Genetics and Dysmorphology

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Autosomal Dominant

Background

- Autosomal dominant (AD) inheritance is determined by the presence of one abnormal gene on one of the autosomes (chromosomes 1–22).
- Autosomal genes exist in pairs with each parent contributing one copy.
- Affected individuals have a 50% chance of passing on the deleterious gene with each pregnancy, therefore having affected child by the disorder (Fig. 1).

Characteristics of genetic transmission in autosomal dominant cases

- Both sexes are equally affected.
- Both sexes can transmit to offspring.
- No generation is skipped (unless not completely expressed).
- Every affected child has a parent with the disorder, except the new or spontaneous mutation.

Mosaic germline mutation

- It is significant because it can be passed to offspring.
- Typically, a person with *only* germline mosaicism will not be affected with the disorder caused by the mutation because the mutation is not in the other cells of the body, it is in sperm or ova.
- Commonly seen with AD and X-linked disorders.
- Because the mosaic germline mutation is present in the egg or sperm cell, it will also be present in all cells of the child developing from that germ cell.
- If it is an autosomal dominant mutation, the child will be affected with the disorder and will not be a mosaic like his or her parent.
- Unaffected parents can have more than one child with an AD disorder. This can be caused by germline mosaicism.
- Example of autosomal dominant diseases:
  - Osteogenesis imperfecta
  - Neurofibromatosis
  - Polycystic kidney disease
  - Achondroplasia

Sporadic mutation

- Unaffected parents have a child with an AD disorder.
- It is because of a new mutation that occurred by chance in only one egg or sperm cell, not in a proportion of them.

Autosomal Recessive

Background

- Involves mutation in both copies (alleles) at a gene locus.

Characteristics of genetic transmission in autosomal recessive cases

- Males and females are equally affected.
- Males and females can each transmit a copy of mutated gene.
- Recurrence risk for parents with a previous affected child is 25%.
- The risk of parents who are carrying a mutated gene to have an affected child is one-fourth or 25%.
- Consanguinity increases the risk of having an offspring with an AR disorder (Fig. 2).

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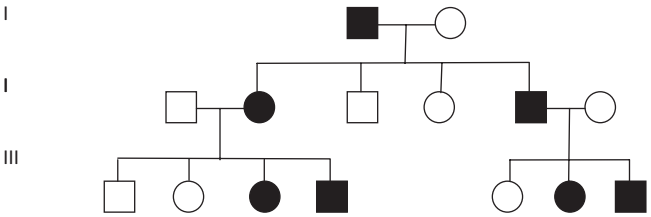


Fig. 1 Autosomal dominant pedigree. *Black* affected patients

X-Linked Disorders

Background

- Only females can transmit the disease to their son.
- If a generation has only female, the disease will appear to have skipped that generation.

Characteristics of genetic transmission in X-linked recessive cases

- Males are more commonly and more severely affected than females.
- Female carriers are generally unaffected, or if affected, they are affected more mildly than males.
- Female carriers have a 25 % risk for having an affected son, a 25 % risk for a carrier daughter, and 50 % chance of having a child that does not inherit the mutated X-linked gene.
- Affected males will have only carrier daughters.
- Affected males will have no chance of having affected son because they will pass their Y chromosome to their sons.
- Male-to-male transmission excludes X-linkage.
- X-linked dominant diseases can manifest in either male or females (Fig. 3).

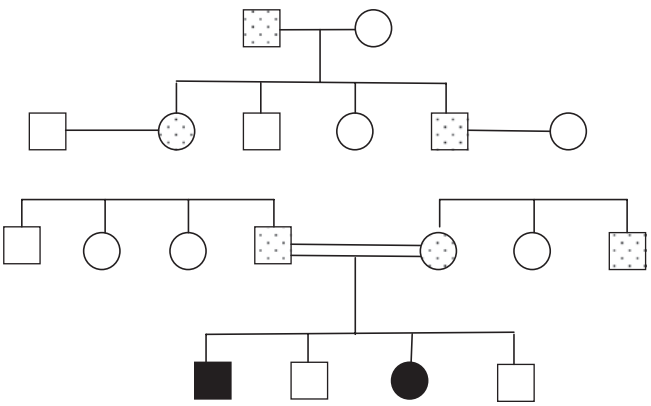


Fig. 2 Autosomal recessive pedigree with parental consanguinity. *Dots* carriers, *black* affected patients

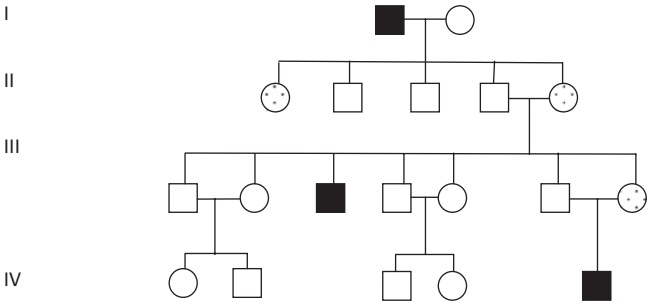


Fig. 3 X-linked recessive pedigree. *Dots* carriers, *black* affected patients (e.g., hemophilia)

Example of X-linked recessive diseases

- Hemophilia A
- Duchenne and Becker muscular dystrophy
- Hunter syndrome
- Fabry disease

Example of X-linked dominant diseases

- X-linked hypophosphatemia
- Incontinentia pigmenti
- Rett syndrome
- Most cases of Alport syndrome

Genomic Imprinting

Background

- Gene expression depends on whether the affected gene is transmitted from the mother or the father.
- Uniparental disomy occurs if both copies of a chromosome in a part or whole come from one parent.

Example of genomic imprinting

- The first imprinted genetic disorders to be described in humans were the reciprocally imprinted Prader–Willi syndrome and Angelman syndrome.
- Both syndromes are associated with loss of the chromosomal region 15q11-13 (band 11 of the long arm of chromosome 15).
- Paternal inheritance of a deletion of this region is associated with Prader–Willi syndrome (characterized by hypotonia, obesity, and hypogonadism).
- Maternal inheritance of the same deletion is associated with Angelman syndrome (characterized by epilepsy, tremors, and a perpetually smiling facial expression).

Mitochondrial Disorders

Background

- Mitochondria have the only genetic material outside of the nucleus.

- The mitochondrial genome is haploid (contains only one copy of each gene) whereas the nuclear genome is diploid.
- An egg contains 100,000–1,000,000 mitochondrial DNA (mtDNA) molecules, whereas sperm contain only 100–1000).
- In mitochondrial inheritance, the ovum not the sperm, transmits all of the mitochondria to their zygote.
- Mother carrying a mtDNA mutation of sufficient frequency—some individuals have mixtures of normal and abnormal mtDNA called heteroplasmy—will pass it on to all her offspring.
- The father will rarely pass mitochondrial mutations on to his offspring because sperm have few mitochondria.

Examples of mitochondrial inherited disease

- MELAS
  - Mitochondrial encephalopathy
  - Stroke-like episodes
  - Lactic acidosis
- MERRF (myoclonic epilepsy and red ragged fibers disease)
  - Progressive myoclonic epilepsy
  - Myopathy
  - Dementia
  - Hearing loss
- Leigh disease
  - Basal ganglia defects
  - Hypotonia
  - Optic atrophy in infancy or early childhood
- Kearns–Sayre syndrome
  - Ophthalmoplegia
  - Retinitis pigmentosa,
  - Myopathy
  - Cardiac conduction defect

Multifactorial Inheritance

Background

- Multifactorial inheritance means that "many factors" (multifactorial) are involved in causing a birth defect.
- The factors are usually both genetic and environmental, where a combination of genes from both parents, in addition to unknown environmental factors, produce the trait or condition.
- Often one gender (either males or females) is affected more frequently than the other in multifactorial traits.
- There appears to be a different "threshold of expression," which means that one gender is more likely to show the problem over the other gender.
  - *For example*, hip dysplasia is nine times more common in females than males.

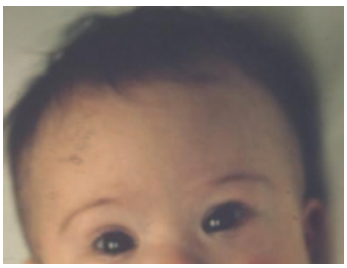
Multifactorial inheritance characteristics

- The higher the number of the affected individuals in the family, the higher the recurrence risks.
- The recurrence risk is higher if the affected individual is a member of the less commonly affected sex
  - e.g., Autism is more common in boys than girls but if a girl in the family has autism, it is twice as likely to recur in a sibling than if a boy is the one with autism.
- Recurrence risk is higher if the affected individual suffers the more severe form of the disease.
- Recurrence risk correlates with the prevalence in the general population.
- Folic acid supplementation early in pregnancy decrease the risk of neural tube defect.

Indications for chromosomal analysis

- Birth defects
- Development delay
- Intellectual disability
- Growth abnormalities

Down Syndrome (Fig. 4)



Background

- Trisomy 21 nondisjunction is most common cause (95% of cases).
- Robertsonian translocation is 4% and 1% is mosaic
- Trisomy 21 recurrence risk if non disjunctional add 1% to maternal age related risk which range from 1–4%, so most likely 96–99% will not have a child with Down syndrome
- If the couple has a child with trisomy 21 the risk of recurrence is 1%
- Trisomy translocation if confirmed; blood test should be requested from parents in order to determine the carrier status and the risk of recurrence
- Risk of recurrence in Robertsonian translocation
  - If the mother is a carrier 14q:21q translocation; the risk is 15% with amniocentesis and 10% for a live-born child with Down Syndrome.
  - If the mother is 21q:21q translocation the risk of recurrence is 100%

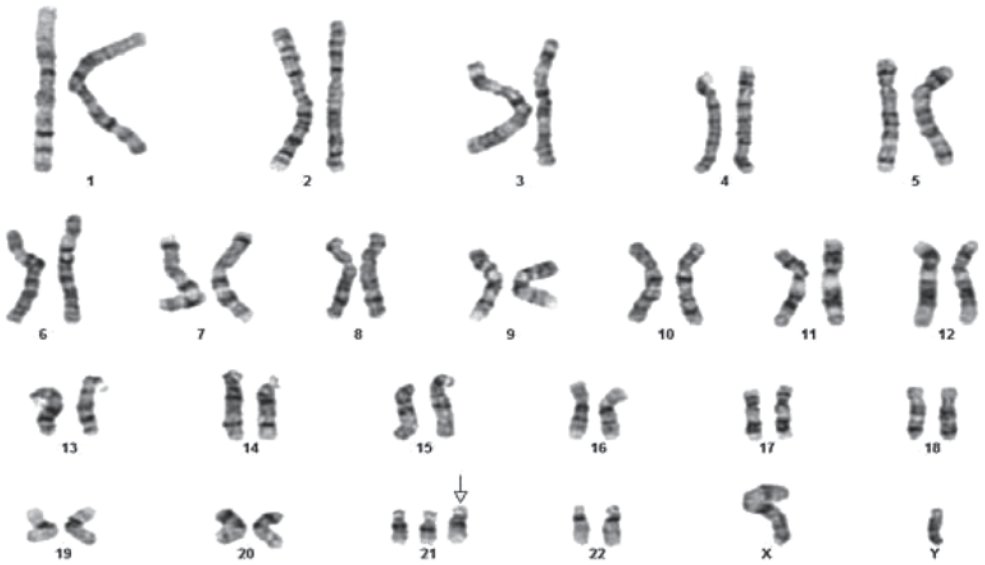


Fig. 4 47,XY.+21: Abnormal male karyotype with trisomy 21, consistent with Down syndrome

Clinical Features

- Most common
  - Hypotonia
  - Small ears
  - Intellectual disability (ID)
- More specific to Down syndrome
  - Brachydactyly (short, broad fingers and toes. Broad space between the first and second toes)
  - Absent to very small nipple buds
  - Central placement of the posterior hair whorl
- Common in Down syndrome but not specific
  - Microcephaly
  - Up-slanted palpebral fissure
  - Flat midface
  - Full cheeks
  - Epicanthal folds
  - Single transverse creases (simian lines)
  - Speckled iris (Brushfield spots)
  - High arched palate
  - Hypoplasia of of the middle phalanx of the fifth finger
- Cardiac defects
  - Nearly 50% are affected
  - Endocardial cushion (atrioventricular septal) defects are most common
  - Ventricular septal defect
- GI defect
  - Duodenal atresia
  - Hirschsprung disease (look for classic double bubble sign indicating duodenal atresia on abdominal X-ray)
- Developmental disorder
  - IQ ranges from 20 to 50
  - Social behavior are beyond that expected for mental age

Evaluations and health supervision

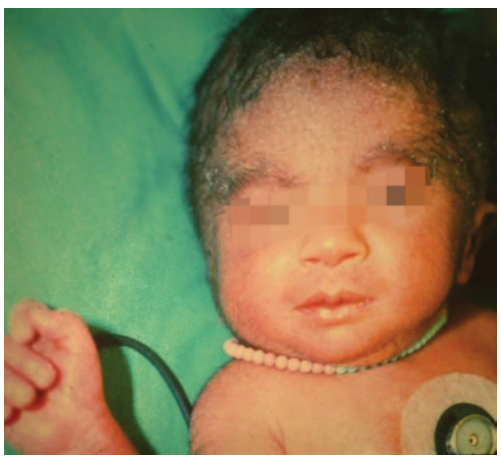
- Cardiac
  - Heart defects (~50% risk). Perform an echocardiogram
  - Refer to a pediatric cardiologist for evaluation any infant whose postnatal echocardiogram results are abnormal.
- Feeding problems
  - Refer all infants who have marked hypotonia as well as infants with slow feeding, choking with feeds, recurrent pneumonia, or other recurrent or persistent respiratory symptoms and unexplained failure to thrive for a radiographic swallowing assessment
- Ophthalmology
  - Check at birth by looking for a red reflex specially for cataract.
  - Cataracts may progress slowly and, if detected, need prompt evaluation and treatment by an ophthalmologist with experience in managing the child with Down syndrome.
  - Check for strabismus and astigmatism.
- Congenital hearing loss
  - Brainstem auditory evoked response or otoacoustic emission, at birth, according to the universal newborn hearing screening guidelines.
  - Complete any needed follow-up assessment by 3 months.
- GI
  - Duodenal atresia or anorectal atresia/stenosis by performing a history and clinical examination.
  - If constipation is present, evaluate for restricted diet or limited fluid intake, hypotonia, hypothyroidism, or gastrointestinal tract malformation, including stenoses or Hirschsprung disease, for which there is an increased risk.

  - Gastroesophageal reflux, which is usually diagnosed and managed clinically. If severe or contributing to cardiorespiratory problems or failure to thrive, refer for subspecialty intervention.
  - Celiac screening at 2 years or with symptoms.
- Respiratory
  - Obstructive apnea due to narrow airway: start screening at 1 year and each visit or anytime if any symptoms.
  - Apnea, bradycardia, or oxygen desaturation in a car safety seat for infants who are at increased risk because they have had cardiac surgery or are hypotonic.
  - A car safety seat evaluation should be conducted for these infants before hospital discharge.
  - Stridor, wheezing, or noisy breathing. If severe or contributing to cardiorespiratory problems or feeding difficulty, refer to pediatric pulmonologist to assess for airway anomalies.
  - Tracheal anomalies and small tracheal size may also make intubation more difficult.
- Hematologic abnormalities
  - Obtain a complete blood cell count.
  - Leukemoid reactions, or transient myeloproliferative disorder (TMD).
  - TMD is found almost exclusively in newborn infants with Down syndrome and is relatively common in this population (10%).
  - TMD usually regresses spontaneously within the first 3 months of life, but there is an increased risk of later onset of leukemia for these patients (10–30%).
  - Polycythemia is also common in infants with Down syndrome (18–64%) and may require careful management.
  - Infants with TMD and polycythemia should be followed according to subspecialty consultation recommendations.
  - Parents of infants with TMD should be counseled regarding the risk of leukemia and made aware of the signs, including easy bruising, petechiae, onset of lethargy, or change in feeding patterns.
  - Leukemia is more common in children with Down syndrome than in the general population but still rare (1%).
- Endocrinology
  - Congenital hypothyroidism (1% risk).
  - Screen for hypothyroidism; at birth, repeat at 3, 6, and 12 months then annually thereafter even if is normal.
  - Obtain thyroid-stimulating hormone (TSH) concentration if state newborn screening only measures free thyroxine (T4).
  - Congenital hypothyroidism can be missed if only the T4 concentration is obtained in the newborn screening.
  - Many children with Down syndrome have mildly elevated TSH and normal free T4 levels.
  - Management of children with abnormal thyrotropin or T4 concentrations should be discussed with a pediatric endocrinologist.
  - Skeletal
  - Atlantoaxial subluxation or instability at each visit by history and physical exam, and radiograph by 3–5 years or when planning to participate in contact sports.
  - Do radiograph if neck pain, torticollis, gait disturbance, or weakness.
- Immunization
  - All routine immunizations should be given.

Trisomy 18 (Edwards Syndrome; Fig. 5)

Background

- Among liveborn children, trisomy 18 is the second most common autosomal trisomy after trisomy 21.
- Four-to-one boys-to-girls ratio.
- Risk of recurrence in future pregnancy is less than 1%.
- The risk is higher with increased maternal age.



Clinical Presentation

- Apneic episodes
- Poor feeding
- Marked failure to thrive
- Intrauterine growth retardation (IUGR)
- Microcephaly
- High forehead
- Intellectual disability
- *Rocker bottom feet*
- Clubfoot/clenched fist
- Overlapping fingers
- Hypoplastic nails
- *Ventricular septal defect (VSD)* is most common (90% have structural heart defect).

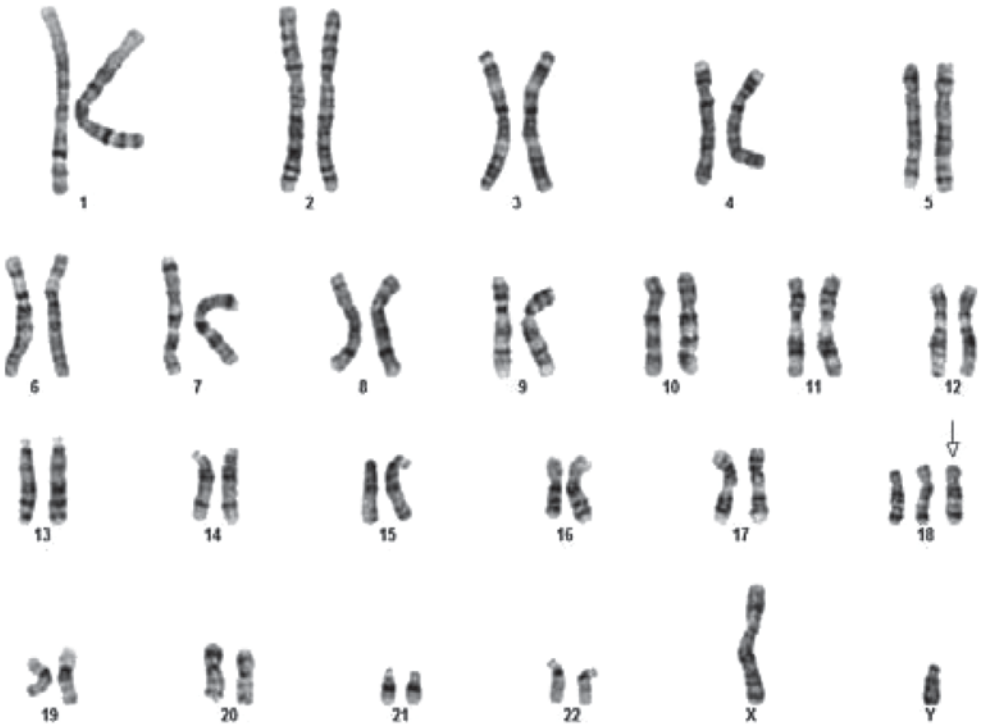


Fig. 5 47,XY,+18: Abnormal male karyotype with trisomy 18, consistent with Edwards syndrome

Prognosis
- Newborns have a 40% chance of surviving to age 1 month.
- Infants have a 5% chance of surviving to age 1 year.
- Children have a 1% chance of surviving to age 10 years.
- Mostly die early because of central apnea.

Trisomy 13 (Patau Syndrome; Figs. 6 and 7)

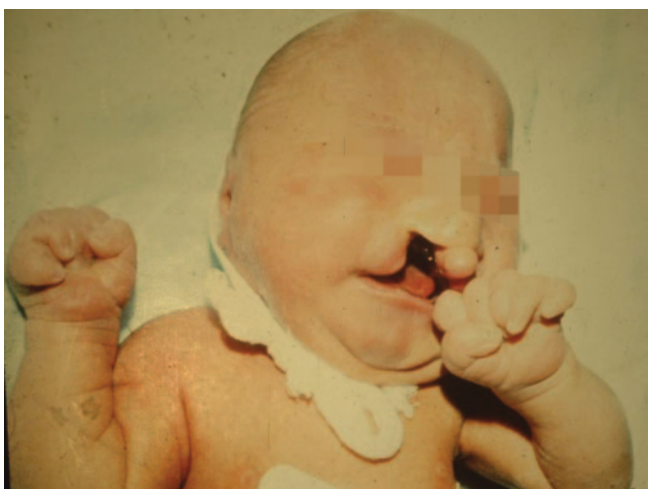


Fig. 6 Cleft lip and palate, postaxial polydactyly consistent with trisomy 13 Patau syndrome

Background
- It is the least common and most severe of the viable autosomal trisomies.
- Risk of recurrence < 1%.
- The risk is higher with increased maternal age.

Clinical presentation
- Cleft lip
- Cleft palate
- Polydactyly (postaxial)
- Microcephaly
- Microphthalmia
- Scalp defects (cutis aplasia)
- Omphalocele
- Hernias
- Neural tube defects
- Cardiac defects occur in 80% of cases, e.g., Patent ductus arteriosus (PDA) or VSD
- Genital anomalies

Prognosis
- Median survival is only 2.5 days; 82% die within 1 month, and 95% die within 6 months.

47,XXY (Klinefelter Syndrome; Fig. 8)

Background
- Klinefelter syndrome is the most common chromosomal disorder associated with male hypogonadism and infertility.

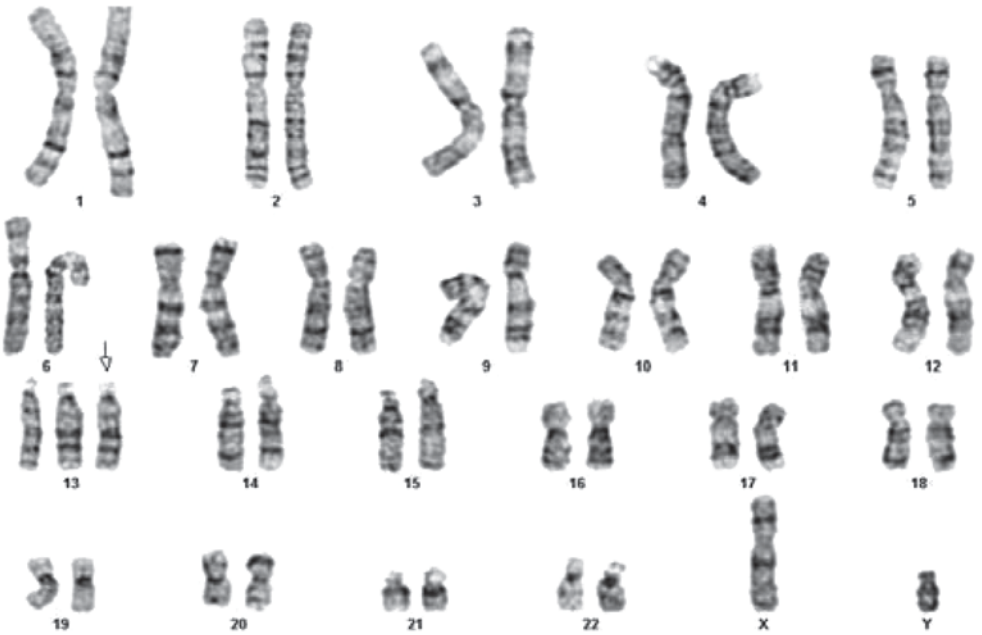


Fig. 7 47,XY,+13: Abnormal male karyotype with trisomy 13, consistent with Patau syndrome

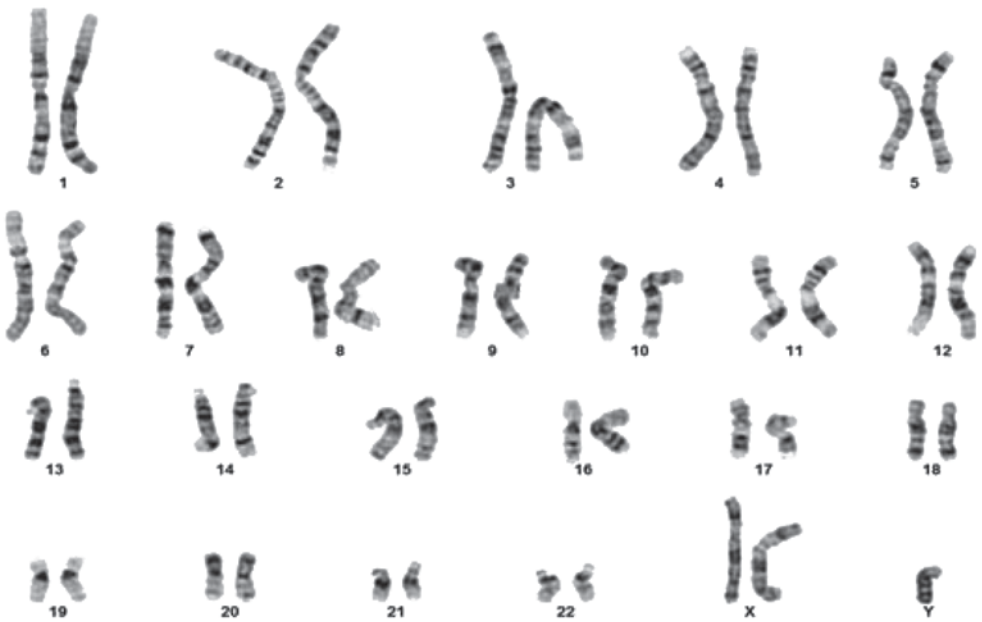


Fig. 8 47,XXY: Abnormal karyotype with an extra X sex-chromosome, consistent with Klinefelter syndrome

- It is defined classically by a 47,XXY karyotype with variants that demonstrate additional X and Y chromosomes.

Clinical presentation

- Language impairment
- Academic difficulty
- Poor self-esteem
- Behavioral problems
- Fatigue and weakness
- Osteoporosis
- Hypogonadism (pathognomonic)
- Subnormal libido
- Erectile dysfunction
- Small penis
- Infertility (azoospermia)
- Delayed secondary sexual characteristics
- Tall with gynecomastia

Risk of cancers

- Patients with Klinefelter syndrome have an increased risk of extra testicular germ cell tumors and possibly increased risk of breast cancer.
- The risk of breast carcinoma in men with the XXY variant may approach 20 times that of healthy men.

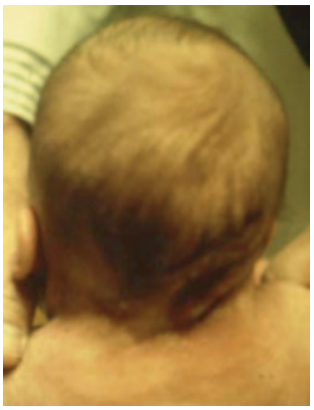


Fig. 9 Female infant with webbed neck and low posterior hairline due to lymphedema consistent with Turner syndrome

- Laboratory (typical patient with Klinefelter syndrome presents with):
- *Low* serum testosterone levels.
- *High* luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and, often, elevated estradiol levels.
- The decline in testosterone production is progressive over the life span, and not all men suffer from hypogonadism.
- Karyotype: 47,XXY

X (Turner Syndrome; Figs. 9 and 10)

Background

- Short female is considered Turner syndrome until otherwise is proved.
- The frequency is approximately 1 in 2000 live-born female infants.
- As many as 15% of spontaneous abortions have a 45,X karyotype.
- Turner syndrome is caused by the absence of one set of genes from the short arm of one X chromosome.
- *45,X karyotype* (about two thirds are missing the paternal X chromosome)
- In addition to monosomy X, a similar clinical picture is found with a 46,XXiq karyotype and in some individuals with mosaic karyotypes.
- A deletion of the *SHOX* gene can cause a similar skeletal phenotype known as Leri-Weill dyschondrosteosis.

Clinical Presentation

- *Lymphedema*: Lymphedema may be present at any age and is one finding that can suggest Turner syndrome on fetal ultrasonography.
- *Webbed neck* and low posterior hairline due to lymphedema.
- *Short stature 95%*
- *Ovarian failure*
  - Suspect ovarian failure in girls who have no breast development by age 12 years or who have not started menses by age 14 years.
  - Elevated levels of LH and FSH confirm ovarian failure.
- *Pubic hair*: Pubic hair development is normal.
- *Dental*: A high arched palate suggests the diagnosis. Patients may have dental crowding or malocclusion.

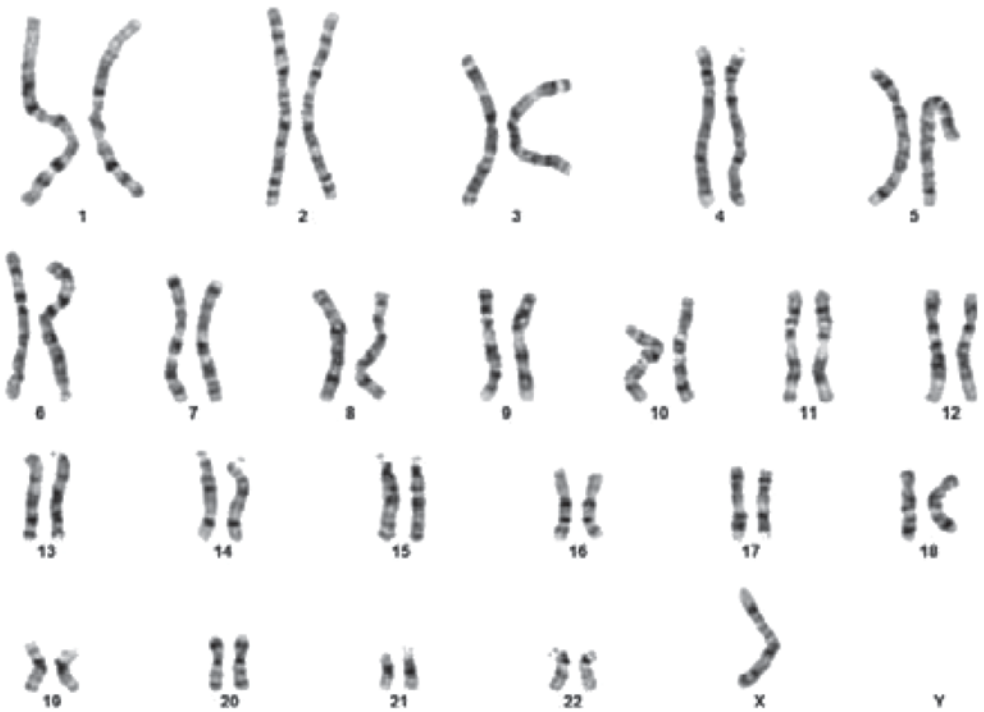


Fig. 10 45, X: Abnormal karyotype with one X sex chromosome, consistent with Turner syndrome

- *Cubitus valgus* (increased carrying angle): This is a common skeletal anomaly in girls due to abnormal development of the trochlear head.
- *Madelung deformities*
- *Short fourth metacarpal or metatarsal*
- *Shield chest:* The chest appears to be broad with widely spaced nipples.
- *Eye*: Ptosis, strabismus, amblyopia, and cataracts are more common in girls with Turner syndrome.
- *Scoliosis*: This occurs in 10% of adolescent girls with Turner syndrome and may contribute to short stature. Scoliosis screening is essential.
- *Cardiac*
  - Bicuspid aortic valve is 50% of the cases
  - Hypertension
  - Coarctation of aorta 15–20%
  - Murmur
  - Hypoplastic left heart
- *Endocrinology*
  - Hashimoto's thyroiditis (50% positive antithyroid antibodies)
  - 10–30% develop hypothyroidism
  - Carbohydrate intolerance (screening for diabetes is best obtain by Hemoglobin A1c or fasting glucose level) avoid glucose tolerance test
- *Horseshoe kidney*
- *Alopecia, nevi, cutis laxa, and vitiligo*
- *Nails:* Many patients have hypoplastic or hyperconvex nails
- *Otitis media*

Diagnosis
- Turner syndrome may be prenatally diagnosed by amniocentesis or chorionic villous sampling.
- Obtain a karyotype by one of these methods if ultrasonography of a fetus reveals a nuchal cystic hygroma.
- Karyotype for females with short stature.
- Elevated levels of LH and FSH confirm ovarian failure.

Health supervision
- Echocardiogram and renal ultrasound at the time of diagnosis
- TSH and free for every 1–2 years
- Audiology screening

Treatment
- See endocrinology chapter

Noonan Syndrome

Background
- Mutations in the RAS-MAPK signaling pathway are responsible for Noonan syndrome.
- Abnormal gene at 12q.

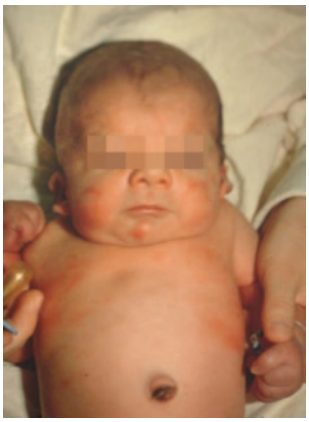
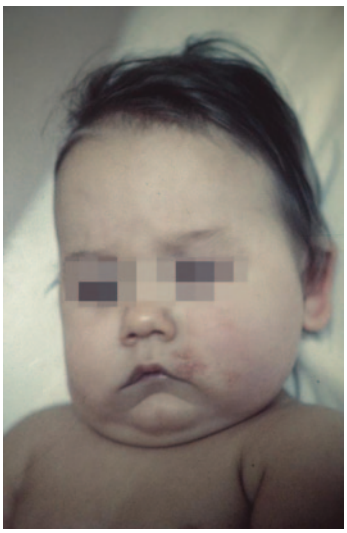


Fig. 11 Short webbed neck of an infant with Noonan syndrome

- Turner-like and affect also the boys.

Clinical presentation
- Short stature
- Cubitus valgus
- Short webbed neck (Fig. 11)
- Small penis
- Cryptorchidism
- Bleeding disorder
- Pulmonary valvular stenosis

Prader–Willi Syndrome (PWS)



Background
- PWS is a disorder caused by a deletion or disruption of genes in the proximal arm of chromosome 15
- Loss of imprinted genomic material within the *paternal* 15q11.2-13 locus

Clinical presentation
- Diminished fetal activity
- *Severe hypotonia at birth*

- Failure to thrive initially
- Hyperphagia
- Obesity
- Short stature
- Small hands and feet
- Hypogonadism
- Intellectual disability (ID)
- Strabismus

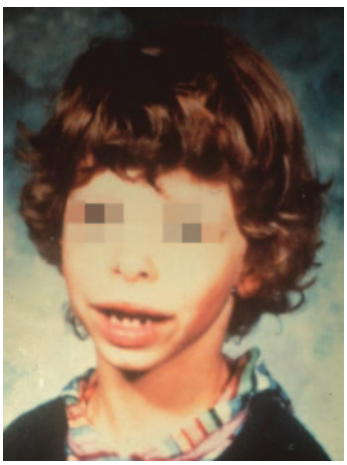
Diagnosis
- DNA Methylation patterns by Southern blot hybridization or polymerase chain reaction (PCR)

Angelman Syndrome

Background
- The loss of maternal genomic material at the 15q11.2-13 locus results in Angelman syndrome

Clinical Presentation
- Consistent (100%)
  - Developmental delay
  - Speech impairment
  - Ataxia of gait and/or tremulous movement of limbs
  - Frequent laughter/smiling; apparent happy demeanor; easily excitable personality
- Other common features
  - Microcephaly
  - Seizures, onset usually <3 years of age
  - Strabismus
  - Hypotonia
  - Fair hair
  - Seizure
  - Severe intellectual disability (ID)

Williams Syndrome (7q11.23)



- **Background**
  - Due to a deletion at chromosome band 7q11.23 that

Clinical Presentation
- Failure to thrive
- Periorbital fullness with downturned, prominent lower lip
- Friendly "cocktail party" personality
- Stellate pattern of the iris
- Strabismus, and cataract
- Supravalvar aortic stenosis (SVAS)
- Intellectual disability (ID)
- Sensorineural hearing loss
- *Idiopathic hypercalcemia*

Diagnosis
- Fluorescent in situ hybridization (FISH) for the 7q11.23 elastin gene deletion

WAGR Syndrome

Background
- Due to deletion on chromosome 11 (11p13-)
- Resulting in absence of the loss of several genes e.g. PAX6 and Wilms tumor I (WTI)

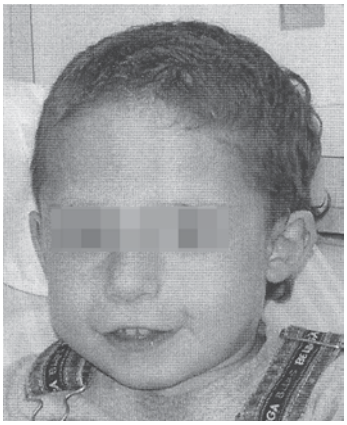
Clinical presentation
- Wilms tumor 50%
- Aniridia
- Genitourinary anomalies (hypospadias, cryptorchidism, small penis, and hypoplastic scrotum)
- Intellectual disability (ID)
- Gonadoblastoma

Alagille Syndrome

Background
- Microdeletion of the 20p12 gene corresponding to JAG1 results in Alagille syndrome

Clinical presentation
- Triangular face and pointed chin
- Cholestasis due to bile duct paucity
- Jaundice, and pruritus
- Xanthomas
- Supravalvar pulmonary stenosis (67% of patients with peripheral pulmonary stenosis, and 7–16% tetralogy of fallot)
- Ocular defect (posterior embryotoxon)
- Butterfly vertebrae

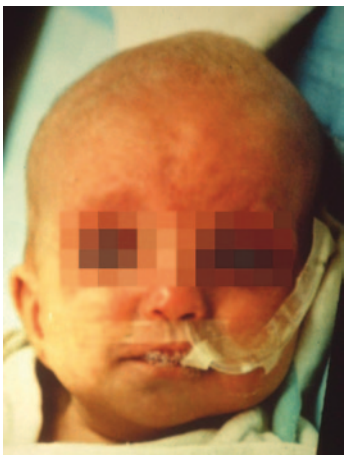
DiGeorge Syndrome



Background
- It is 22q11.2- deletion syndrome
- It is referred to as DiGeorge syndrome, and velocardiofacial (VCF) syndrome or CATCH 22

Clinical presentation
- *Cleft* palate
- *Absent thymus* (thymus agenesis and immune deficiency)
- *Congenital heart disease*
  - Tetralogy of fallot is the most common
  - Interrupted aortic arch
  - Truncus arteriosus
- *Hypocalcemia (17–60%)*
  - Due to hypoplasia or agenesis of parathyroid gland
  - Can cause seizures
  - This is frequently a self-limiting problem (usually 50% resolve by 1 year)
- *Immunodeficiency (77%)*
  - Recurrent infections secondary to immune deficiency may be observed
  - Mild-to-moderate defect in T-cell lineage as a consequence of thymic hypoplasia.
  - Variable secondary humoral defects, including hypogammaglobulinemia and selective antibody deficiency, may be present.
- Short stature
- Behavioral problem

4P-Wolf–Hirschhorn Syndrome



Background
- 4p deletion.
- Thirteen percent are due to one of the parents having a balance chromosome translocation.

Clinical Presentation
- Greek helmet facies (ocular hypertelorism, prominent, glabella, and frontal bossing)
- Growth deficiency
- Microcephaly
- Beaked nose
- Hypertension
- Hypotonia
- Congenital cardiac malformation
- Seizures 90%

5p-Cri-Du-Chat Syndrome

Background
- Due to a deletion of the short arm of chromosome 5

Clinical Presentation
- Mewing cry in infants (may be due to laxity or abnormities in the larynx)
- Hypotonia
- Down-slanting palpebral fissures
- Short stature
- Microcephaly

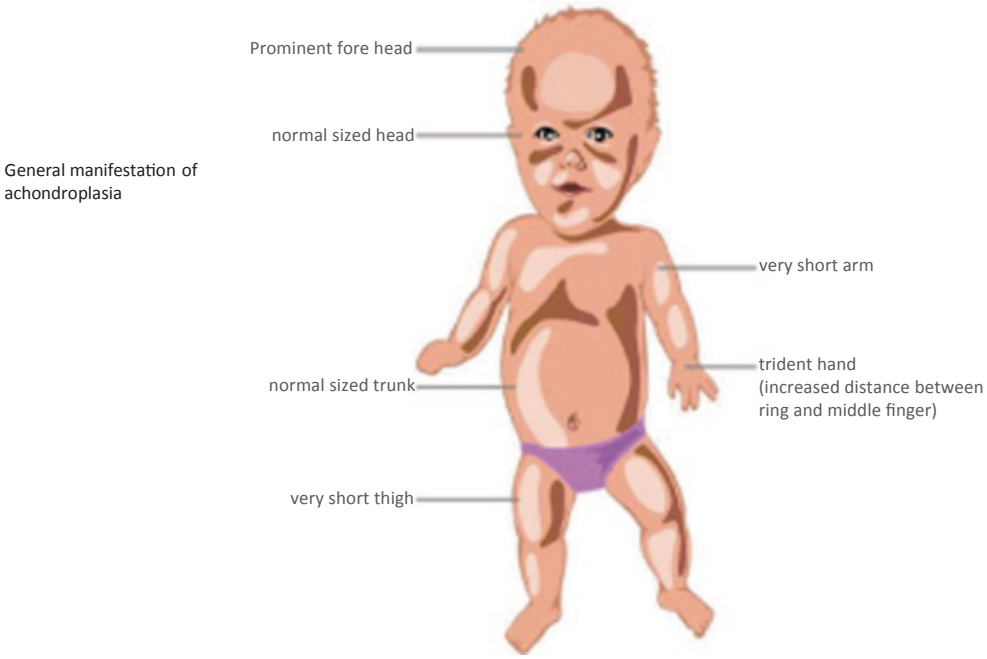


Fig. 12 General manifestations of achondroplasia

- High arched palate
- Intellectual disability (ID)
- Moon face, and wide and flat nasal bridge
- Cardiac manifestation occurs in about one-third of affected children.

De Grouchy Syndrome

Background
- Deletion of the long arm of chromosome 18

Clinical Presentation
- Narrowed ear canal
- Depressed midface
- Protruded mandible
- Elevated lower lip
- Deep set eyes
- Intellectual disability (ID)
- Hypotonia
- Club foot
- Cryptorchidism

Achondroplasia

Background
- Mutation in the gene for fibroblast growth factor receptor 3 (FGFR3) on chromosome 4.
- Autosomal dominant.
- More than 80% of these are new mutations.
- Achondroplasia is the most common type of short limb disproportionate dwarfism.
- Short-limb dwarfing conditions.

Clinical Presentation (Fig. 12)
- Short stature below third percentile
- *Motor milestones* such as head control and independent sitting, standing, and ambulation may lag by 3–6 months.
- Short lengths of most proximal segment of upper arms and legs compared to distal segment (disproportionate short stature with rhizomelic shortening)
- Trident hands
- Macrocephaly
- Flat nasal bridge, prominent forehead, and mid-facial hypoplasia
- *Stenosis of foramen magnum* and/or craniocervical junction can cause; apnea, quadriparesis, growth delay, and hydrocephalus
- Abnormal curvature of the spine (e.g., kyphosis, lordosis, scoliosis)

Management
- Growth hormone is currently being used to augment the height of patients with achondroplasia
- Limb lengthening

Marfan Syndrome (Figs. 13, 14, and 15)

Background
- It is heritable genetic defect of connective tissue.
- Autosomal dominant mode of transmission.

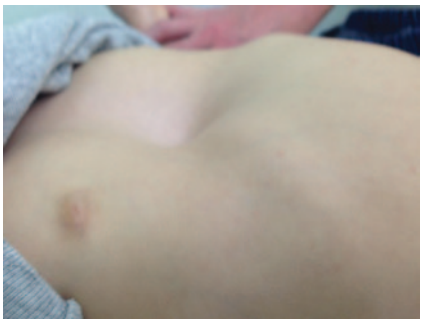


Fig. 13 A child with Marfan syndrome, the chest showing pectus excavatum

- Defect in *FBN1* gene on chromosome 15; which codes for fibrillin.
- Boys and girls are equally affected.
- Most common cause of death due to aortic dissection and rupture of aorta.

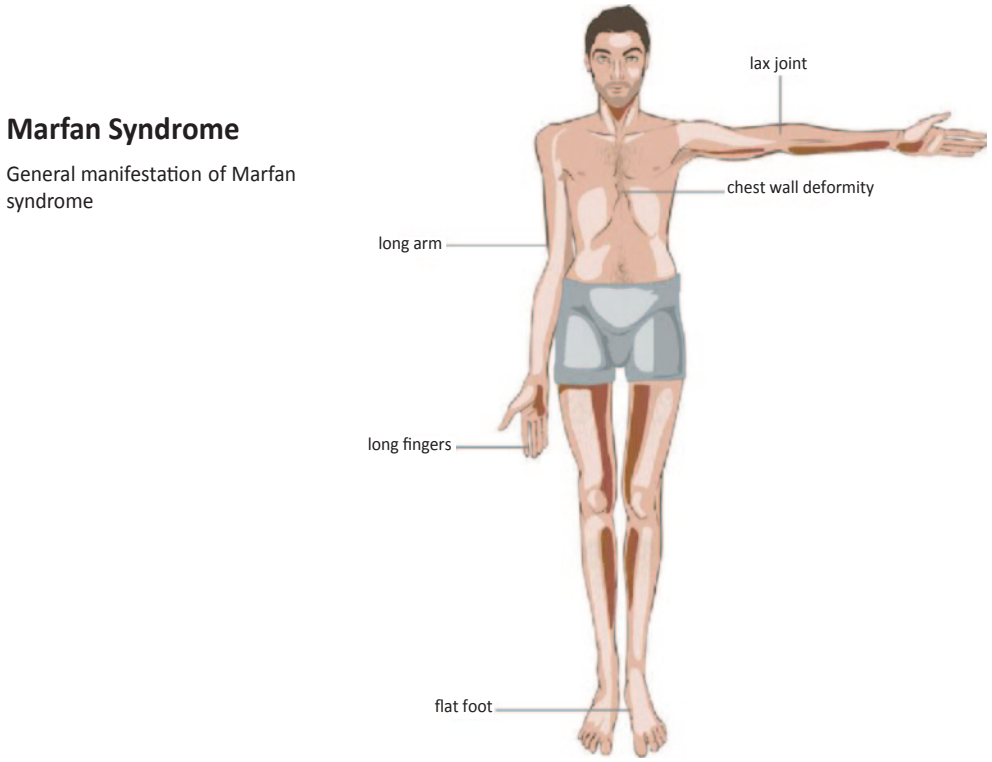
Major criteria

- Skeletal system
  - *Pectus carinatum* (pigeon breast)
  - Pectus excavatum (funnel chest) (Fig. 13)
  - Wrist sign (overlapping of the thumb and 5th finger when encircling the wrist (Fig. 14)
  - Scoliosis > 20 %
  - Reduced extension of the elbow (< 170 %)
  - Protrusio acetabuli (inward bulging of acetabulum)
- Ocular system
  - *Ectopia lentis* (upward displacement of the lens or dislocated lens)
- Cardiovascular
  - Dilatation *of the ascending aorta*
  - *Dissection of* the ascending aorta
- Dura
  - Lumbosacral dural ectasia (dilatation)

Minor Criteria

- Skeletal
  - *High arc*hed palate
  - Moderate pectus excavatum
  - Joint hypermobility
- Cardiovascular
  - *Mitral valve prolapse*
- Pulmonary
  - Dilatation of the main pulmonary artery
  - Spontaneous pneumothorax
  - Apical blebs
- Skin
  - Striae atrophicae
  - Recurrent incisional hernias

Fig. 14 General manifestation of Marfan syndrome



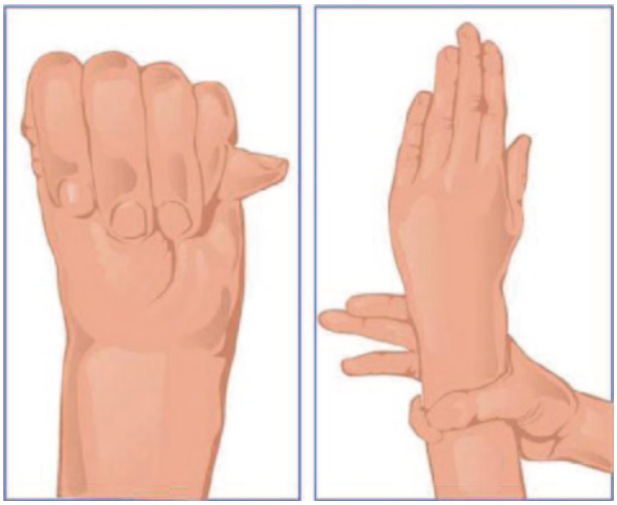


Fig. 15 Thumb and wrist signs in Marfan syndrome

Diagnosis

- Diagnosis based on clinical diagnostic criteria (Ghent Criteria)
  - A first-*degree relative and/or positive results of molecular studies*
  - *Plus major inv*olvement in one organ system and minor involvement in a second organ system
- *Major criteria* in at least two different organ systems and involvement in a third organ system
- *Family member*—Presence of a major criterion in the family history, one major criterion in an organ system, and involvement of a second organ system
- *Skeletal system*: at least two major criteria or one major criterion plus two minor criteria must be present
- *Ocular*: at least two minor criteria must be present
- *Dura*: one major criterion
- *Skin and CVS*: at least one minor criterion
- *Pulmonary*: at least one minor criterion
- No specific laboratory test exists with which to make the diagnosis of MFS
- Genetic test may assist in the diagnosis

Management

- Early identification and appropriate management is critical for patients with MFS
- Echocardiogram every 6 months or 1 years
- Beta-blockers have been demonstrated to slow aortic growth and thus delay the time to aortic surgery

Ehlers–Danlos Syndrome (Fig. 16)

Background

- Due to a mutations in over 40 genes, including collagens 3 and 5

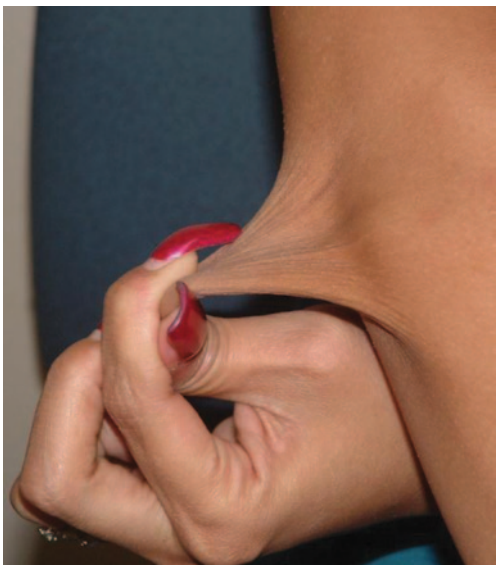


Fig. 16 Marked skin extensibility in a patient with Ehlers-Danlos syndrome

- Autosomal dominant
- More than 40 different inherited disorders; often involving a genetic defect in collagen or related genes that modify connective-tissue synthesis and structure.
- In 20% of families with autosomal dominant Ehlers-Danlos syndrome, the disease appears to be linked to loci that contain the COL5A1 or COL5A2 genes.
- Clinical recognition of the types of Ehlers-Danlos syndrome is important.
- Type IV is associated with arterial rupture and visceral perforation, with possible life-threatening consequences.
- Type I is the most common.

23 days old female with blue sclera (Figure A), the mother (Figure B) and the older brother has osteogenesis imperfecta Type 1 and multiple fractures

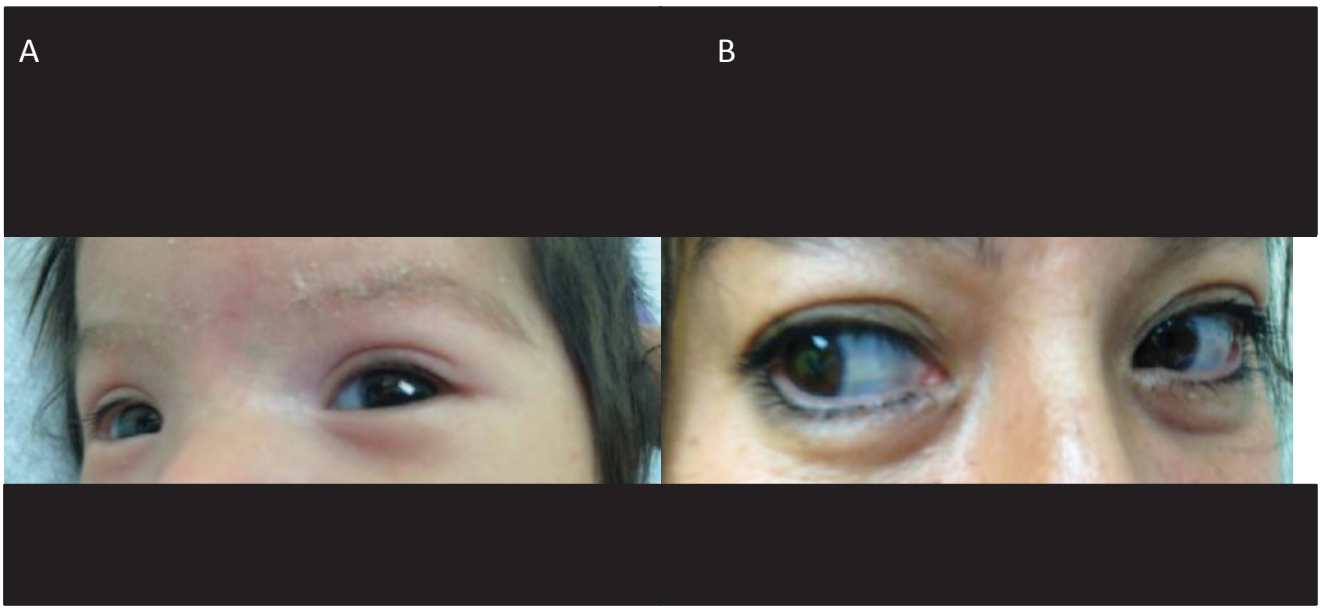


Fig. 17 Blue sclera in a 23 days old female infant and her mother who has type I osteogenesis imperfecta

Clinical presentation of Type I

- Skin
  - Marked skin extensibility with frequent lacerations and subsequent scarring in different body locations.
  - Surgical sutures heal poorly, with easy dehiscence.
  - Bruises are less common in this type than in other forms.
  - Varicosities and molluscoid pseudotumors are common.
- Joints
  - Joint hypermobility is severe and affects all parts of the body.
  - Spontaneous dislocations can occur, but immediate reduction is easy.
- Skeletal
  - Kyphoscoliosis
  - Hallux valgus
  - Pes planus (i.e., flat feet)
- Cardiac defects
  - Aortic root dilatation
  - Mitral valvular prolapse
- Prematurity with rupture of the fetal membranes is specific to this type.

Osteogenesis Imperfecta (Fig. 17)

Background

- It is a defect in collagen type 1 which is an important constituents of bone, ligaments, dentin, and sclera.
- The defect can be qualitative or quantitative reduction in type collagen.
- Mutations in genes encoding type 1 collagen (COL1A1 or COL1A2 genes) accounting for approximately, 80% of osteogenesis imperfecta cases.
- Types I–IV are all autosomal dominant.

Classically four types of osteogenesis imperfecta have been reported (Silence Classification):

- Type I: Mild forms
- Type II: Extremely severe (lethal); is often lethal due to fractures in utero
- Type III: Severe
- Type IV: Moderate
- Other types has been added

Clinical presentation

- General Manifestations
  - *Blue sclera (Fig. 17)*
  - *Growth retardation*

  - *Easy bruising*
  - *Osteoporosis*
  - *Presenile hearing loss*
  - *Dentinogenesis imperfecta may be present*
- Skeletal manifestation
  - *Repeated fractures*
  - *Macrocephaly*
  - *Triangular facies*
  - *Malocclusion of the jaw*
  - *Barrel ches*t
  - Kyp*hoscoliosis*
  - *Progressive limb deformities*
  - *Generaliz*ed bone aches

Diagnosis
- Genetic testing
  - Direct seq*uencin*g of COL1A1 or COL1A2 genes
- Skin biopsy
  - C*ollagen can be isolated from cultured fibroblasts and assesse*d for defects, with an accuracy of 85–87%.

Management
- Bisphosphonate therapy
- Vitamin D
- Calcium supplement
- Genetic, endo, orthopedic, and audiology consultations

Beckwith–Wiedemann Syndrome

Background
- Eighty percent of patients demonstrate genotypic abnormalities of the distal region of chromosome arm 11p
- Sporadic appearance

Clinical Presentation
- Severe hypoglycemia
- Macrosomia
- Organomegaly
- Large tongue
- Hemihypertrophy
- Posterior helical indentation (pits of the external ear)
- Omphalocele
- Wilms tumor

Sotos Syndrome (Fig. 18)

Background
- Cerebral gigantism

Clinical Presentation
- Large for gestational age (LGA)

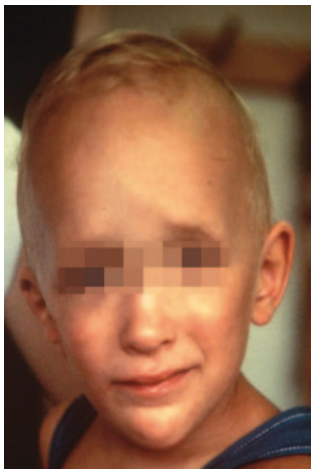


Fig. 18 Macrocephaly in a child with Sotos syndrome

- Increased growth velocity
- Advanced bone age
- Macrocephaly
- Facial dysmorphism
- Autism
- Mild intellectual disability (ID)

Poland Sequence

- Pectoral muscle defect
- Rib defect
- Dextrocardia if the defect on the left

Treacher Collins Syndrome

Background
- Autosomal dominant
- Most new mutations
- Due to mutation of gene 5

Clinical Presentation
- Facial bone
  - Underdev*eloped mandibular and zygomatic bones*
  - *Small and* malformed jaw and malocclusion may occur
- Ears
  - External ear anomalies
  - Stenosis or atresia of the external auditory canals is described
  - Conductive hearing loss
- Eye
  - Coloboma of the lower eyelids
  - Aplasia of lid lashes to short eye lashes
  - Downslanting palpebral fissures

  - Vision loss can occur
- Cleft palate

Waardenburg Syndrome

Background
- Autosomal dominant

Clinical presentation
- Sensorineural hearing loss
- Iris pigmentary abnormality (two eyes different color or iris bicolor or characteristic brilliant blue iris)
- Hair hypopigmentation (white forelock or white hairs at other sites on the body; poliosis)
- Dystopia canthorum (lateral displacement of inner canthi)
- First-degree relative previously diagnosed with Waardenburg syndrome
- Premature graying of the hair (before age 30).

Pierre–Robin Sequence

- Mandibular hypoplasia (micrognathia)
- Displacement of the tongue (glossoptosis) interrupted closure of the lateral palatine ridges, and cleft palate
- Respiratory distress and feeding problem

Amniotic Band Sequence or Amniotic Rupture Sequence (Fig. 19)

Background
- Cocaine is a common cause

Clinical Presentation
- Disruptive cleft as resulting from adherent of amniotic bands to any body parts
- Cleft of the face
- Constricting bands causing limb or digit amputations

Goldenhar Syndrome (Fig. 20)

- Hemifacial microsomia
- Epibulbar lipodermoids
- Vertebral defect
- Cardiac anomalies (VSD or outflow tract obstruction)
- Renal anomalies
- Incomplete development of the ear (Fig. 20)
- Conductive hearing loss

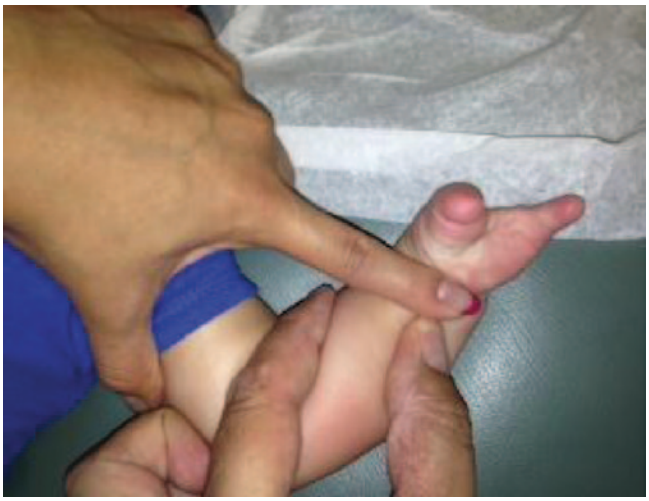


Fig. 19 Six-month-old female with amniotic band sequence in the her left hand and amputated three middle fingers

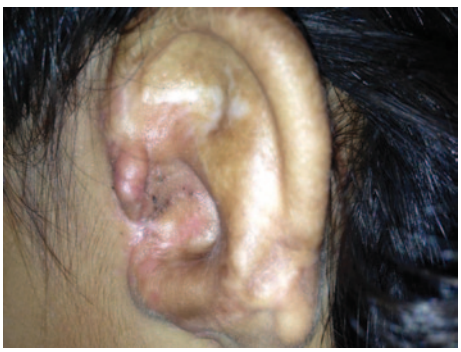


Fig. 20 A child with Goldenhar syndrome has incomplete development of the ear

Craniosynostosis

Background
- Craniosynostosis consists of premature fusion of one or more cranial sutures, often resulting in an abnormal head shape.
- It may result from a primary defect of ossification (primary craniosynostosis) or, more commonly, from a failure of brain growth (secondary craniosynostosis).

Types of craniosynostosis
- Scaphocephaly
  - Early fusion of sagittal sutures
  - Long and narrow head shape
- Anterior plagiocephaly
  - Early fusion of one coronal suture
  - Unilateral flattening of the forehead

- Posterior plagiocephaly
  - Early closure of one lambdoid suture
- Brachycephaly
  - Early bilateral coronal suture fusion
- Trigonocephaly
  - Early fusion of metopic sutures
  - Keel-shaped forehead and hypotelorism
- Turricephaly
  - Early fusion of coronal, sphenofrontal, and frontoethmoidal sutures
  - Cone-shaped head

Syndromes are associated with craniosynostosis

- Apert syndrome
  - Craniosynostosis
  - Syndactyly
- Crouzon syndrome
  - Craniosynostosis
  - Ear canal malformation
  - Exophthalmos
  - Mandibular prognathism
  - Concave face
- Pfeiffer syndrome
  - Craniosynostosis
  - Broad thumb and toes
- Carpenter syndrome
  - Tower-shaped skull (craniosynostosis)
  - Additional or fused digits (fingers and toes)
  - Obesity
  - Reduced height

Plagiocephaly

- Positional flattening of the skull.
- Ipsilateral frontal prominence.
- Anterior displacement of the ipsilateral ear

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Suggested Readings

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