impinging physical on the fetus during development usually second trimester. • Most of them are reversible.	maternal or fetal force: • Oligohydramnios • Breech presentation • • Bicornuate uterus
Disruption	• Developmental process is normal, but interrupted. • Destruction of irreplaceable normal fetal tissue--->actual loss of tissue. • Vascular insufficiency , trauma, or teratogen.	• Amniotic band sequence • Fetal Cocaine exposure
Malformation	• Morphological defect from an intrinsically abnormal developmental process. • Malformation in one part is often but not always associated with malformation elsewhere.	• holoprosencephaly, • congenital heart disease • neural tube defect • polydactyly
Dysplasia	• Abnormal tissue organization, microscopic structure.	• Skeletal or connective tissue dysplasia • Ectodermal dysplasia

Developmental genetic

Dysmorphology cont.

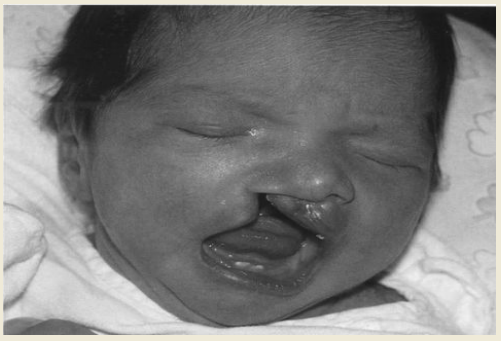
Deformation



Clubbed feet Reversible can be treated with physiotherapy

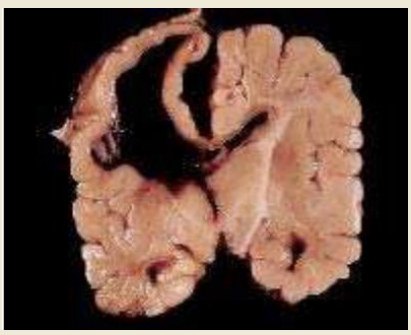
spina bifida

Malformation

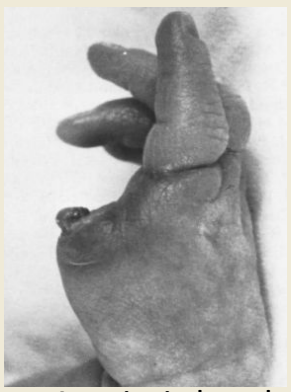


Unilateral cleft lip and palate

Disruption

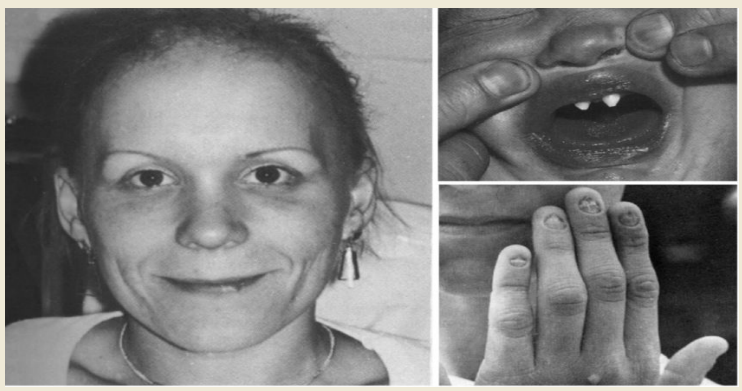


Porencephaly vascular insufficiency leading to tissue loss



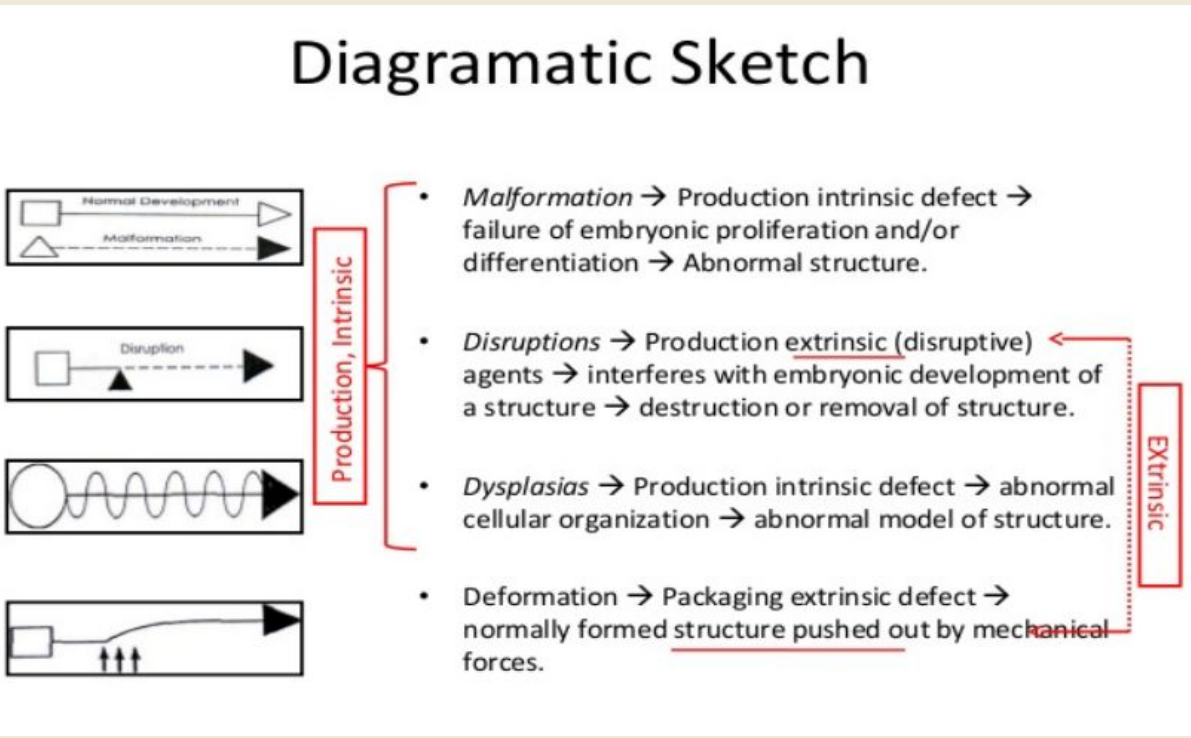
Amniotic band

Dysplasia



Ectodermal Dysplasia

Diagramatic Sketch



Malformation Urogenital (PUV) → **Oligohydramnios** → **Fetal deformation**

Vascular malformation → **Vascular insufficiency** → **Disruption of distal structure**

Developmental genetic

Pleiotropy: Syndrome and Sequences

- 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 structure that arise at different times during development.
- Causative agents could be a **gene** or **teratogen**.
- When causative agent causes multiple abnormalities in **parallel**, the collection called **Syndrome**

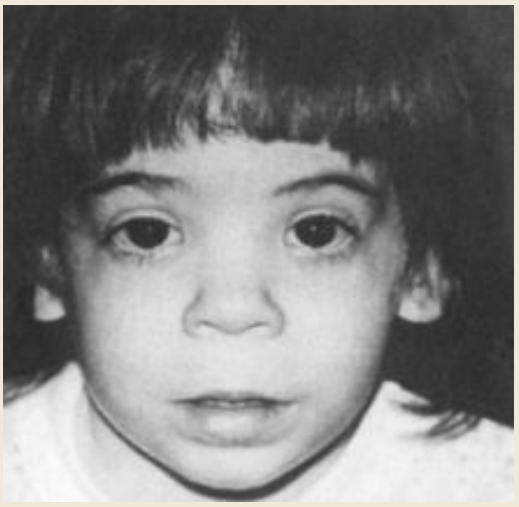
• When a causative agent affects **only a single organ** at one point of time which then causes the rest of constellation of pleiotropic defect , secondary effect , this referred as **Sequence**

Syndrome

A recognizable pattern of anomalies presumed to be causally related		
Genetic	**Environmental**	**Complex**
chromosomal, single gene	alcohol, retinoic acid	more than one genetic and/or environmental factor

Association:
A group of malformations that occur together more often than expected by chance, but in different combinations from case to case, e.g. vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, limb defects (VACTERL) association.
Single-system defects:
These include single congenital malformations, such as spina bifida, which are often multifactorial in nature with fairly low recurrence risks.

Fetal alcohol Syndrome:



- Growth retardation.
- Mental retardation.
- Short nose.
- Thin upper lip.
- Hypoplastic fingernails.
- Microcephaly.
- Smooth philtrum.
- Small distal phalanges.
- Cardiac defects.

Syndrome

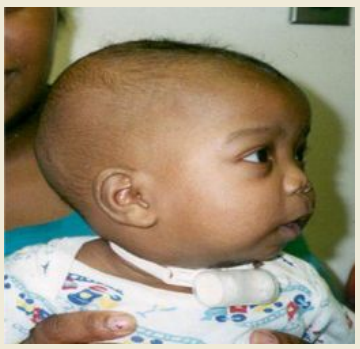
Pierre robin sequence:

Small jaw → Primary anomaly

Displacement of tongue in superior direction → Protruding tongue due to inadequate room

Cleft palat → Development of Pierre robin syndrome from constellation of the three

- Micrognathia, [U- shaped] cleft palate, glossoptosis
- 50% syndromic
  - Stickler (50%).
  - del22q11 (25%)
  - Treacher Collins, Ribgap...

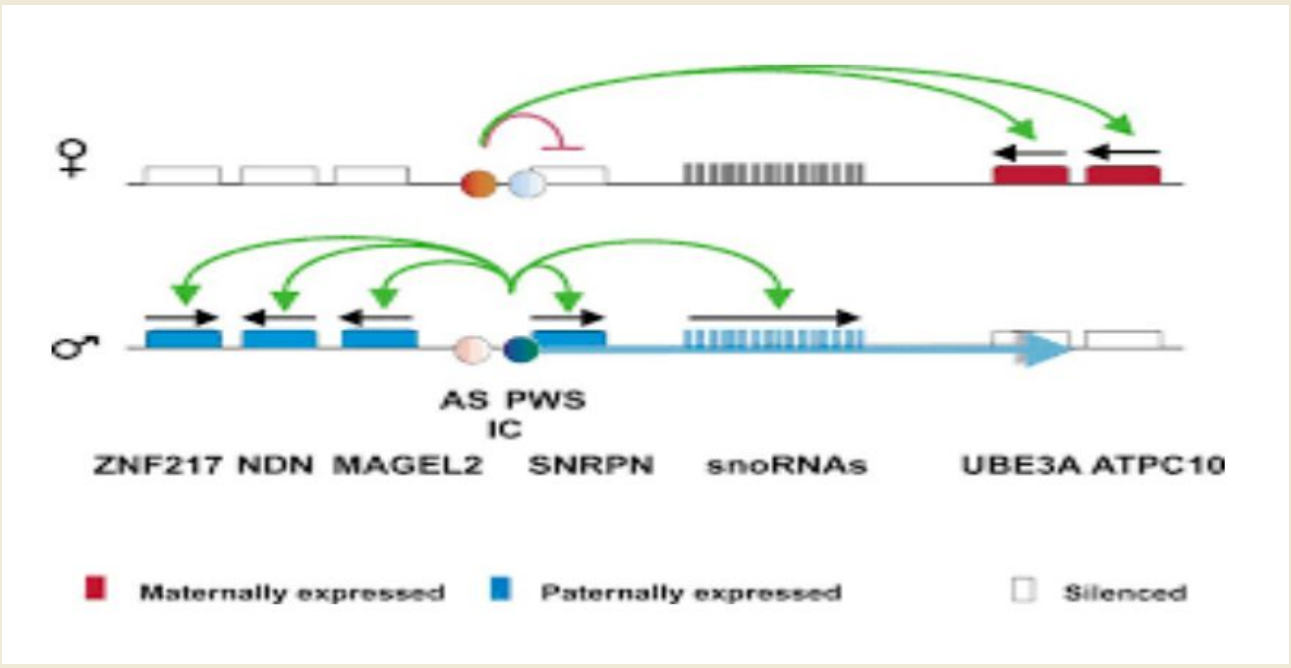


Micrognathia --> cleft palate ---> glossoptosis

Imprinting disorders

- ❖ 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 only 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.



Imprinting disorders

Prader Willi syndrome:

Responsible gene	Paternally expressed genes within the imprinted locus on 15q11-13 (SNURF-SNRPN, MKRN3, MAGEL2, and NDN)
Cytogenetic locus (loci)	15q11-13
Inheritance	autosomal, expressed from paternal Ch 15
Clinical Features and Diagnostic Criteria	Hypothalamic insufficiency, neonatal hypotonia, developmental delay, hyperphagia leading to obesity, short stature, small hands and feet, hypogonadism, ID.
Molecular Tests	3-5 Mb deletion of 15q11.2-q13 (~70%), matUPD (15%), PWS imprinting center defect (1-2%).
Disease Mechanism	unknown
Treatment/Prognosis	Monitor for feeding problems in infancy, obesity, OCD, psychosis, scoliosis, obstructive sleep apnea, diabetes, osteopenia

- They don’t have facial characteristics
- They usually present initially IUGR, failure to thrive in the 1st year of life, severely hypotonic. After the 1st year they’ll have hyperphagia and short stature...

Imprinting disorders

Angelman syndrome:

Responsible gene	UBE3A
Protein	Ubiquitin protein ligase E3A
Cytogenetic locus (loci)	15q11-q13
Inheritance	loss of the maternally imprinted contribution in the 15q11.2- q13 (AS/PWS) region. Their problem is in the same area as prader-willi but the opposite, it's in the maternal copy
Clinical Features and Diagnostic Criteria	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 Tests	acquired microcephaly by age two years, Seizures before age three, abnl EEG: large amp. slow-spike waves.
Molecular Tests	4-6 Mb del (65-75%), UBE3A mutation (11%), imprinting defect (2.5%), unbal chrom transloc (<1%), Pat UPD 15 (<1%), del of imprinting center (0.5%).
Disease Mechanism	Disruption of E6AP ultimately causes an abnormality in the ubiquitin protein degradation pathway, but no clear AS- causing target protein yet identified.
Treatment/Prognosis	Typical care for medical issues, PT, OT, ST, and individualized education and behavior program.

Facial features:
Protruding tongue
Prognathia
Wide mouth
Widely spaced teeth
Strabismus
Light hair and eye color

Questions

1- Following are true about Turner's syndrome, EXCEPT

- (1) Adult height < 150 cm
- (2) Coarctation of aorta
- (3) Cubitus varus of elbow
- (4) Horseshoe kidney

Ans. 3

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 spaced nipples.
- Horseshoe kidney, cubitus valgus of the elbow.

2- All are true regarding Trisomy 21, EXCEPT

- 1) Chromosomal nondisjunction during maternal meiosis responsible for 80-90% of cases
- (2) Brushfield spots on iris
- (3) Epicanthal fold
- (4) Hypertonic at birth

Ans. 4

92% of Down's syndrome have trisomy with an extra. 21 chromosome in all body cells. Chromosomal nondisjunction 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**

- 1) "Premutations" may expand to full mutations in future generations
- (2) Offspring of male carriers inherit a premutation
- (3) Offspring of female carriers may inherit a premutation or a full mutation
- (4) Individuals with premutation are likely to have mental retardation

Ans. 4

several disorders have recently been found to be the result of expanding series of triplet repeats.

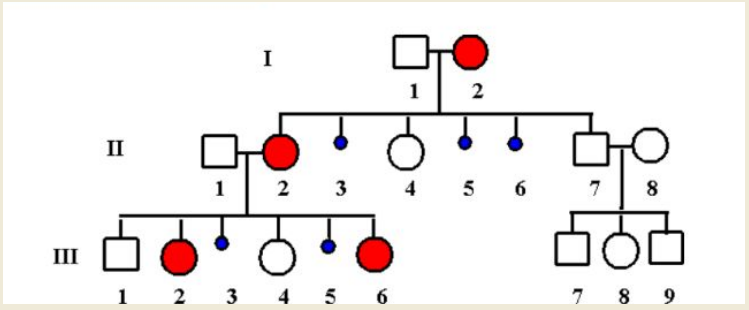
- These include the fragile X syndrome, myotonic dystrophy, and Huntington's disease.
- Although the length of the region is variable in normal individuals, unaffected female carriers, and non-penetrant, transmitting males have "permutations" which are generally 50 to 230 repeats in length.
- Individuals with permutations are, therefore, phenotypically unaffected. Nonpenetrant males transmit only unstable permutations; female carriers may transmit either permutations or full mutations, which are associated with mental retardation and the other phenotypic features of the syndrome.

Questions

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

- (1) X-linked recessive inheritance
- (2) X-linked dominant inheritance
- (3) Autosomal recessive inheritance
- (4) Autosomal dominant inheritance

Solid figure = Affected individuals
Open figure = Unaffected individuals



Ans. 2

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 hemizygous.
- 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.

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

- (1) Embryonic
- (2) Fetal
- (3) Childhood
- (4) Adult

Ans. 1

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.

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?**

- (1) Sequence
- (2) Syndrome
- (3) Disruption
- (4) Deformation

Ans. 2

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.

Questions

Fluorescent in situ hybridization (FISH) analysis is useful in all the following situations, EXCEPT

- (1) Determination of sex in cases of ambiguous genitalia
- (2) Determination of uniparental disomy
- (3) Rapid diagnosis of trisomies
- (4) Identification of submicroscopic deletions

Ans. 2

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 chromosome cannot be determined with this technique, uniparental disomy cannot be detected.

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).**

- (1) Most patients will have an affected parent
- (2) Males are more commonly affected than females
- (3) The recurrent risk is 1 in 4 for each subsequent sibling
- (4) The trait is never transmitted directly from father to son

Ans. 3

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.

Indications for genetic counselling include all of the following, EXCEPT

- (1) Consanguinity
- (2) Family history of cystic fibrosis
- (3) Family history of congenital infection
- (4) Advanced maternal age

Ans. 3

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.

Questions

Which of the following are due to micro deletion, EXCEPT

- (1) Beckwith-Wiedemann syndrome OR TRISOMY 13
- (2) Retinoblastoma
- (3) Prader-Willi syndrome
- (4) Angelman syndrome

Ans. 1

Beckwith-Wiedemann syndrome is due to microduplication on ‘p’ arm of chromosome 11.

- Microdeletion is seen in:
- (a) WAGR complex (11p13)
- (b) Retinoblastoma (13q14)
- (c) Prader-Willi syndrome (15q11)
- (d) Angelman syndrome (15q11)
- (e) DiGeorge syndrome (22q11)