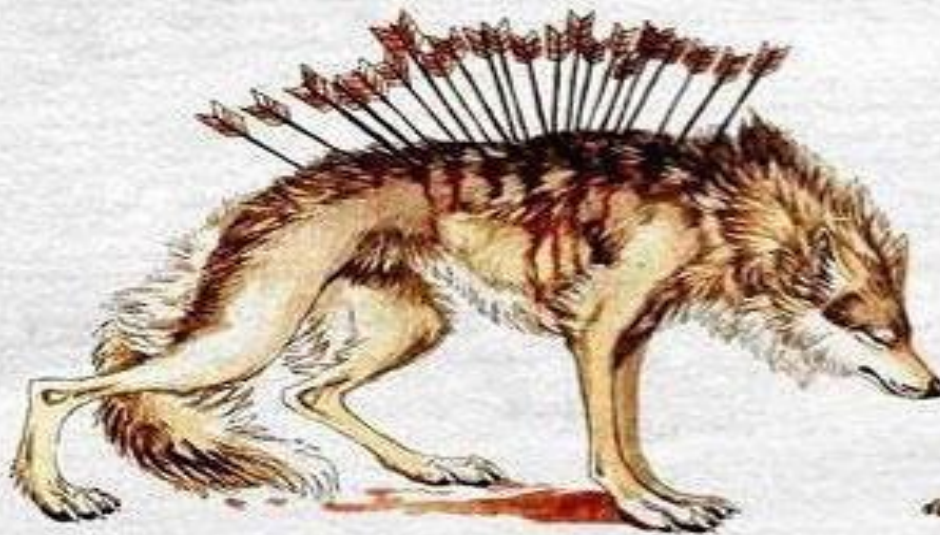


**Life doesn't get easier,
you just get stronger!**

Me Now

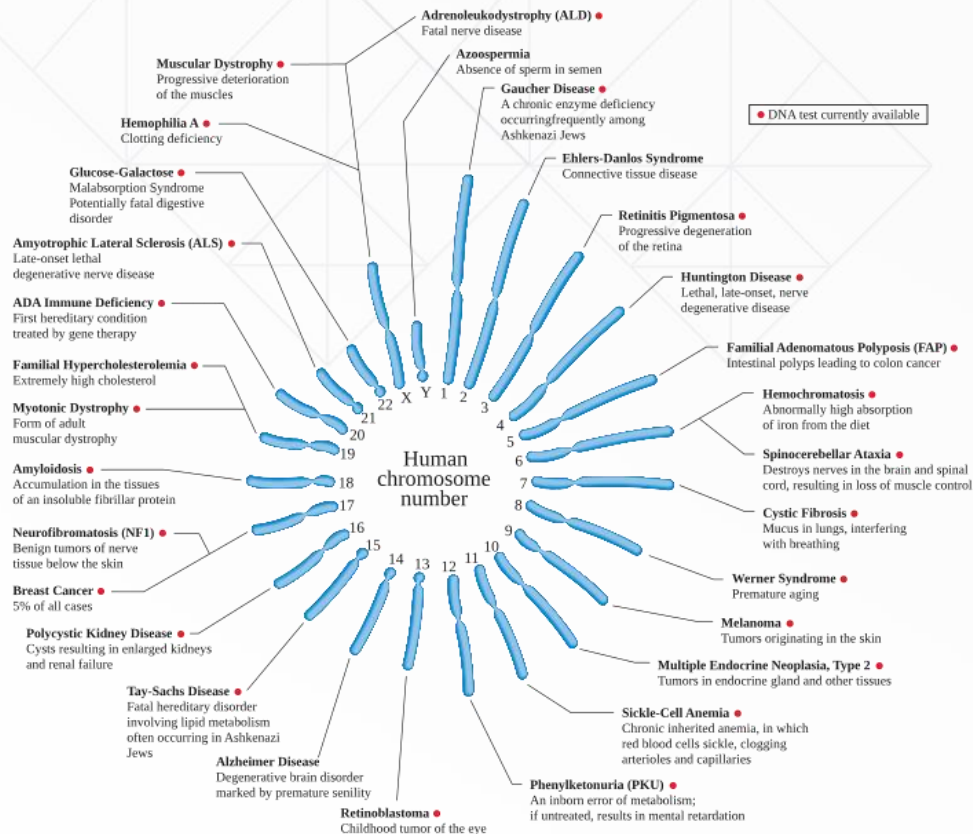


The old me





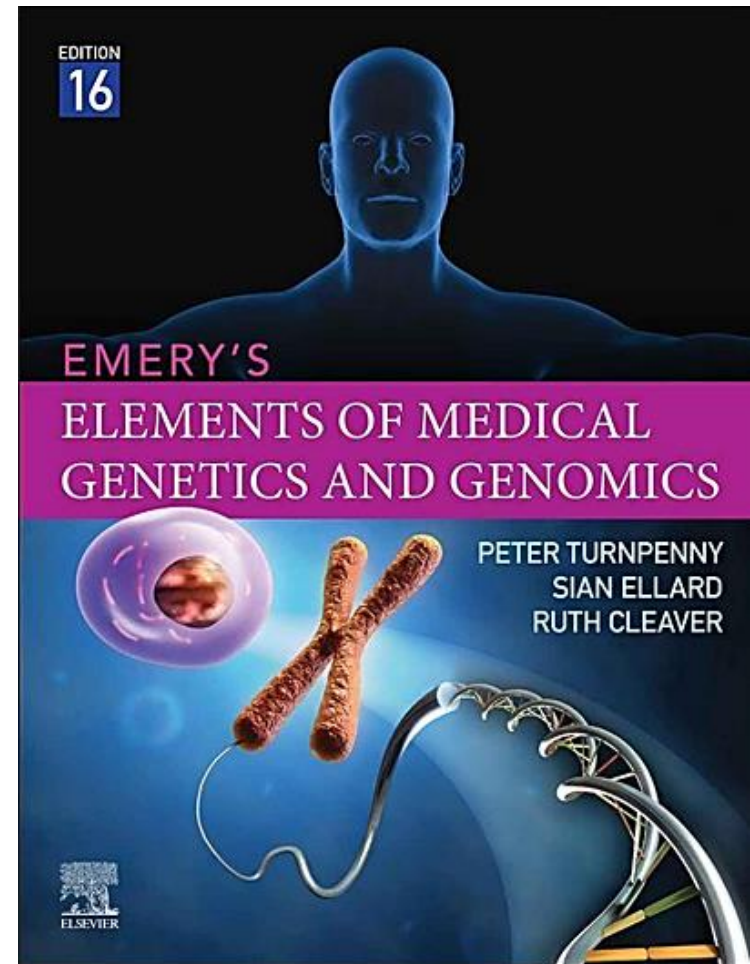
Chromosomal Disorders



Chromosomal disorders topics

Chapter 17:

- Abstract
- Incidence of Chromosome Abnormalities
- Disorders of the Autosomal Chromosomes
- Disorders of the Sex Chromosomes
- “Classic” Chromosome Deletion Syndromes
- Chromosome Breakage Syndromes
- Indications for Chromosome Microarray Analysis



Chromosomal Abnormalities

- The development of a reliable technique for chromosome analysis in 1956 soon led to the discovery that several previously described conditions were caused by an abnormality in chromosome number.
- Within 3 years, the causes of Down syndrome (47,XX+21/47,XY+21), Klinefelter syndrome (47,XXY), and Turner syndrome (45,X) had been established.
- Shortly after, other autosomal trisomy syndromes were recognized, and over the ensuing years many other multiple malformation syndromes were described in which there was loss or gain of chromosome material.

Abstract

Presently, there **are tens of thousands** of chromosome abnormalities registered in laboratory databases.

- Most conditions are very rare, but **together** they make a **major contribution** to human **morbidity** and **mortality**.
- Chromosome abnormalities account for:
 - ❖ A large proportion of **spontaneous pregnancy loss** and **childhood disability**
 - ❖ **Malignancy** throughout life as a consequence of **acquired** translocations and other aberrations.

Incidence of Chromosome Abnormalities

Incidence

- Chromosome abnormalities are present in at least 10% of all spermatozoa and 25% of mature oocytes.
- Some 15% to 20% of all recognized pregnancies end in spontaneous miscarriage, and many more zygotes and embryos are so abnormal that survival beyond the first few days or weeks after fertilization is not possible.
- Approximately 50% of all spontaneous miscarriages have a chromosome abnormality and the incidence of chromosome abnormalities in morphologically normal embryos is approximately 20%.
- As many as 80% of embryos generated for in vitro fertilization can be identified as possibly having genomic imbalances.

Table 17.1 Chromosome abnormalities in spontaneous abortions (percentage values relate to total of chromosomally abnormal abortuses)

Abnormality	Incidence (%)
Trisomy 13	2
Trisomy 16	15
Trisomy 18	3
Trisomy 21	5
Other trisomy	25
Monosomy X	20
Triploidy	15
Tetraploidy	5
Other	10

Table 17.2 Incidence of chromosome abnormalities in the newborn

Abnormality	Incidence per 10,000 Births
<u>Autosomes</u>	
Trisomy 13	2
Trisomy 18	3
Trisomy 21	15
<u>Sex Chromosomes</u>	
Female Births	
45,X	1-2
47,XXX	10
Male Births	
47,XXY	10
47,XYY	10
Other unbalanced rearrangements	10
Balanced rearrangements	30
Total	90

Table 17.3 Spontaneous pregnancy loss in commonly recognized aneuploidy syndromes

Disorder	Proportion Undergoing Spontaneous Pregnancy Loss (%)
Trisomy 13	95
Trisomy 18	95
Trisomy 21	80
Monosomy X	98

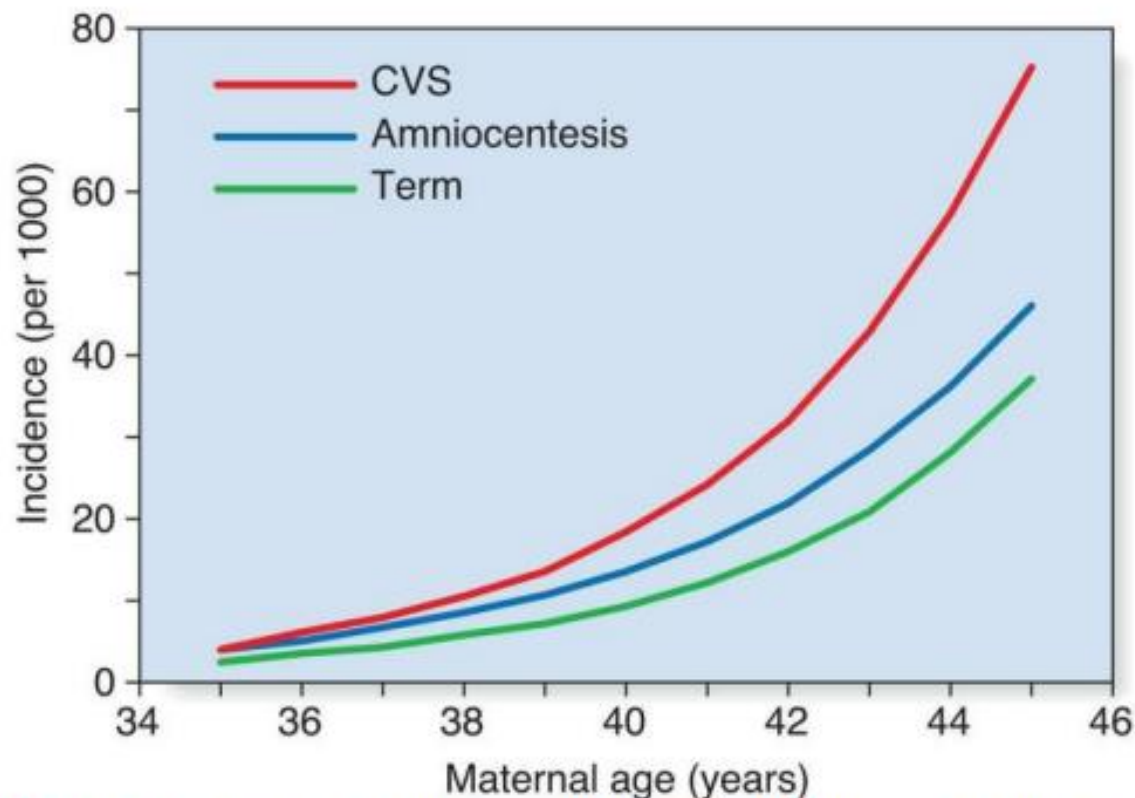
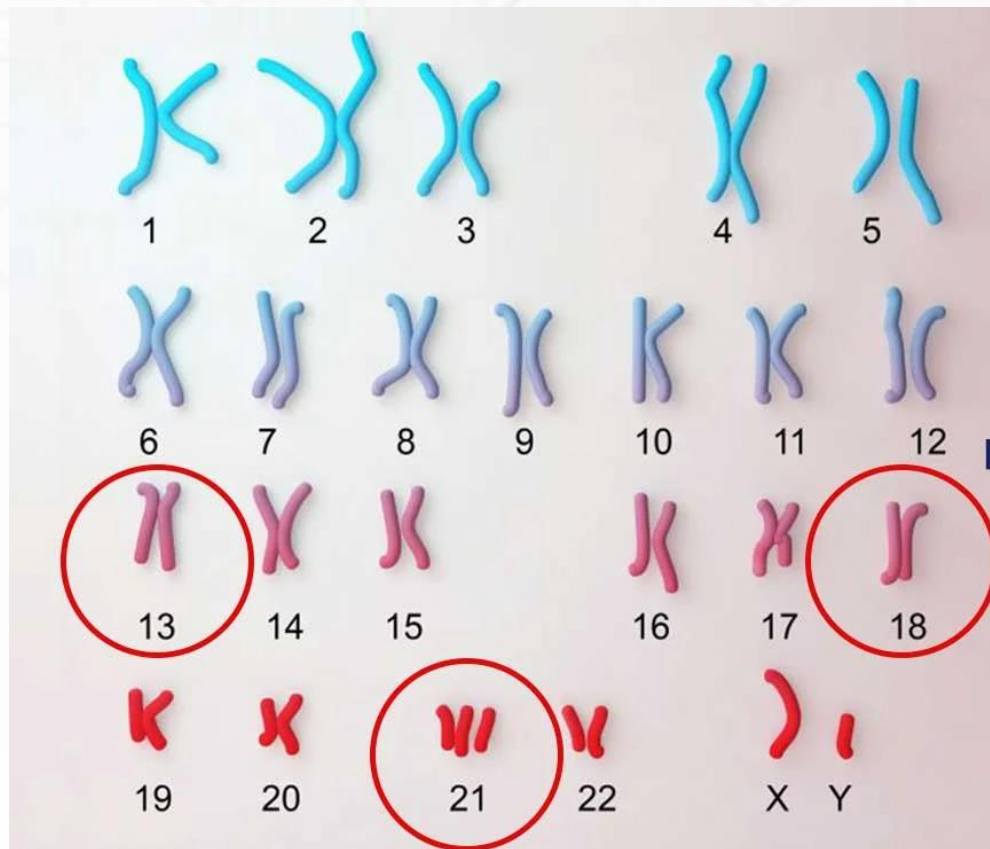


FIG. 17.1 Approximate incidence of trisomy 21 at the time of chorionic villus sampling (CVS) (11–12 weeks), amniocentesis (16 weeks) and delivery. From Hook EB, Cross PK, Jackson L, et al. Maternal age-specific rates of 47, +21 and other cytogenetic abnormalities diagnosed in the first trimester of pregnancy in chorionic villus biopsy specimens.

Table 17.4 Incidence of Down syndrome in relation to maternal age

Maternal Age at Delivery (Years)	Incidence of Down Syndrome
20	1 in 1500
25	1 in 1350
30	1 in 900
35	1 in 400
36	1 in 300
37	1 in 250
38	1 in 200
39	1 in 150
40	1 in 100
41	1 in 85
42	1 in 65
43	1 in 50
44	1 in 40
45	1 in 30

Disorders of the Autosomal Chromosomes



Box 17.1

Common Findings in Down Syndrome

Newborn period

Hypotonia, sleepy, excess nuchal skin

Craniofacial

Brachycephaly, epicanthic folds, protruding tongue, small ears, upward sloping palpebral fissures

Limbs

Single palmar crease, small middle phalanx of fifth finger, wide gap between first and second toes

Cardiac

Atrial and ventricular septal defects, common atrioventricular canal, patent ductus arteriosus

Other

Anal atresia, duodenal atresia, Hirschsprung disease, short stature, strabismus

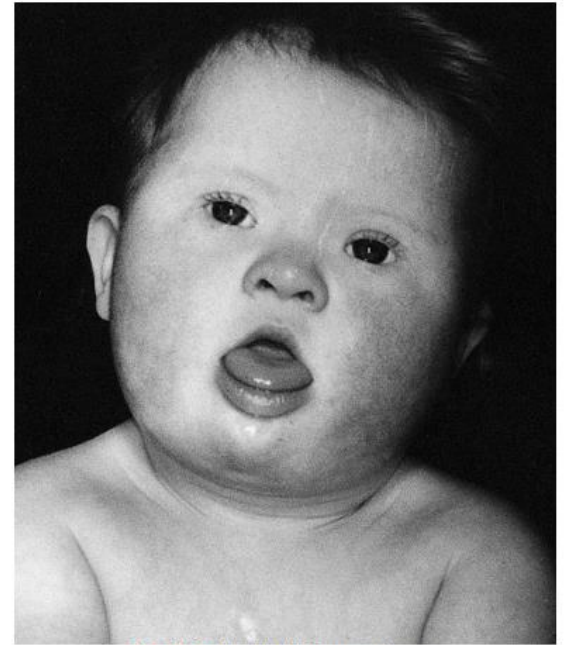
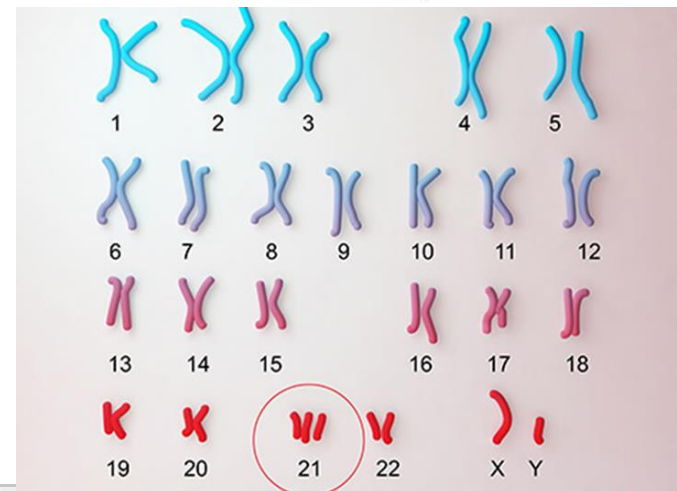


FIG. 17.2 A child with Down syndrome.



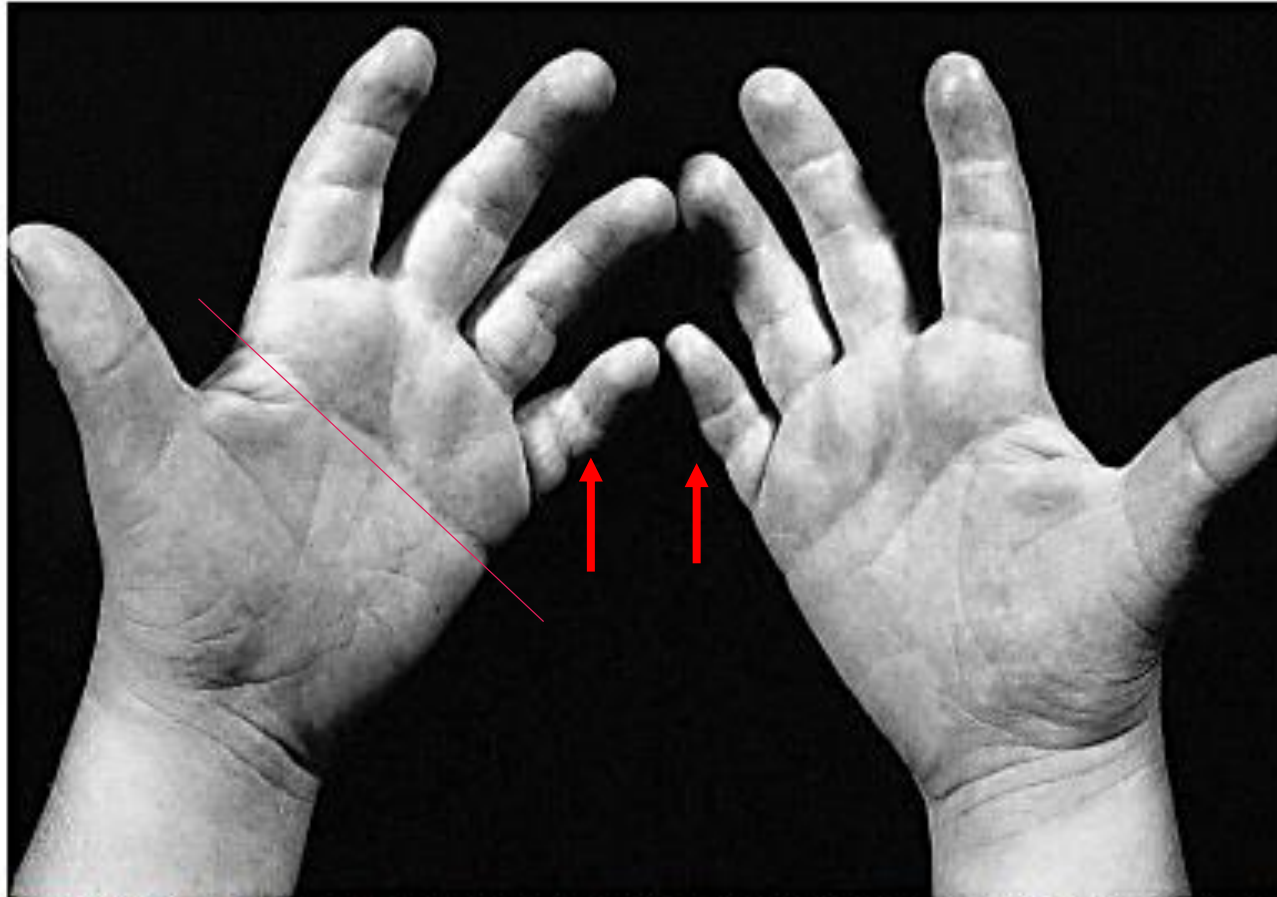


FIG. 17.4 The hands of an adult with Down syndrome. Note the single palmar crease in the left hand plus bilateral short curved fifth fingers (clinodactyly).



FIG. 17.3 Close-up view of the eyes and nasal bridge of a child with Down syndrome showing upward sloping palpebral fissures, Brushfield spots, and bilateral epicanthic folds.

Natural History

- ✓ Intelligence quotient (IQ) scores ranging from 25 to 75.
- ✓ The average IQ of young adults is around 40 to 45.
- ✓ Social skills are relatively well advanced, and most children are happy and very affectionate.
- ✓ Adult height is approximately 150 cm.
- ✓ In the absence of a severe cardiac anomaly, which despite modern surgery and intensive care leads to early death in 15% to 20% of cases, average life expectancy is 50 to 60 years.
- ✓ Overall, about 90% of live-born individuals with Down syndrome reach 20 years of age.
- ✓ Most affected adults develop Alzheimer disease in later life, possibly because of a gene dosage effect the amyloid precursor protein (APP) gene is on chromosome 21. This gene is known to be in some familial cases of Alzheimer disease.

Chromosome Findings

- In cases resulting from trisomy 21, the additional chromosome is maternal in origin in more than 90% of cases, and DNA studies have shown that this arises most commonly as a result of nondisjunction in maternal meiosis I.
- Robertsonian translocations account for approximately 4% of all cases, in roughly one-third of which a parent is found to be a carrier.
- Children with mosaicism are often less severely affected than those with the full syndrome.
- a Down syndrome “critical region” at the distal end of the long arm (21q22) because children with trisomy for this region alone usually have typical Down syndrome facial features.
- At present the only reasonably well-established genotype-phenotype correlation in trisomy 21 is the high incidence of Alzheimer disease (APP gene dosage).

Table 17.5 Chromosome abnormalities in Down syndrome

Abnormality	Frequency (%)
Trisomy	95
Translocation	4
Mosaicism	1

Recurrence Risk

- ❑ For **straightforward trisomy 21**, related to maternal age (**variable**) and the simple fact that trisomy has **already occurred** (**approximately 1%**).
- ❑ In **translocation** cases, similar figures apply **if neither parent is a carrier**.
- ❑ In **familial translocation cases**, the recurrence risks vary from **1% to 3%** for **male** carriers and up to **10% to 15%** for **female** carriers.
- ❑ In **very rare carriers of a 21q21q translocation**, for whom the recurrence risk is **100%**.
- ❑ **Prenatal diagnosis** can be offered based on analysis of **chorionic villi** or cultured amniotic cells.
- ❑ **Triple or quadruple tests** of **maternal serum** at **16 weeks'** gestation.

Patau Syndrome (Trisomy 13) and Edwards Syndrome (Trisomy 18)

- The incidence of **Edwards** syndrome is approximately **1:6000**.
- **Patau** syndrome is **two or three times less frequent**, and **prognosis is very poor**, with most infants dying during the first **days or weeks** of life, although most cases are now detected prenatally with **intrauterine growth retardation** and **some abnormal fetal ultrasound features**, often leading to termination.
-
- In the **unusual** event of **longer-term survival**, there is **severe intellectual disability (ID)**. **Cardiac abnormalities** occur in **at least 90% of cases**.

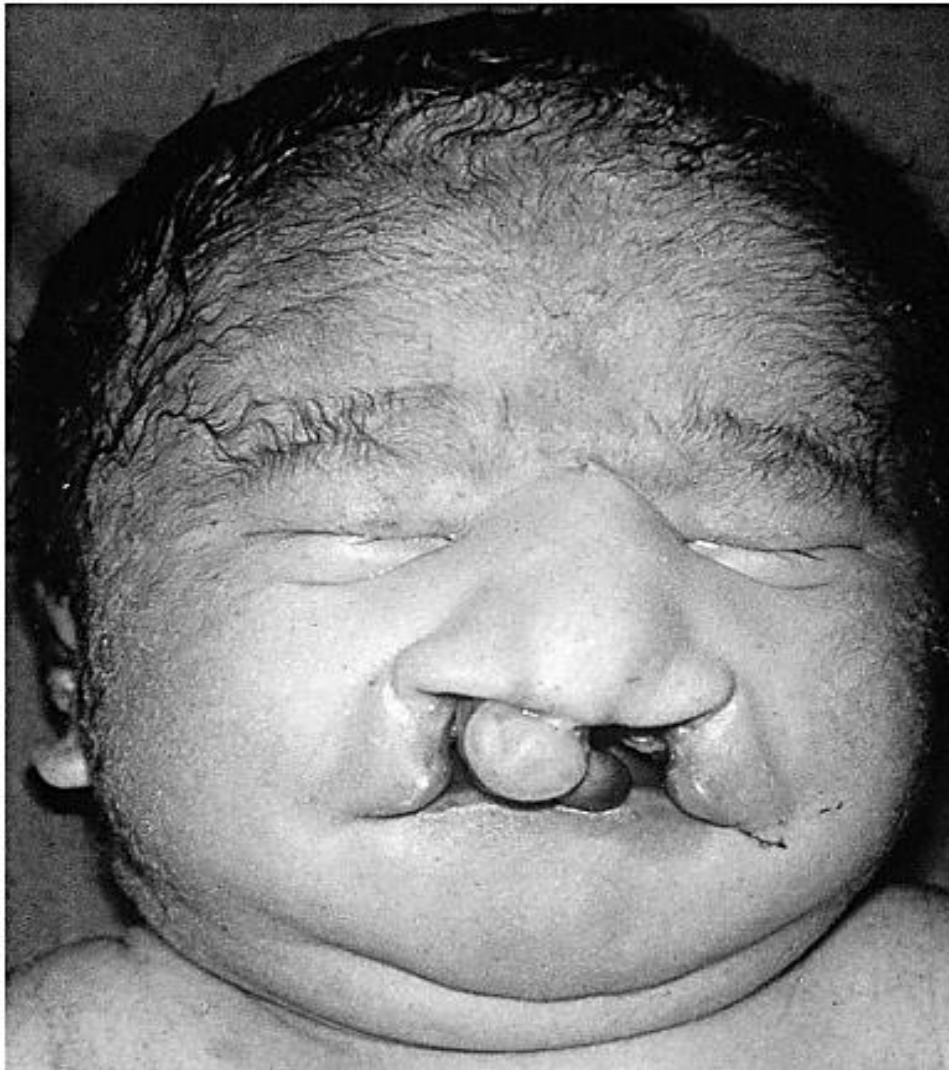


FIG. 17.5 Facial view of a child with **trisomy 13** showing severe bilateral cleft lip and palate, and a typical broad nose.

Main symptoms



Cleft lip
and palate



Small head, small
eyes and ear
malformations



Extra
fingers
or toes



Heart
defects



Spinal cord
abnormalities



Kidney
cysts

Not all symptoms are listed, and symptoms may vary in type and severity between affected people.

Trisomy 13 Patau Syndrome Symptoms

- Cleft lip or palate
- Clenched hands (with outer fingers on top of the inner fingers)
- Close-set eyes -- eyes may actually fuse together into one
- Decreased muscle tone
- Extra fingers or toes
- Hole, split, or cleft in the iris
- Low-set ears
- Mental Retardation, severe
- Scalp defects (missing skin)
- Small eyes
- Small head
- Small lower jaw

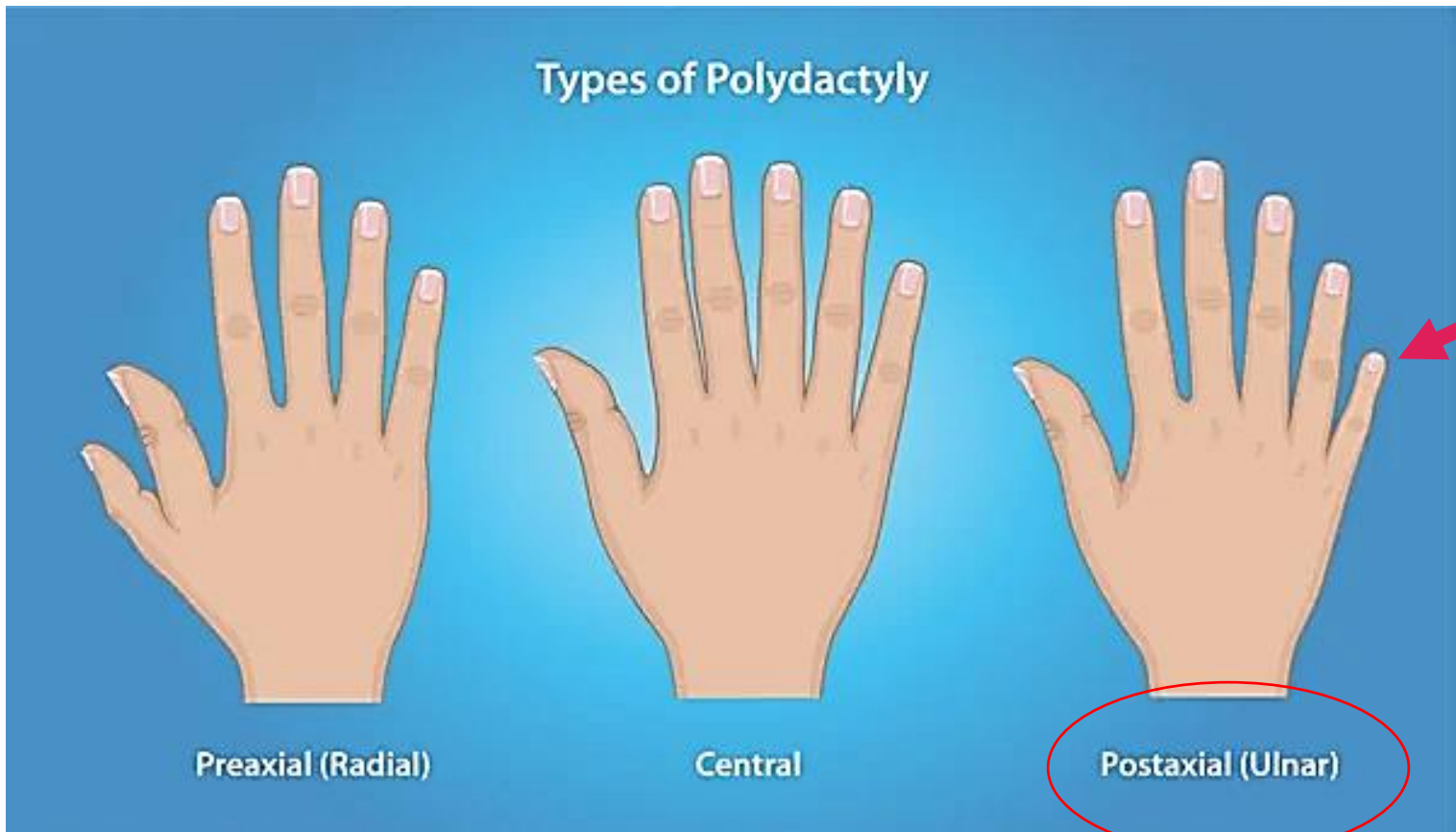


Bartholin-Patau syndrome, Patau's syndrome, T13

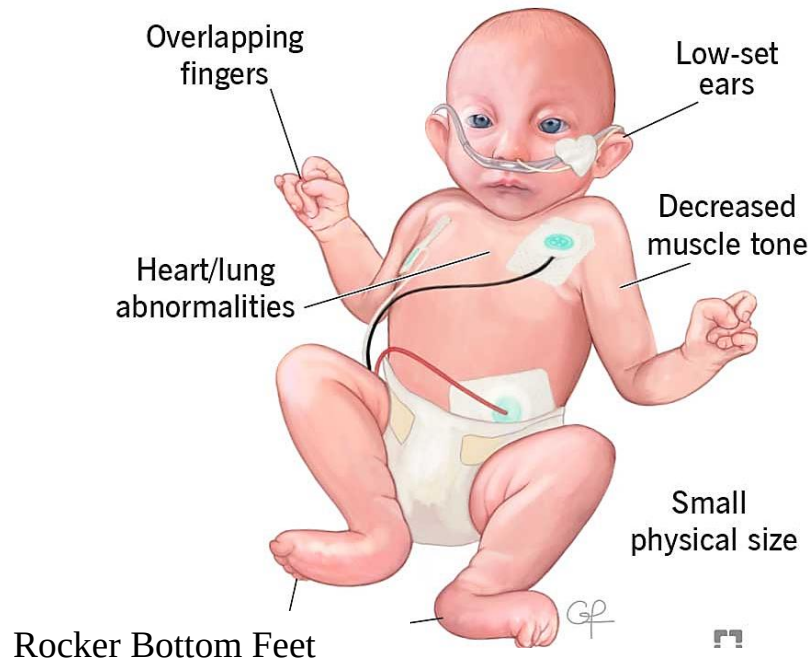


Exomphalos

The **facial** features in trisomy 13 are **characteristic**, **often** with **clefting**, and affected infants frequently have **scalp defects**, **exomphalos**, and **postaxial polydactyly**.



Trisomy 18 is characterized by **poor growth, microcephaly, micrognathia, clenched hands** and **“rocker bottom” feet**.



Edwards Syndrome (Trisomy 18)

The **prominent occiput** and **tightly clenched hands**.





Rocker Bottom Feet

Also known as a Congenital vertical talus (CVT)

Associations

- **aneuploidic syndromic**
 - Trisomy 13
 - Trisomy 18
 - Trisomy 9
 - 18q deletion syndrome
 - Genetic syndromes such as Cri du Chat syndrome
- **non-aneuploidic non-syndromic**
 - Spina Bifida
 - Arthrogryposis

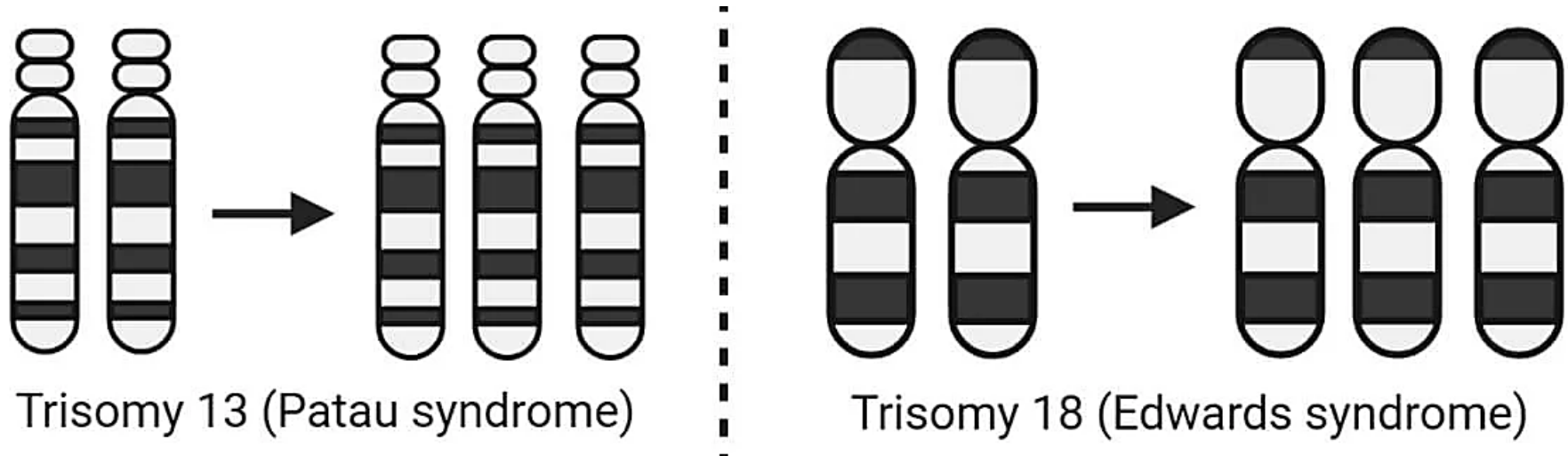


Normal Foot



Charcot Foot





- Chromosome analysis **usually** reveals **straightforward trisomy**.
- **Both** disorders occur more frequently with **advanced maternal age**, the additional chromosome being of **maternal origin**.
- Approximately **10%** of cases are caused by **mosaicism** or **unbalanced rearrangements**, particularly **Robertsonian translocations** in Patau syndrome.

Congenital **clubfoot**, also called **talipes equinovarus**

Clubfoot, a condition where a baby's foot is **twisted inward** and **downward**, can be associated with chromosomal disorders.

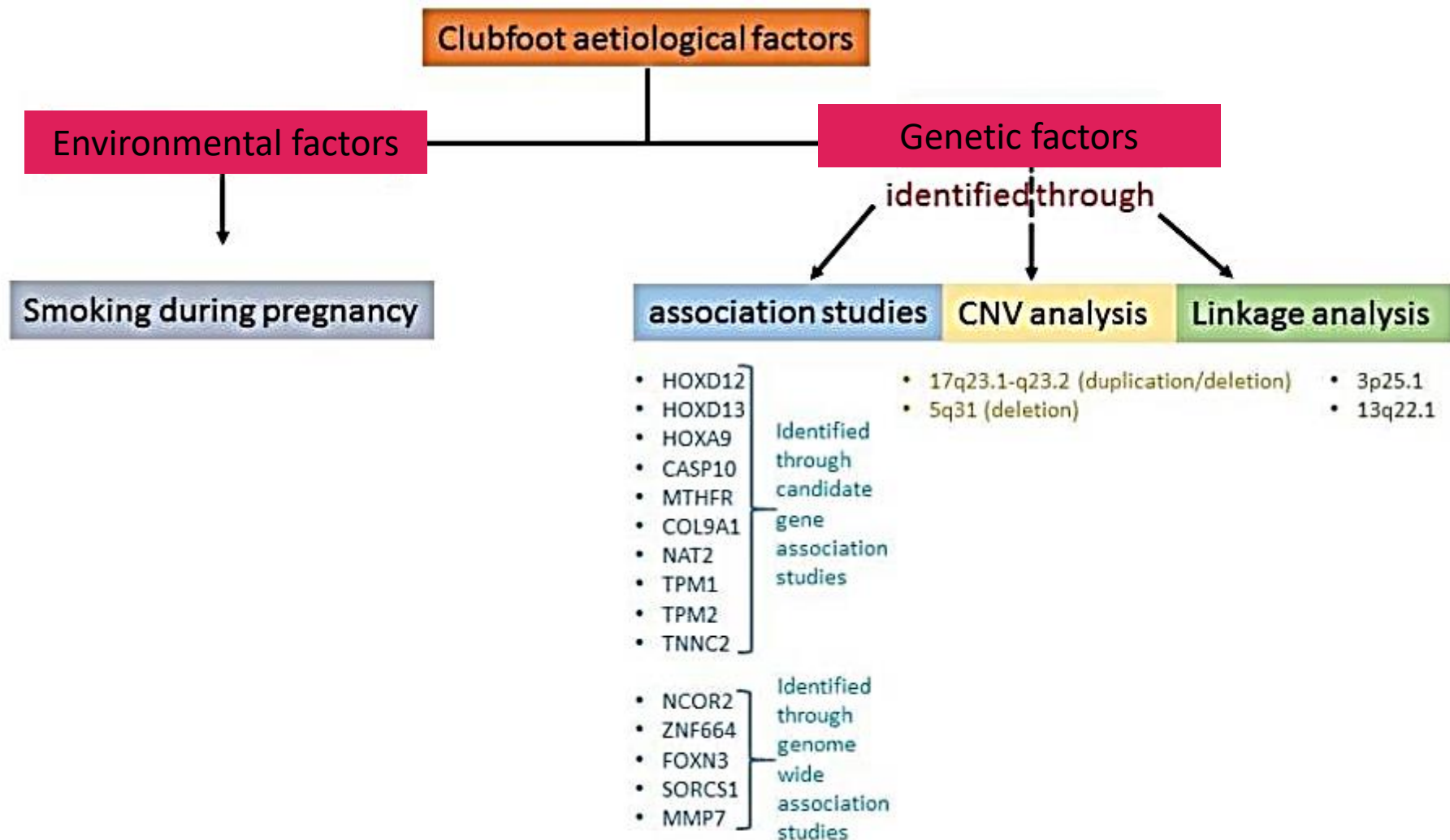
- Trisomies **13** and **18**
- Deletions on chromosome **22q11**
- **HOXD10** missense mutation
- and other genetic syndromes like **Larsen syndrome**.



Varus

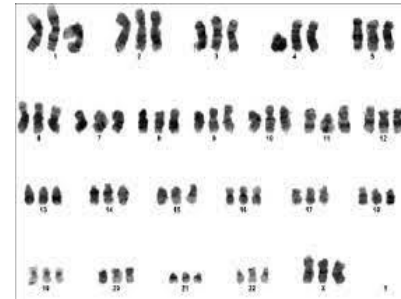


Equinus



Triploidy

- ❑ Triploidy (69,XXX, 69,XXY, 69,XYY) is a relatively common finding in material cultured from spontaneous abortions but is seen only rarely in a live-born infant.
- ❑ Such a child almost always shows severe intrauterine growth retardation with relative preservation of head growth at the expense of a small narrow trunk. Syndactyly involving the third and fourth fingers and/or the second and third toes is a common finding.
 - Cases of triploidy resulting from a double paternal contribution usually miscarry in early to midpregnancy and are associated with partial hydatidiform changes in the placenta.
 - Cases with a double maternal contribution survive for longer but rarely beyond the early neonatal period.



Hypomelanosis of Ito

Alfred Blaschko is credited with the first demonstration of these lines in 1901.

- Hypomelanosis of Ito (HOI) is a rare neurocutaneous syndrome characterized by skin patches of reduced pigmentation, often following Blaschko's lines, and may be associated with neurological and musculoskeletal abnormalities. It is considered a mosaicism, meaning that some cells in the body have a genetic change while others do not.
- Blaschko's lines are only visible in those with a mosaic skin condition (**Mosaicism for diploidy/triploidy**) or in chimeras where different cell lines contain different genes.
- These lines may express different amounts of melanin, or become visible due to a differing susceptibility to disease.
- The lines are believed to trace the migration of embryonic cells.



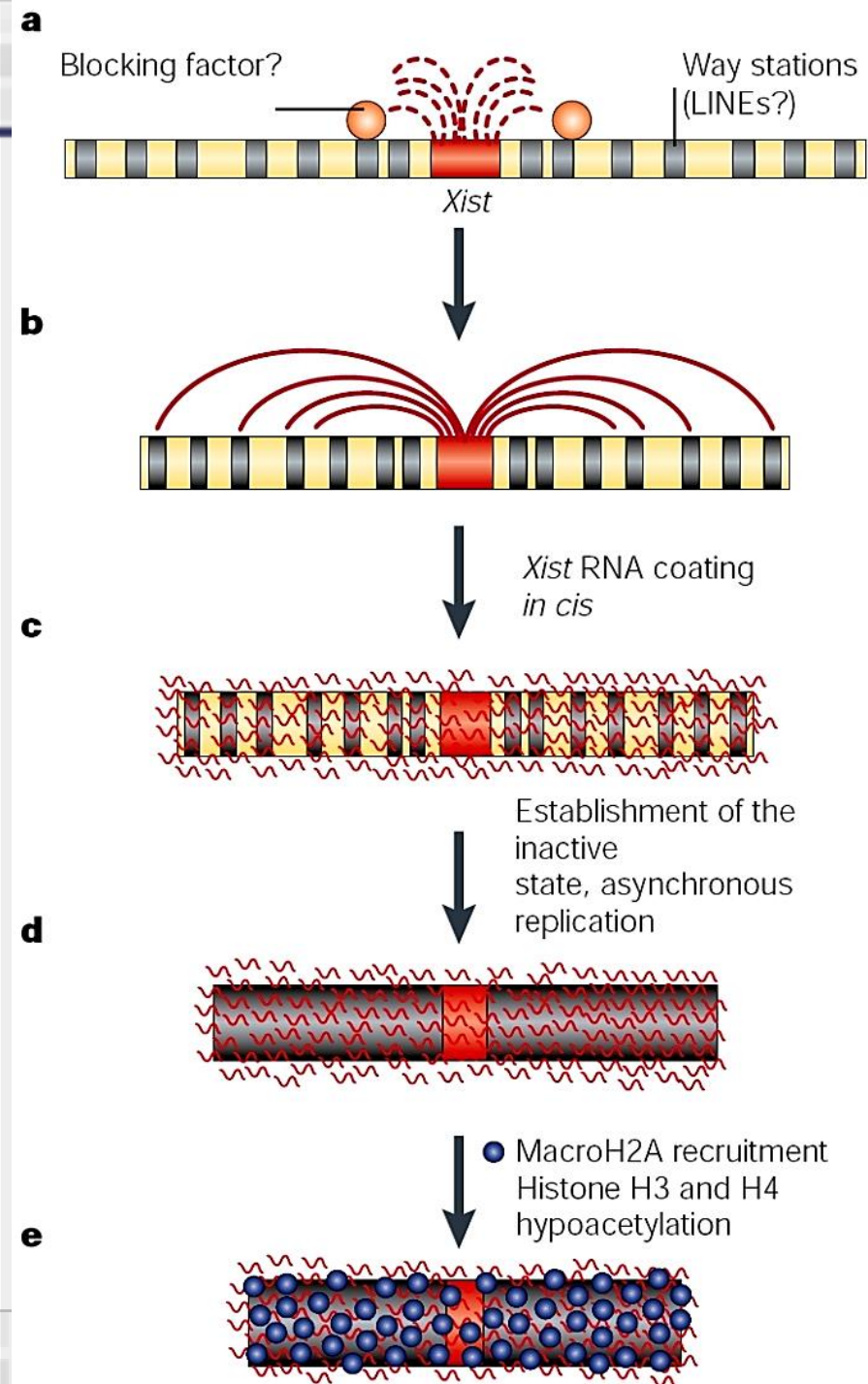
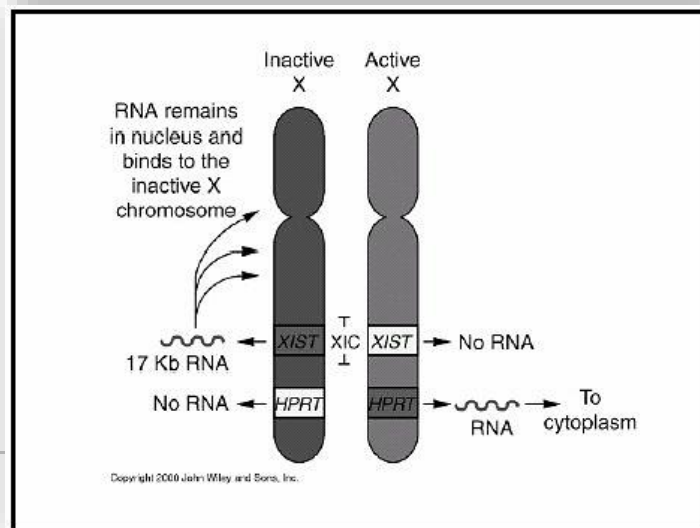
Hypomelanosis of Ito

- **Mosaicism** for **diploidy/triploidy** can demonstrate:
 - The clinical picture seen in **full triploidy** but in a milder form.
 - The condition known as **hypomelanosis of Ito**.
- In this **curious disorder** the skin shows alternating patterns of **normally pigmented and depigmented streaks** that correspond to the **embryological developmental lines of the skin** known as **Blaschko lines**.
- Most children with hypomelanosis of Ito have **moderate ID** and **convulsions** that can be particularly difficult to treat.
- There is increasing evidence that this clinical picture represents a nonspecific embryological response to cell or tissue mosaicism. A similar pattern of skin pigmentation is sometimes seen in women with one of the **rare XL dominant disorders** with skin involvement, such as **Incontinentia Pigmenti**.
- Such **women** are essentially **mosaic** because some cells express **the normal gene**, whereas others express only **the mutated gene**.

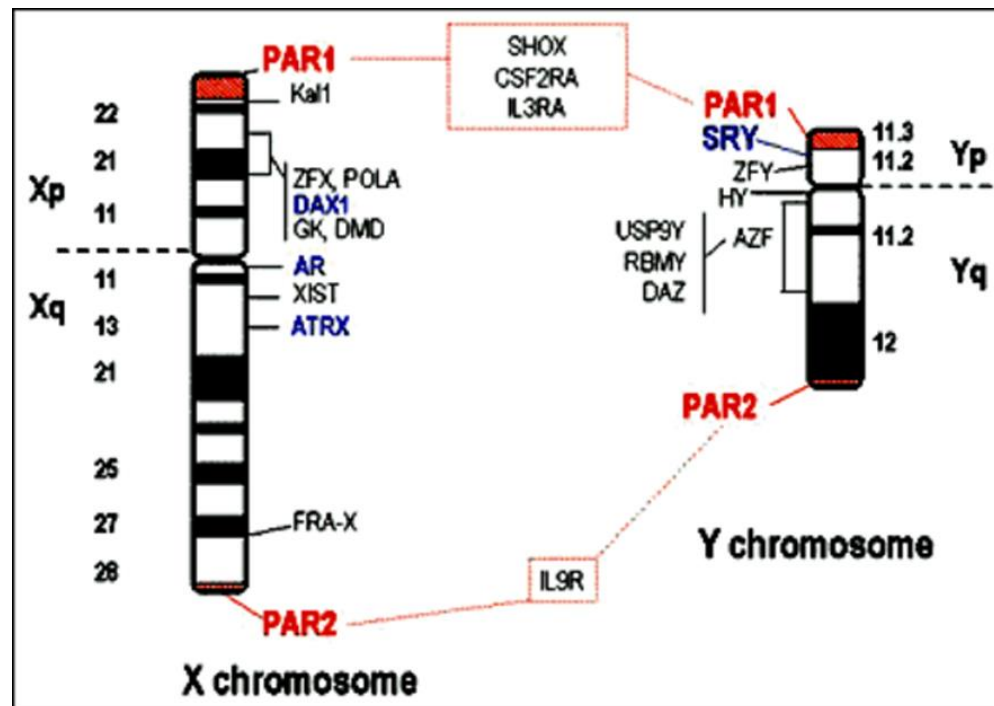
Disorders of the Sex Chromosomes

X-inactivation process

- **Xist** (X-inactive specific transcript) is a **non-coding RNA** on the X chromosome of the placental mammals that acts as a major effector of the X-inactivation process.
- It is a component of the **XIC** (X-chromosome inactivation center)
- The **XIC** is located on the **q arm** of the X chromosome (**Xq13**)



- The **SHOX** gene is located on the **pseudoautosomal region 1 (PAR1)** of both the **X and Y chromosomes**, specifically at **Xp22.3** and **Yp11.3**.
- This region is unique because genes within it are present **on both sex chromosomes**, unlike most genes which are exclusive to either **X or Y**.



Klinefelter Syndrome

- 47,XXY
- 46,XY/47,XXY
- 48,XXX
- 49,XXXXY

BACKGROUND

- * XXY SYNDROME or KLINEFELTER SYNDROME
- * PRESENCE of EXTRA X CHROMOSOME (47, XXY)
- * MOST COMMON SEX CHROMOSOME DISORDER
- * AFFECTS APPROXIMATELY 1 in 500 to 1,000 GENETIC MALES



SIGNS & SYMPTOMS

- * TALL STATURE
- * REDUCED MUSCLE TONE
- * WEAKER BONES
- * LACK of FACIAL & BODY HAIR
- * ENLARGED BREAST TISSUES
- * INFERTILITY
- * STRUCTURAL GENITOURINARY ABNORMALITIES
- * DEVELOPMENTAL & BEHAVIORAL ABNORMALITIES
 - ~ SPEECH & LANGUAGE DELAYS
 - ~ DEPRESSION
 - ~ ADHD
 - ~ EMOTIONAL IMMATURITY
 - ~ MILD EXECUTIVE FUNCTIONING IMPAIRMENTS



DIAGNOSIS

- * REVIEW SYMPTOMS & MEDICAL HISTORY
- * ASSESS PHYSICAL DEVELOPMENT STAGES DURING PUBERTY
- * EVALUATE HORMONE LEVELS
- * IMAGING to ASSESS SIZE & STRUCTURE of GONADS
- * CONFIRMED via KARYOTYPING or CHROMOSOME ANALYSIS



CAUSES

- * RANDOM ERROR DURING MEIOSIS
 - ~ RESULTS in EXTRA COPY of X CHROMOSOME in ALL CELLS in the BODY
- * MAY OCCUR AFTER CONCEPTION
 - ~ CAN LEAD to MOSAIC KLINEFELTER SYNDROME WHERE SOME CELLS MAY HAVE the NORMAL XY GENOTYPE



TREATMENT

- * TESTOSTERONE REPLACEMENT THERAPY
- * FERTILITY MANAGEMENT
 - ~ IN-VITRO FERTILIZATION
- * EARLY INTERVENTIONS
 - ~ SPEECH & LANGUAGE
 - ~ SPECIAL EDUCATION
- * ROUTINE MONITORING & FOLLOW-UP



Turner Syndrome (45,X)



FIG. 17.8 Ultrasonographic scan at 18 weeks' gestation showing hydrops fetalis. Note the halo of fluid surrounding the fetus. Courtesy Dr D. Rose. City Hospital, Nottingham, UK.

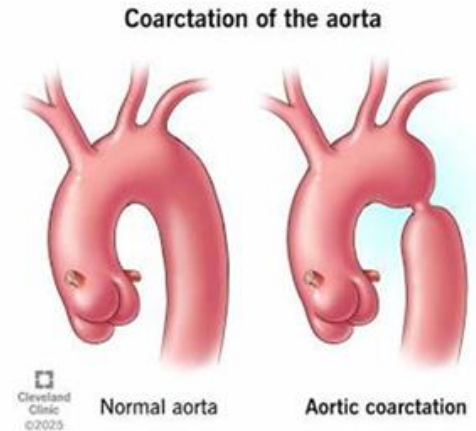


FIG. 17.9 The foot of an infant with Turner syndrome showing edema and small nails.

Turner Syndrome (45,X)

- ❑ Intelligence in Turner syndrome is within the **normal** range.
- ❑ Although **common** at conception and in **spontaneous abortions**, the incidence in **live-born female** infants is **low**, with estimates ranging from **1:5000 to 1:10,000**.
- ❑ Increasingly, Turner syndrome is detected during **the second trimester** through routine **ultrasonography**, showing either generalized edema (**hydrops**) or swelling localized to the neck (**nuchal cyst or thickened nuchal pad**).

Turner Syndrome (45,X)

- At birth many babies with Turner syndrome look **entirely normal**.
- Others show the residue of **intrauterine edema**, with **puffy extremities** and **neck webbing**.
- Other findings may include a **low posterior hairline**, **increased carrying angles at the elbows**, **short fourth metacarpals**, **widely spaced nipples**, and **coarctation of the aorta**, which is present in approximately 15% of cases.

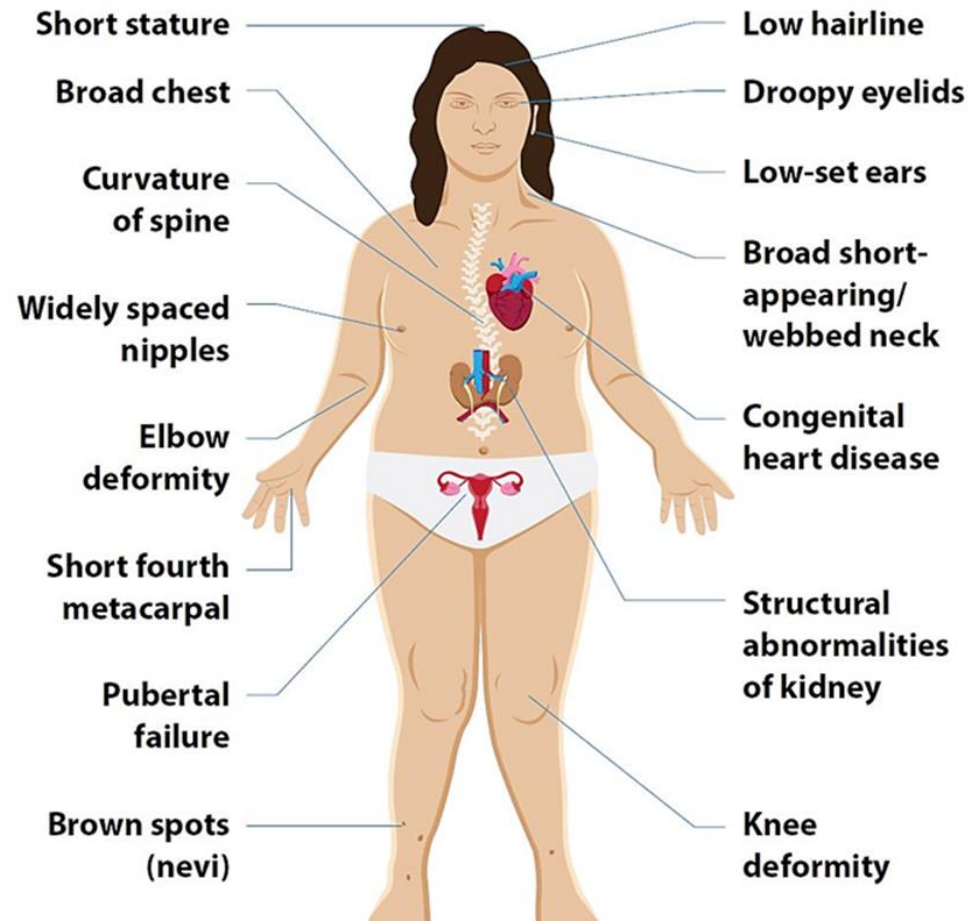
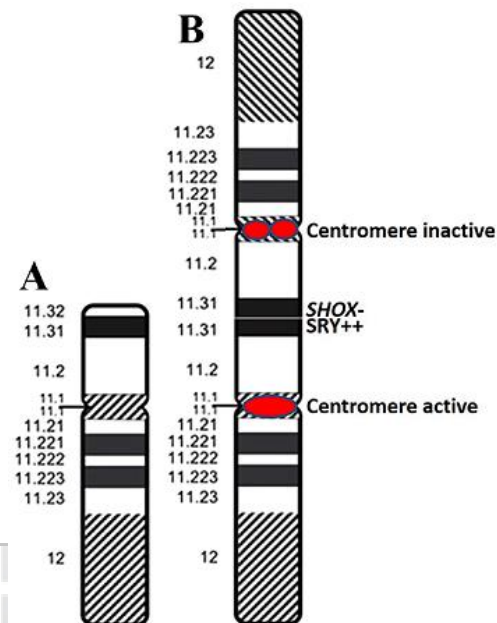
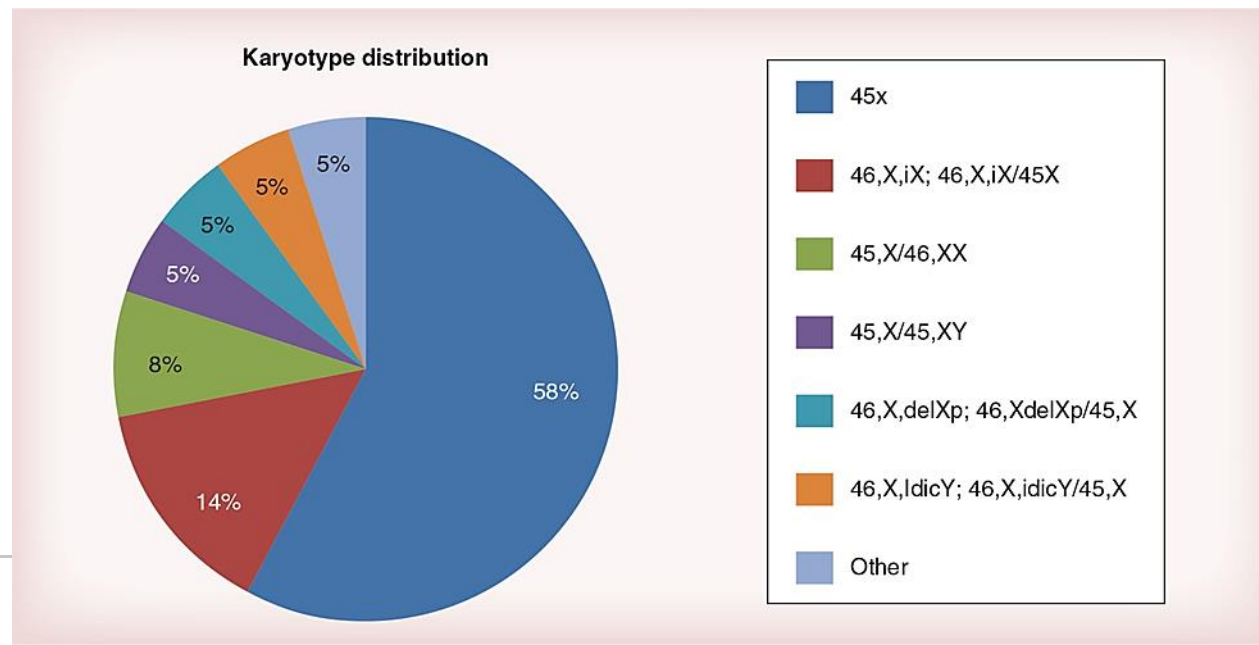


Table 17.6 Chromosome findings in Turner syndrome

Karyotype	Frequency (%)
Monosomy X: 45,X	50
Mosaicism (e.g., 45,X/46,XX)	20
Isochromosome: 46,X,i(Xq)	15
Ring: 46,X,r(X)	5
Deletion: 46,X,del(Xp)	5
Other	5



Sex chromosomal aneuploidy	Prenatal aspects	Phenotypical postnatal aspects
45,X Turner syndrome	• Nuchal translucency enlargement • Septated hygroma colli • Fetal edema • Cardiac abnormality • Growth restriction	• Webbed neck • Puffy hands and feet • Small stature • Health problems: heart, kidney, autoimmune, and metabolic diseases • Estrogen deficiency • No or late puberty • No mammary growth • Infertility • Risk of gonadal dysplasia • Behavioral disturbances
47,XXY Klinefelter syndrome	• None	• Large stature • Health problems: autoimmune and metabolic diseases • Testosterone deficiency • Risk of bone fragility • No or late puberty • mammary growth, risk of mammary carcinoma • Infertility • Risk of gonadal dysplasia • Behavioral disturbances

XXX Females/ Triple X syndrome

- ❑ Birth surveys have shown that approximately **0.1%** of all females have a 47,XXX karyotype.
- ❑ These women **usually** have **no obvious physical abnormalities** (though **head circumference** is usually in the **lower** centiles) but can show a **mild reduction of 10 to 20 points in intellectual skills** and **sometimes quite oppositional behavior**. This is rarely of sufficient severity to require special education.
- ❑ Studies have shown that the additional X chromosome is of **maternal origin in 95%** of cases and usually arises from an error in **meiosis I**.
- ❑ Adults are **usually fertile** and have **children with normal karyotypes**.
- ❑ As with males who have more than two X chromosomes, women with **more than three X chromosomes** show a **high incidence of ID**, the **severity** being directly related to the **number** of X chromosomes.



Main symptoms



Above average height



Delayed speech development



Mild intellectual disabilities



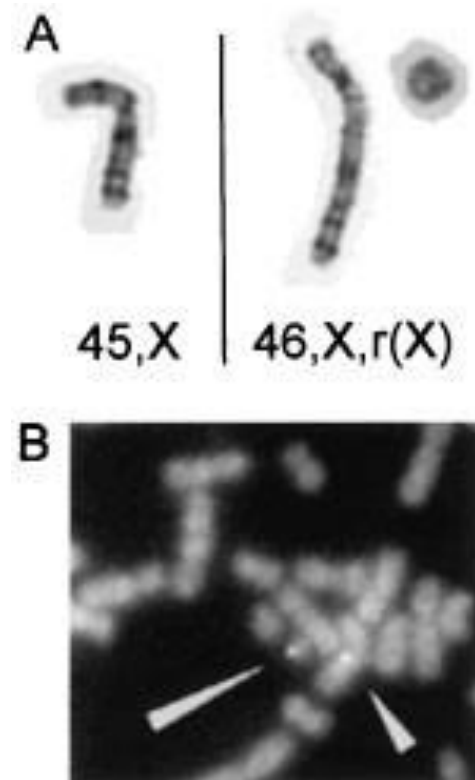
Menstrual irregularities



Premature ovarian failure

46,Xr(X) karyotype

- A ring chromosome X is found in **some** women with **typical features of Turner** syndrome. This is consistent with the ring lacking X-chromosome sequences, which are **normally not inactivated** and which are needed for a normal phenotype.
- Curiously, a few 46,Xr(X) women have **congenital abnormalities** and show **intellectual impairment**. In these women it has been shown that **XIST is not expressed on the ring X**, so their relatively severe phenotype is likely to be caused by **functional disomy for genes** present on their ring X chromosome.



XYY Males

- **1:1000** in males in newborn surveys but is found in 2% to 3% of males who are in institutions because of **ID** or **antisocial criminal behavior**.
- However, it is important to stress that **most** 47,XYY men have **neither** learning difficulty nor a criminal record, although they can show **emotional immaturity** and **impulsive behavior**.
- **Fertility** is normal.
- **Physical appearance** is normal, and **stature** is usually above average. **Intelligence** is mildly impaired, with an overall IQ score of 10 to 20 points below controls. The additional Y chromosome must arise either as a result of **nondisjunction** in **paternal meiosis II** or as a **postzygotic event**.

Some features of 47,XYY syndrome may include:



Tall stature.



Low muscle tone.



Asthma.



Larger teeth.



Delays in speech and language.



Behavioral issues.

Fragile-X syndrome (FXS)/ Martin-Bell syndrome

- Could equally well be classified as a single-gene disorder rather than a chromosome abnormality, has the unique distinction of being one of the most common inherited causes of ID and the first disorder in which a dynamic mutation (triplet repeat expansion) was identified.
- It affects approximately 1:5000 males and accounts for 4% to 8% of all males with ID.
- The FMR1 gene (Fragile X Mental Retardation 1) is located on the X chromosome and is crucial for normal brain development and female reproductive function.
- High forehead, large ears, long face,
- and prominent jaw
- After puberty most affected males have large testes (macro-orchidism), connective tissue weakness, with hyperextensible joints, stretch marks on the skin (striae), and mitral valve prolapse.



RARE DISEASE DAY

SYMPTOMS

- Autism spectrum disorders
- Intellectual disability
- Abnormal facial features

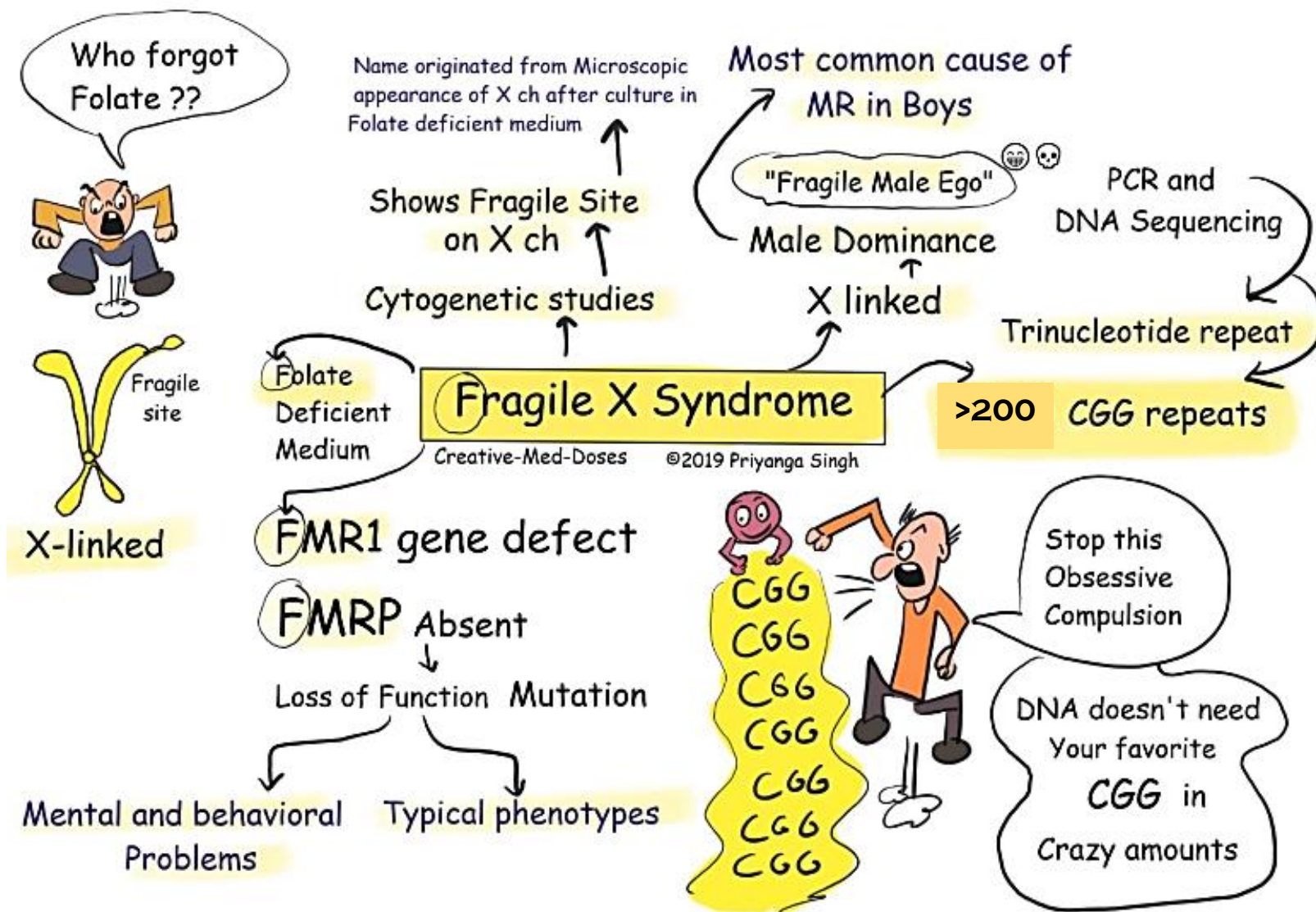
PROMINENT FOREHEAD

LARGE EARS

LONG FACE

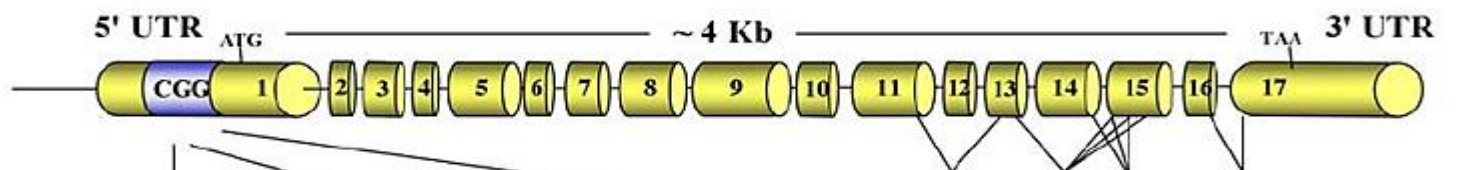
PROMINENT JAW





Xq27.3

FMR1
gene



CGG
repeats



Normal

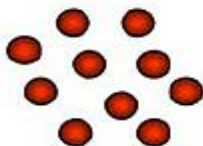
6-50



FMR1
mRNA



FMRP
protein

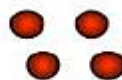
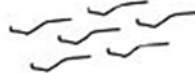


15-25% females

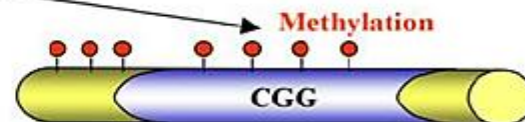


Premutation

55-200



10% males



Full-mutation

>200



100%

Phenotype

Premature Ovarian
Failure (POF)

Tremor/Ataxia
Syndrome (FXTAS)

Fragile X
Syndrome (FXS)

Southern blot of DNA from a family showing expansion of the CGG triplet repeat being passed from a normal transmitting male (I1) through his obligate carrier daughter (II2) to her son (III1) with **fragile-X intellectual disability**.

A **normal** allele and **premutation** can be identified by polymerase chain reaction (**PCR**), whereas Southern blotting is necessary to detect **full mutations** because the long CGG expansion is often refractory to PCR amplification.

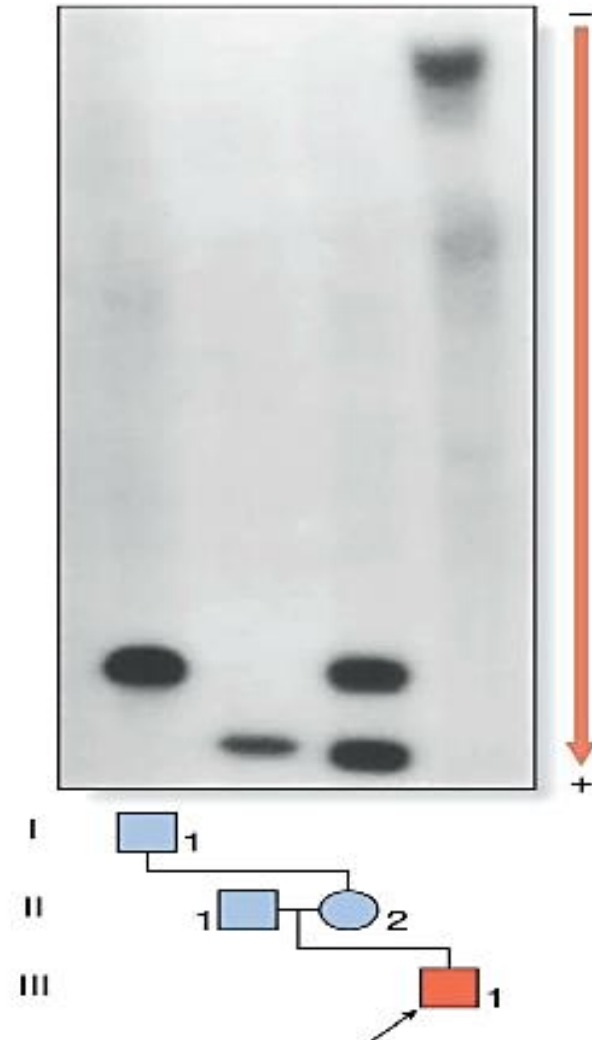


Table 17.7 Fragile-X syndrome: genotype-phenotype correlations

Number of Triplet Repeats (Normal Range 5–44)	Fragile Site	Intelligence Detectable
<u>Males</u>		
45–54 (intermediate alleles)		
55–200 (premutation)	No	Normal (normal transmitting male)
200–2000 (full mutation)	Yes (in up to 50% of cells)	Moderate-to-severe intellectual disability (ID)
<u>Females</u>		
45–54 (intermediate alleles)		
55–200 (premutation)	No	Normal
200–2000 (full mutation)	Yes (usually <10% of cells)	50% normal, 50% mild ID

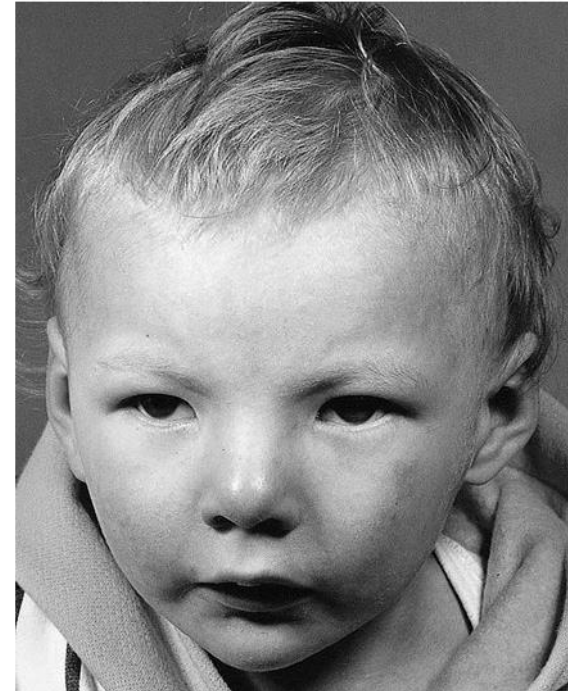
FRAXE and FRAXF

- FRAXA in Xq27.3
- The expansion mutations at FRAXE at Xq28 also involve CGG triplet repeats but are much rarer than FRAXA mutations.
- Some males with these mutations have mild learning difficulties, whereas others are just as severely affected as men with pathogenic FRAXA variants.
- FRAXE may show up as a fragile site cytogenetically, but the PCR test is separate.
- A third fragile site, FRAXF, has been identified close to FRAXA and FRAXE. This does not seem to cause any clinical abnormality.

“Classic” Chromosome Deletion Syndromes

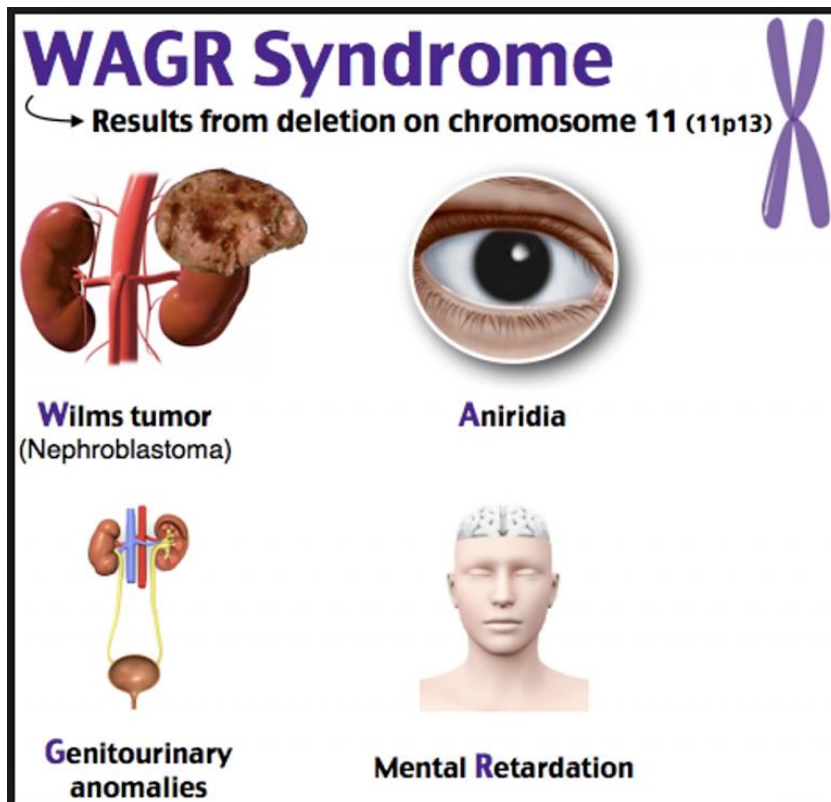


Wolf-Hirschhorn (4p⁻)

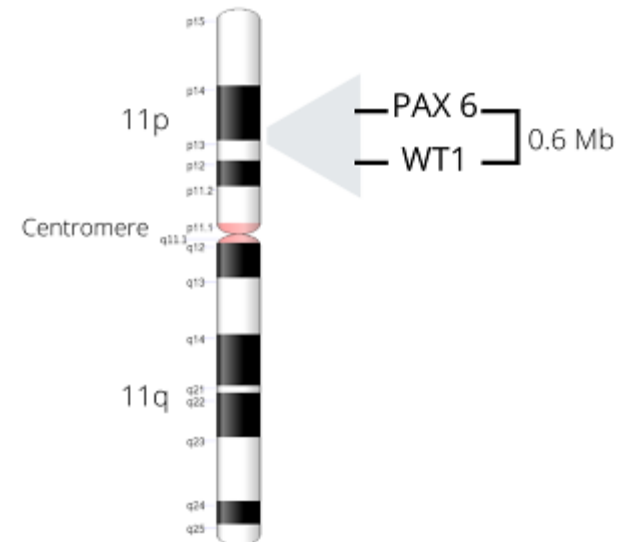


cri-du-chat (5p⁻)

- ☐ 1:50,000 Births
- ☐ Severe ID
- ☐ Failure To Thrive

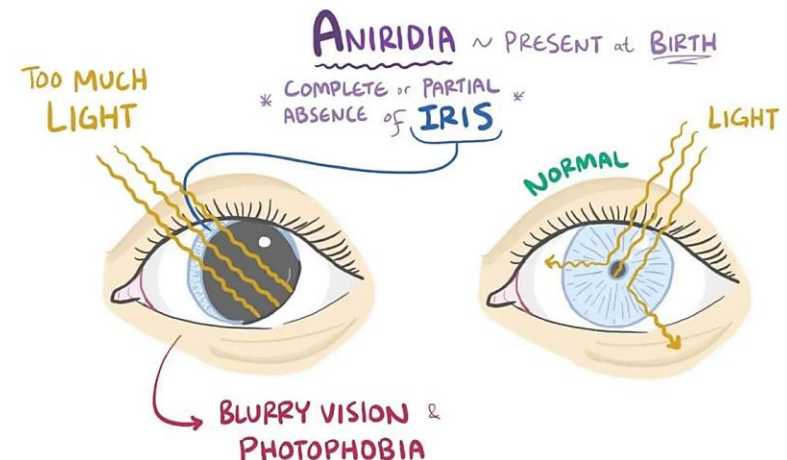


Chromosome 11: WAGR Syndrome



Wilms Tumor/WAGR syndrome/
Hypernephroma

Aniridia, **G**enitourinary abnormalities, and
Retardation of growth and development: 11p13
deletion; PAX6 gene





Angelman



Prader-Willi

☐ Genomic imprinting

- ☐ A microdeletion in 15q11–13, **paternally in Prader-Willi** and **maternally in Angelman** syndrome.
- ☐ Non-deletion: **uniparental disomy**: with both number 15 chromosomes being **paternal in origin in Angelman** syndrome, and **maternal in Prader-Willi** syndrome.

Angelman



FIG. 6.24 (A) and (B) Two young girls with Angelman syndrome. (C) Adult male with Angelman syndrome.

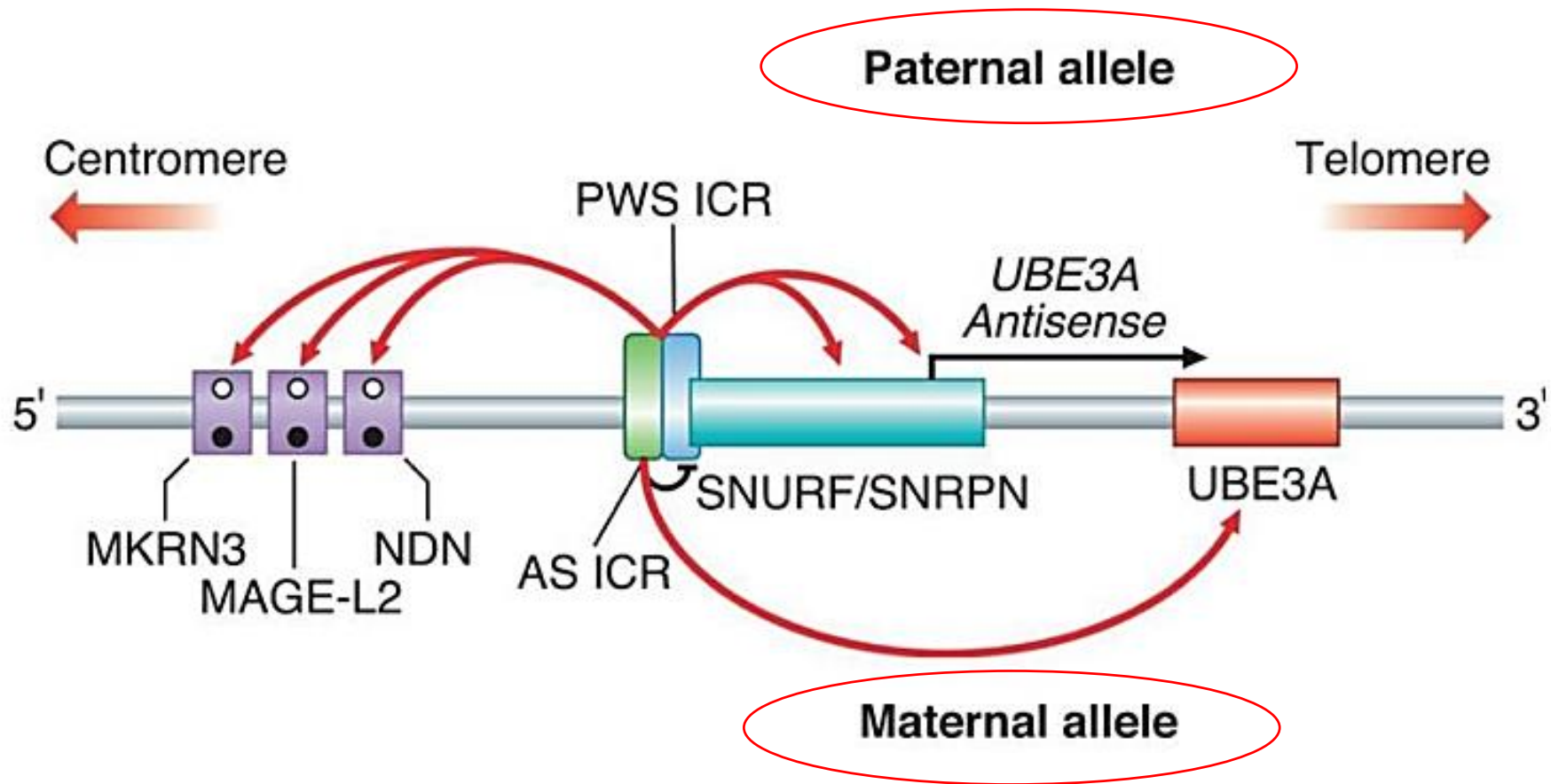
- ☐ inappropriate laughter
- ☐ convulsions,
- ☐ poor coordination (ataxia), and
- ☐ severe learning difficulties

Prader-Willi



FIG. 6.22 Female child with Prader-Willi syndrome.

- ☐ very hypotonic with poor feeding in infancy
- ☐ later develop hyperphagia and obesity
- ☐ mild to moderate ID



Chromosome Microarray (CMA)

**Microarray-Comparative Genomic
Hybridization/ Array CGH**

Contiguous Gene Syndromes

- ❑ CMA is currently **the most widely** used technique to diagnose **submicroscopic losses** of genomic material, that is, **microdeletions**.
- ❑ Some microdeletions involve **loss of several genes at closely adjacent loci**, resulting in **contiguous gene syndromes**.
- ❑ For example, **several boys** with **Duchenne muscular dystrophy (DMD)** have been described who also have **other XL disorders**, such as **retinitis pigmentosa** and **glycerol kinase deficiency**. The loci for these disorders are very close to the DMD locus on **Xp21**.



Deletion Xp22.3

- As with the rare example already described in relation to Xp21, a microdeletion at Xp22.3 is **a classic contiguous gene syndrome**.
- The locus incorporates XL recessive chondrodysplasia punctata (aryl sulfatase-E, ARSE gene), mental retardation (VCX-A gene), ichthyosis (steroid sulfatase, STS gene), and Kallmann syndrome (KAL1 gene).
- **Short stature** also usually occurs because of loss of the short stature homeobox-containing gene (**SHOX**), which when mutated on its own gives rise to Leri-Weill dyschondrosteosis.
- **Depending on the size and extent of the deletion**, therefore, individuals may present **variably** with **short stature, a flat face and small nose with a flat nasal tip, short digits, dry skin and hair, hypogonadotropic hypogonadism, anosmia, and ID**.

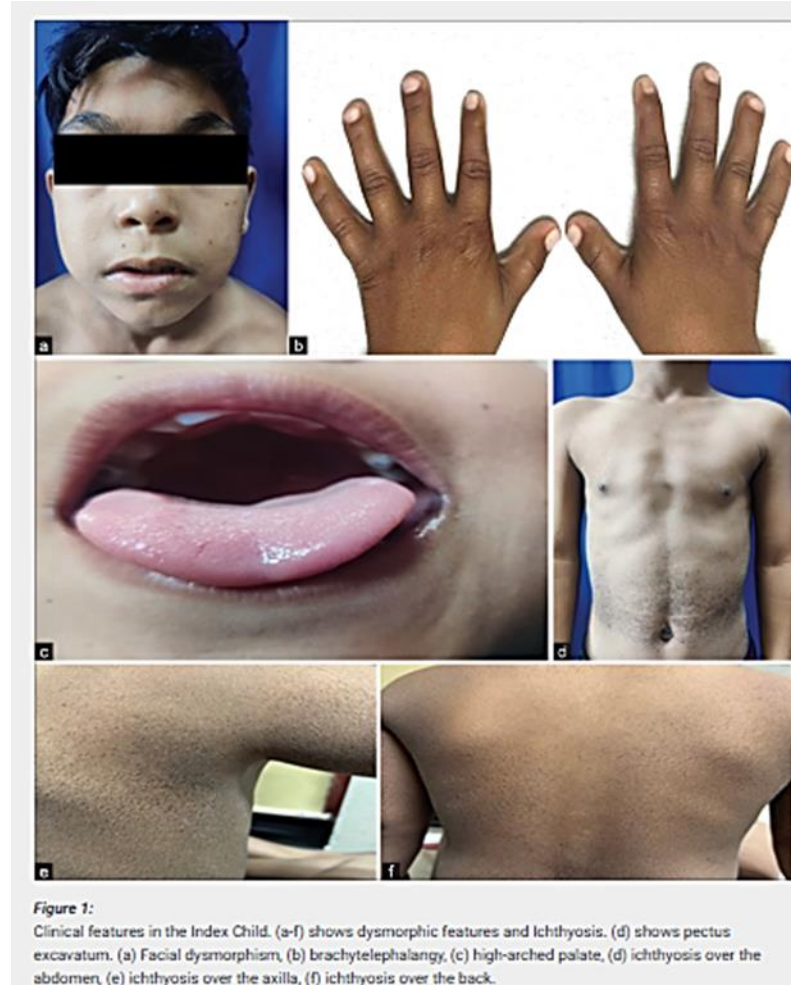


Figure 1:
Clinical features in the Index Child. (a-f) shows dysmorphic features and Ichthyosis. (d) shows pectus excavatum. (a) Facial dysmorphism, (b) brachytelephalangy, (c) high-arched palate, (d) ichthyosis over the abdomen, (e) ichthyosis over the axilla, (f) ichthyosis over the back.

doi: 10.25259/JNRP_467_2023

Table 1: Genes of interest in Xp22.3 region and its phenotypes.

S. No	Location	Genes		MIM	Phenotype	Phenotype MIM
1.	Xp22.31	<i>ANOS1</i>	Anosmin-1	300836	Kallmann syndrome	308700
2.	Xp22.31	<i>STS</i>	Steroid sulfatase	300747	Ichthyosis	308100
3.	Xp22.32	<i>NLG4X</i>	Neurologin-4	300427	ASD, ID	300495
4.	Xp22.33	<i>ARSL</i>	Arylsulfatase-L	300180	Chondrodysplasia punctata, Short stature	302950
5.	Xp22.33	<i>SHOX</i>	Short stature homeobox	312865	Short stature LWD, MD	300582

ASD: Autism spectrum disorder; ID: Intellectual disability; LWD: Leri-Weill dyschondrosteosis; MD: Madelung deformity; MIM: Online Mendelian inheritance in man.

Table 17.8 Well-known microdeletion syndromes

Syndrome	Chromosome	Key Gene(s)
Deletion 1p36	1p36	
Deletion 2q37	2q37	
Wisconsin	3q24-q25	<i>MBNL1</i>
Wolf-Hirschhorn	4p	
Cri-du-chat	5p	
Williams (Williams-Beuren)	7q11.23	<i>ELN</i> (Supravalvular aortic stenosis) <i>LIMK1</i> (Neurologic features)
Langer-Giedion	8q24.11	<i>TRPS1</i> (Trichorhinophalan features) <i>EXT1</i> (Exostoses)
Kleefstra	9q34.3	<i>EHMT1</i>
WAGR	11p13	<i>RB1, WT1</i>
Jacobsen	11q23	
Angelman	15q11.2	<i>UBE3A</i>
Prader-Willi	15q11.2	<i>SNRPN</i>
Deletion 16p11.2	16p11.2	<i>TBX6</i> (Scoliosis)
Rubinstein-Taybi	16p13.3	<i>CREBBP</i>
Miller-Dieker	17p13.3	<i>LIS1</i>
Smith-Magenis	17p11.2	<i>RAI1</i>
Koolen-de Vries	17q21.31	<i>KANSL1</i>
DiGeorge/Sedláčková/velocardiofacial	22q11.2	<i>TBX1</i>
Phelan-McDermid	22q13	<i>SHANK3</i>

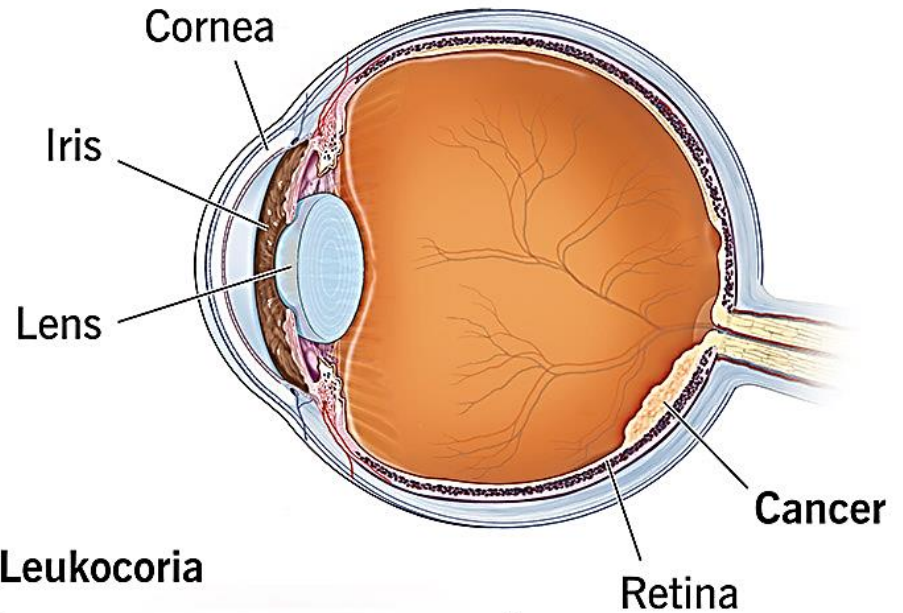
WAGR, Wilms tumor, aniridia, genitourinary malformations and retardation of growth and development.

Retinoblastoma

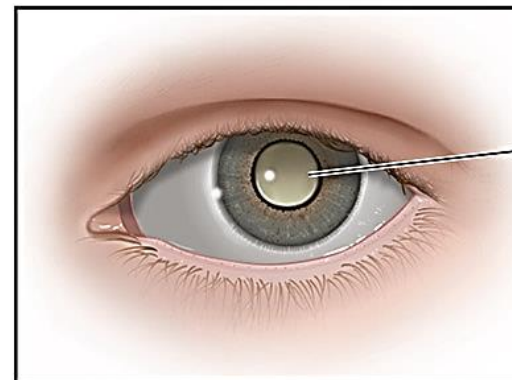
Mutations in the **RB1** gene at **13q14**



Retinoblastoma



Leukocoria

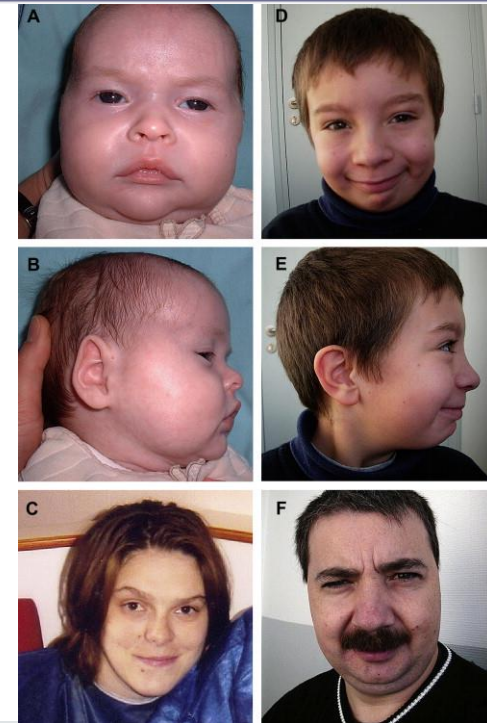


Pale-colored
retina



**Deletion 22q11 syndrome
DiGeorge/Sedláčková/Velocardiofa
cial Syndrome**

- ☐ 1:4,000 Births
- ☐ Heart malformations
- ☐ Thymic and parathyroid hypoplasia
- ☐ Cleft palate
- ☐ typical facies



Duplication 22q11.2

- ☐ Mild ID
- ☐ Nonspecific dysmorphic features
- ☐ congenital heart disease
- ☐ cleft palate
- ☐ hearing loss
- ☐ Postnatal growth deficiency

Williams Syndrome (WS)/ Williams-Beuren syndrome/ microdeletion at chromosome 7q11.23

- **Hypocalcemia**
- Supravalvular aortic stenosis (**SVAS**)
- **Peripheral pulmonary artery stenosis**
- Loss of one copy of the gene that encodes **elastin**, a component of **connective tissue**
- **Mild short stature**, a full lower lip, and sloping shoulders
- **Behavior**: They are typically very outgoing in childhood having a “**cocktail party manner**” but become withdrawn and sensitive as adults. All are intellectually impaired to the extent that they cannot lead independent lives, and the majority do not reproduce, although parent-child transmission has been reported.



Smith-Magenis Syndrome/ microdeletion at 17p11.2

- Homologous recombination between flanking low-copy repeats (**LCRs**). The physical characteristics are not highly distinctive
- Congenital heart disease in one-third
- Scoliosis develops in late childhood in more than one-half
- Hearing impairment occurs in about two thirds
- **The syndrome is most likely to be recognized by the behavioral characteristics:** as children, patients exhibit **self-harming** (head banging, pulling out nails, and inserting objects into orifices), a persistently disturbed sleep pattern and characteristic “self-hugging.” **ID is the norm** and is usually **moderate-severe**. The sleep pattern can often be managed by judicious use of melatonin. The same phenotype may be caused by a mutation in **the RAI1 gene**, which is located within the deleted segment.

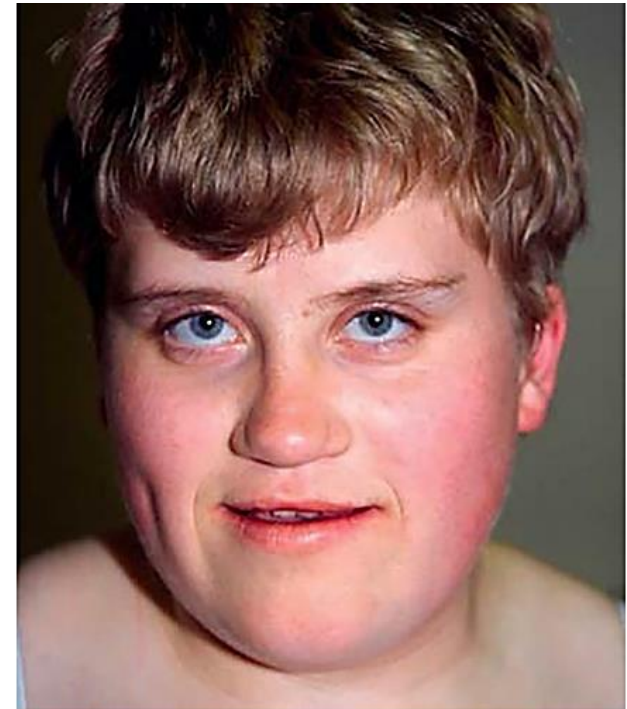


FIG. 17.20 A young person with Smith-Magenis syndrome; the facial features are not highly distinctive, but the philtrum is usually short. As babies, chromosome studies are often requested because the possibility of Down syndrome is raised.

Deletion 1p36 Syndrome



FIG. 17.21 A child with deletion 1p36 syndrome; very straight eyebrows, epilepsy, and learning difficulties.

- ❑ This microdeletion syndrome emerged through improved cytogenetic techniques and the use of **FISH** in the 1990s
- ❑ deletion 1p36 syndrome has no eponym
- ❑ The features are hypotonia, microcephaly, growth delay, severe learning difficulties, epilepsy (including infantile spasms), characteristically straight eyebrows with slightly deep-set eyes, and midface hypoplasia
- ❑ Some cases develop dilated cardiomyopathy.

Deletion 9q34 (Kleefstra) Syndrome



FIG. 17.22 A child with deletion 9q34 syndrome. She has arched eyebrows, narrow upslanting palpebral fissures, brachycephaly, prognathism, and severe intellectual disability. She was initially investigated for possible Angelman syndrome.

- ❑ A condition featuring significant **ID**, hypotonia, obesity, brachycephaly, arched eyebrows, synophrys, anteverted nostrils, prognathism, sleep disturbances, and behavioral problems.
- ❑ Many patients have severe speech delay, and not all manifest obesity.
- ❑ some patients with the phenotypic features but **no microdeletion** have mutations in **the euchromatin histone methyl transferase 1 (EHMT1) gene**, which lies within the region. The syndrome might therefore be mainly caused by haploinsufficiency for this gene

Deletion 17q21.31 (Koolen-de Vries) Syndrome



FIG. 17.23 This child shows the characteristic facial features of

- ❑ This was one of the first new deletion syndromes delineated through CMA, has a prevalence of approximately **1:16,000** and is probably significantly underdiagnosed.
- ❑ The main features are **severe ID**, hypotonia and characteristic facial dysmorphisms including a long face with a high forehead and tubular or **pear-shaped nose**, a bulbous nasal tip, large ears, and everted lower lip
- ❑ Tendency to be friendly
- ❑ Epilepsy, heart defects, kidney anomalies, and long, slender fingers.
- ❑ The **KANSL1** gene is key, and there are patients with pathogenic variants who do not have CMA-detectable deletions

Deletion 22q13 (Phelan-McDermid) Syndrome



FIG. 17.24 A young adult with a pathogenic variant in the *SHANK3* gene, giving rise to features consistent with a severe form of Phelan-McDermid syndrome—moderate-severe intellectual disability and absent speech. The nose is rather bulbous, and many individuals with this syndrome have only soft, dysmorphic features.

- ❑ Cytogenetically visible deletions
- ❑ Before diagnosis some patients were considered to possibly have Angelman syndrome because of **the very poor speech acquisition** and **happy affect**.
- ❑ **Small** deletions are associated with **mild** difficulties
- ❑ Hypotonia, significant speech delay or absent speech, **general ID**, behavior problems that do not strictly meet the criteria for autistic spectrum disorder and soft, dysmorphic features.
- ❑ There is a recurrent breakpoint on distal 22q which disrupts the **SHANK3** gene, and indeed patients have been identified with pathogenic variants in this gene without deletions

Deletion 1q21.1 Syndrome



FIG. 17.25 (A) This mother and child have deletion 1q21.1 syndrome. They bear a resemblance to each other, and there is evidence of mild development delay and small head size. (B) The same child nearly 1 year after the first picture was taken

- ❑ This condition was first identified in three individuals from a cohort of 505 with congenital heart disease.
- ❑ The phenotype is broad and includes mild-moderate ID, small head size, growth retardation, heart defects, cataracts, hand deformities, and skeletal problems, seizures and autism.
- ❑ Some are only mildly affected, and sometimes apparently unaffected.
- ❑ Variable penetrance and lack of highly distinctive features make genetic counseling for this genomic imbalance highly problematic.

Deletion 1q21.1 Syndrome



FIG. 17.26 A child with thrombocytopenia-absent radius syndrome. In this limb malformation the thumb is preserved. From Goldfarb CA,

- ❑ This locus is now known for its role in determining the **thrombocytopenia-absent radius (TAR) syndrome**.
- ❑ The absence of the radius but preservation of the thumb.
- ❑ In cohort studies, a common 200 kb microdeletion of 1q21.1 (adjacent to, but distinct from, the 1q21.1 microdeletion already described) was found in all **affected** individuals and **one-third** of **unaffected** family members: **suggesting that the deletion alone is not sufficient to cause the phenotype**.
- ❑ A truncating mutation of the **RBM8A** gene at the same locus
- ❑ The non-deleted allele always harbored one of two low frequency **SNPs** in regulatory elements of **RBM8A**.
- ❑ TAR is therefore a syndrome caused by compound heterozygosity at this locus, usually with a typical microdeletion on one allele

Deletion 16p11.2 Syndrome



FIG. 17.27 A child with deletion 16p11.2. The phenotype is not highly distinctive, and dysmorphic features are "soft." Apart from mild

- ❑ One of the most **common** imbalances seen in clinical practice occurs at 16p11.2
- ❑ very variable clinically, and the precise **extent** and **position** of the loss of genomic material tends to be related to the **severity**. So-called "type 1" deletion cases are most likely to give rise to the recognizable features, characterized by:
- ❑ Low muscle tone, delay in speech and in language development, **mild ID**, **susceptibility to autism/autistic spectrum disorder and seizures**, minor facial dysmorphisms, and a tendency to both be **overweight** and have an enlarged **head circumference**.
- ❑ Some individuals show no unusual features or neurodevelopmental problems, and, when familial, there may be marked variation between those with the deletion.
- ❑ Overall, del16p11.2 is found in approximately 1% of children with autism, and around three in 10,000 people from the general population.

Duplication 16p11.2

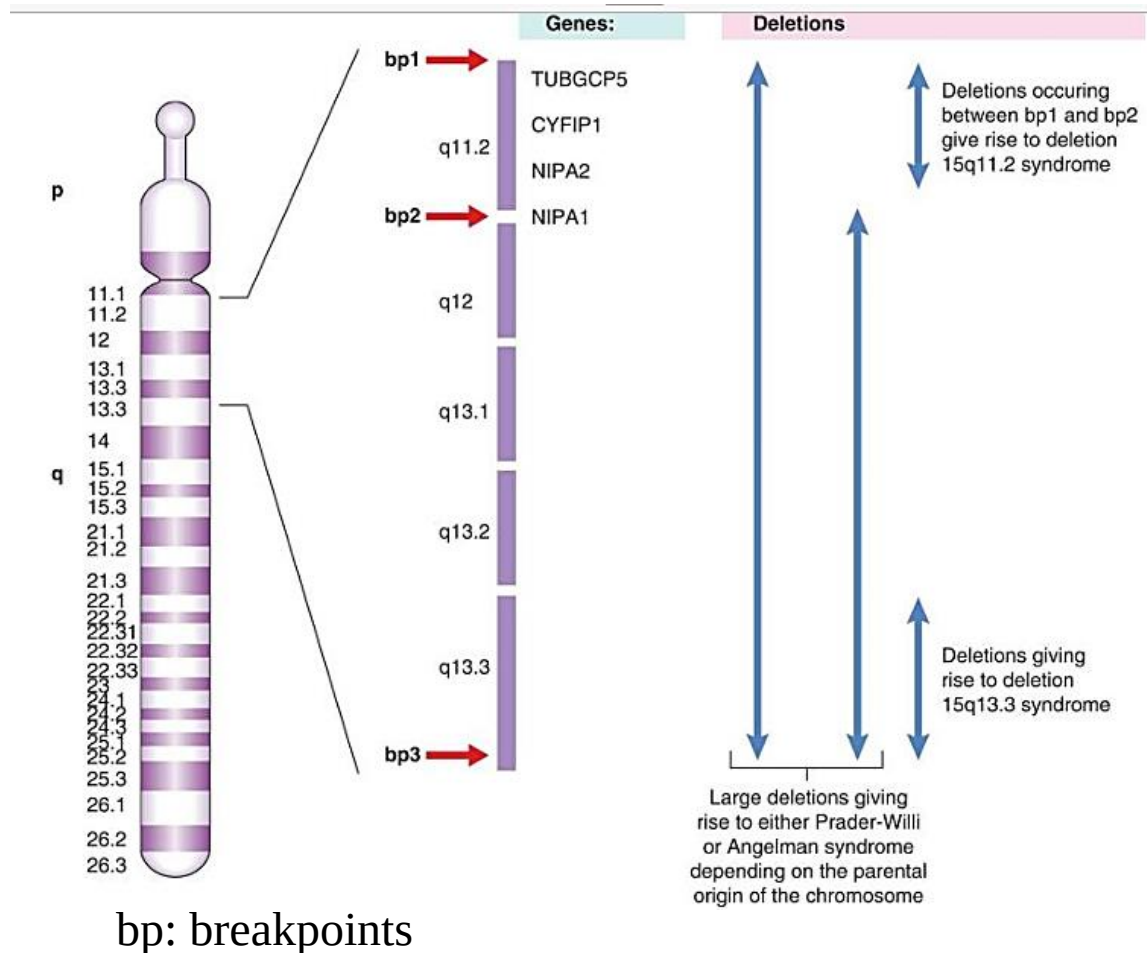


FIG. 17.28 A child with duplication 16p11.2. Apart from mild neurodevelopmental problems and soft dysmorphic features, there is a tendency towards small stature and a relatively small head.

- ❑ The reciprocal imbalance at 16p11.2, the microduplication, probably occurs at roughly the same frequency as the microdeletion both in the **general population** and in **autistic spectrum disorder**.
- ❑ The features overlap considerably regarding **mild ID** and language delay, susceptibility to both seizures and mental health problems, and the presence of minor facial dysmorphisms. It is also very variable.
- ❑ If anything, there is a tendency to display the opposite physical characteristics compared with deletion cases, that is, individuals are more likely to have **mild short stature**, be **underweight** and have a **small head circumference**.

Chromosome 15q Deletions and Microdeletions

- ❑ The **complexity** of deletions and microdeletions affecting chromosome 15q illustrate the vast range of molecular cytogenetic aberrations.
- ❑ Deletions can occur anywhere on 15q, and, in general, the **larger the deletion the more severe** the phenotype and clinical problems.
- ❑ However, the **proximal** 15q region has been an area of particular interest, largely because of its association with **Prader-Willi** and **Angelman** syndromes.



Chromosome Breakage Syndromes

- An excess of **chromosome breaks and gaps**
- An increased susceptibility to **neoplasia**

Ataxia Telangiectasia

❑ Autosomal recessive (**AR**) disorder presents in early childhood with:

Ataxia, oculocutaneous telangiectasia, radiation sensitivity and susceptibility to sinus and pulmonary infection

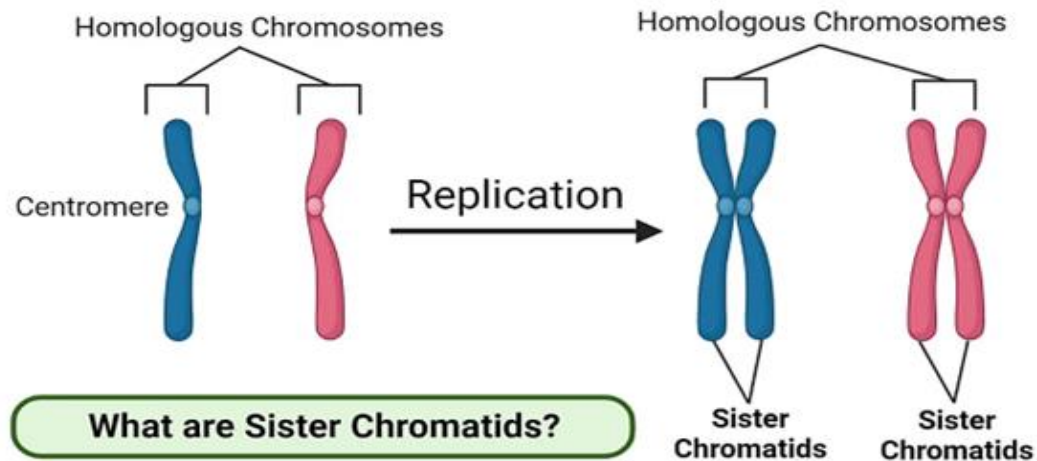


FIG. 17.30 Ocular telangiectasia in a child with ataxia telangiectasia.

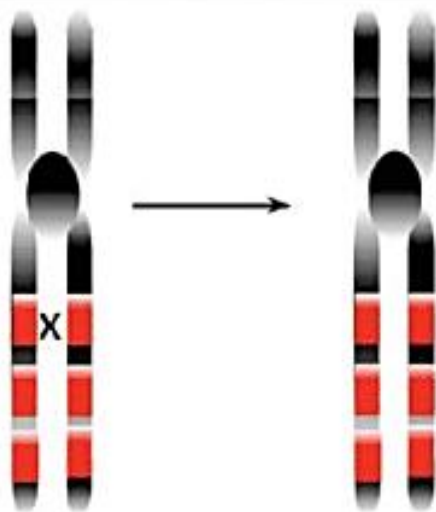
- ❑ The risk of **neoplasia** developing is in the region of **35% to 40%**, of which approximately **85%** are **leukemias** or **B-cell lymphomas**.
- ❑ **Increased several-fold** risk for other cancers, a two- to threefold increased risk of **breast cancer**.
- ❑ The ataxia telangiectasia gene is **ATM** at chromosome region **11q23**.
- ❑ However, the breast cancer risk may be variant-specific, as a significant association has emerged with c.7271 T>G (p.Val2424Gly).
- ❑ **Chromatid gaps and breaks**, which are enhanced by radiation.
- ❑ The protein product is thought to act as a **“checkpoint” protein kinase**, which interacts with the TP53 and BRCA1 gene products to **arrest cell division** and thereby allow repair of radiation-induced chromosome breaks **before the S phase** in the cell cycle

Bloom Syndrome

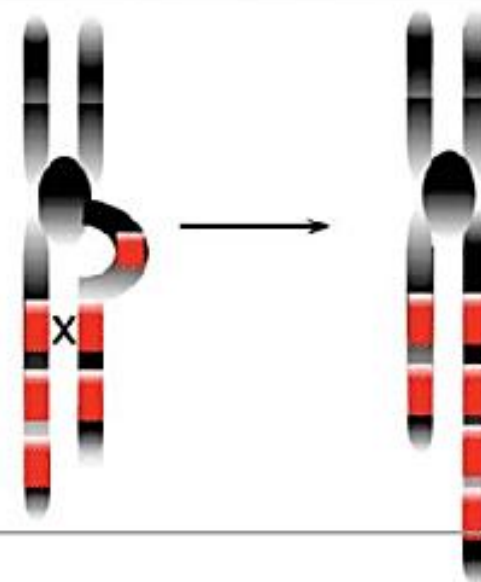
- ❑ Children with this **AR** disorder are **small**, with a **light-sensitive facial rash** and **reduced immunoglobulin (IgA and IgM) levels**.
- ❑ The risk of **lymphoreticular malignancy** is approximately 20%.
- ❑ Cultured cells show an increased frequency of chromosome breaks, particularly if they are exposed in vitro to **ultraviolet light**.
- ❑ The gene for Bloom syndrome (BLM), **RECQL3** (RecQ-like DNA helicase BLM), is at chromosome region **15q26**, and encodes one member of a group of enzymes called the **DNA helicases**.
- ❑ These are responsible for **unwinding double-stranded DNA before replication, repair, and recombination**
- ❑ Normally RECQL3 plays a major role in maintaining **genome stability**. When defective in the **homozygous** state, DNA repair is impaired, and **the rate of recombination between sister chromatids** is increased dramatically. This can be demonstrated by looking for **sister chromatid exchanges**.



Sister chromatid exchange



Unequal sister chromatid exchange



Fanconi Anemia

- ❑ This **AR** disorder is associated with **upper limb abnormalities** involving the radius and thumb
- ❑ Increased **pigmentation** and **bone marrow failure** leading to deficiency of all types of blood cells (i.e., **pancytopenia**).
- ❑ An increased risk of **neoplasia** particularly leukemia, lymphoma, and hepatic carcinoma.
- ❑ Multiple chromosomal breaks in cultured cells and
- ❑ The basic defect in the **repair** of **DNA strand cross-links**
- ❑ There are **at least 16 known subtypes** of Fanconi anemia, each caused by variants at different autosomal loci
- ❑ The most common of which is **type A**



FIG. 17.31 Bilateral radial aplasia with absent thumbs in an infant with Fanconi anemia.

Sister Chromatid Exchanges (SCEs)

- There are normally about 10 SCEs per cell, but the number is greatly increased in cells from patients with Bloom syndrome and xeroderma pigmentosa.
- In the latter condition this is apparent only after the cells have been exposed to UV light.

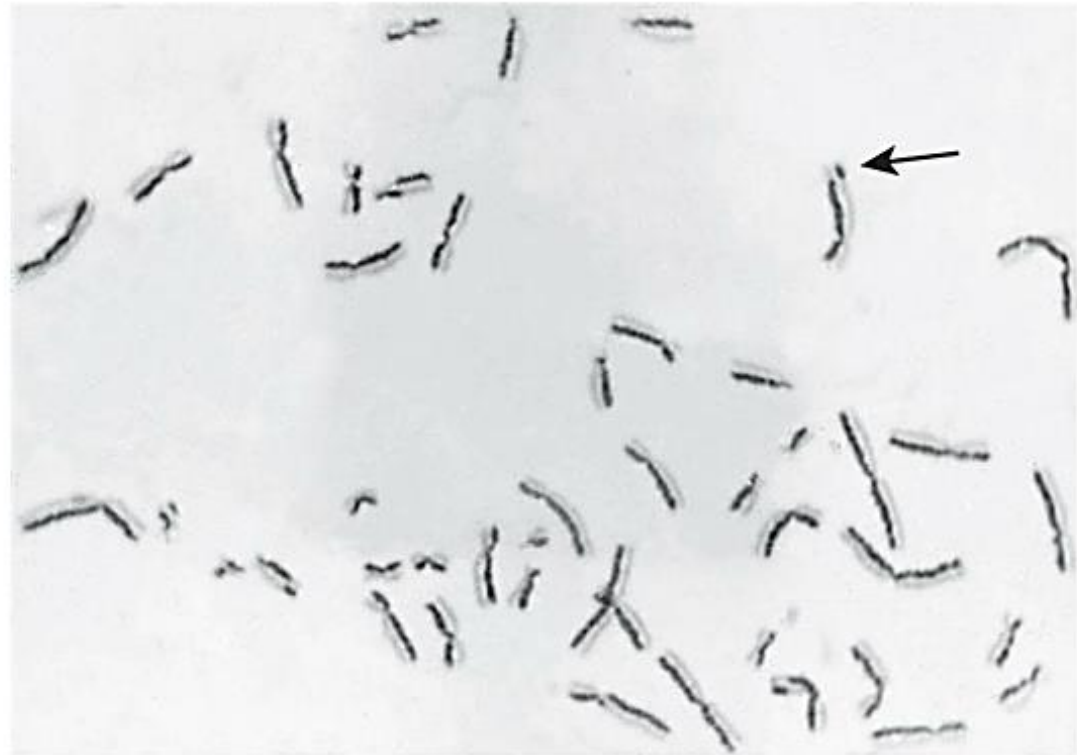


FIG. 17.34 Chromosome preparation showing sister chromatid exchanges (arrow).

Table 17.9 The subtypes of Fanconi anemia: genes and loci

Fanconi Subtype	Fanconi Gene	Chromosome Locus
FANCA	<i>FANCA</i>	16q24.3
FANCB	<i>FANCB</i>	Xp22
FANCC	<i>FANCC</i>	9q22
FANCD1	<i>BRCA2</i>	13q12
FANCD2	<i>FANCD2</i>	3p25
FANCE	<i>FANCE</i>	6p22
FANCF	<i>FANCF</i>	11p15
FANCG	<i>XRCC9</i>	9p13
FANCI	<i>FANCI</i>	15q25
FANCI	<i>BRIP1</i>	17q22
FANCL	<i>PHF9</i>	2p16
FANCN	<i>PALB2</i>	16p12
FANCO	<i>RAD51C</i>	17q22
FANCP	<i>SLX4</i>	16p13
FANCP	<i>ERCC4</i>	16p13
FANCT	<i>UBE2T</i>	1q31

Xeroderma Pigmentosum

- ❑ This exists in **at least seven different forms**, all of which follow **AR** inheritance.
- ❑ Patients present with a **light-sensitive pigmented rash** and usually **die from skin malignancy in sun-exposed areas before the age of 20 years**
- ❑ Cells cultured from these patients show chromosome abnormalities **only after exposure to UV light**.
- ❑ These disorders are caused by defects in **the nucleotide excision repair (NER) pathway**, which involves endonuclease cleavage 5' and 3' to each damaged nucleotide, excision of the damaged nucleotide(s), and finally restoration of the damaged strand using the intact opposite strand as a template



FIG. 17.33 Xeroderma pigmentosum: skin features with multiple melanomas and non-melanoma skin cancers. Courtesy of Dr. Hiva Fassihi, London.

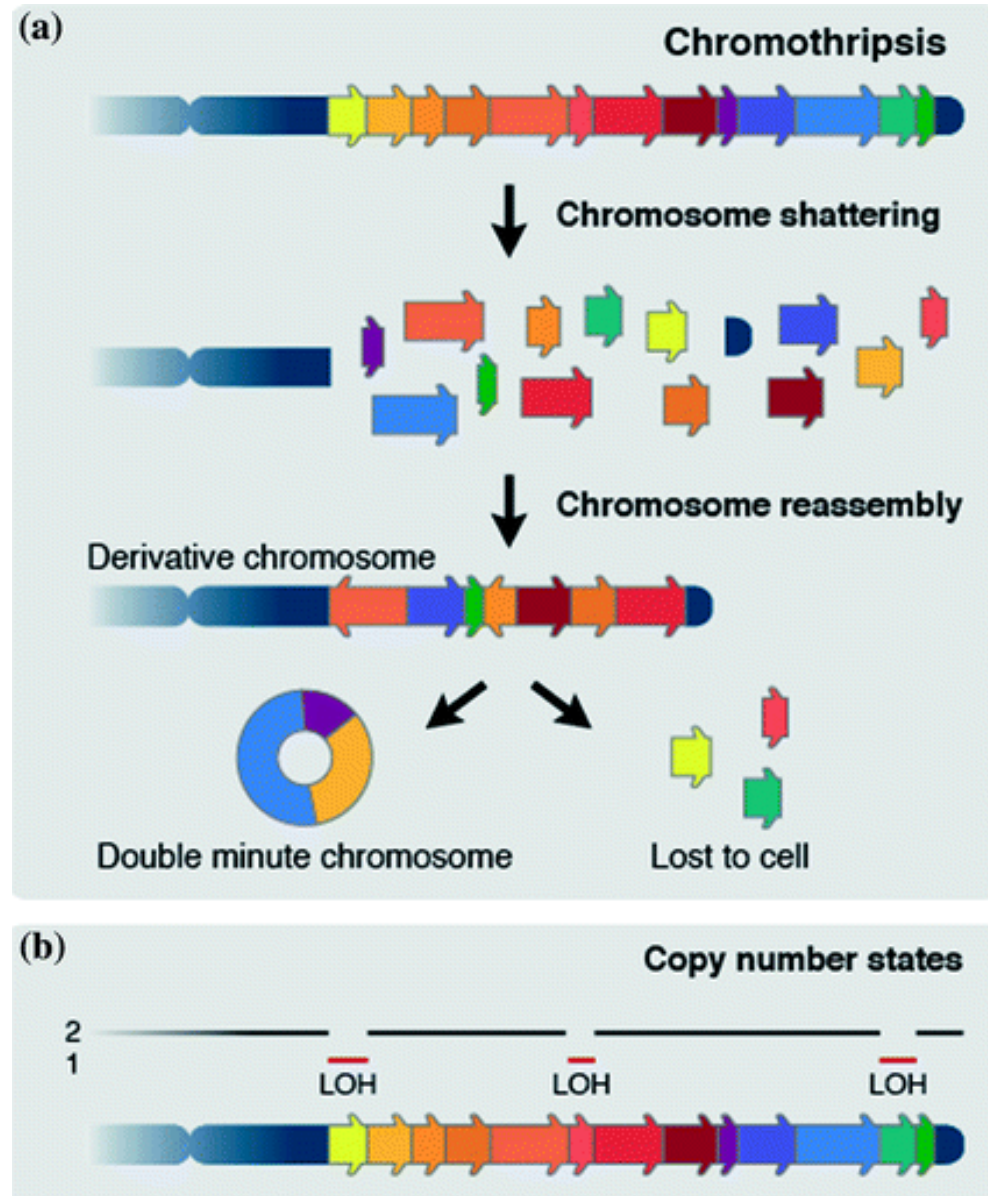
Chromosomal Abnormalities in Human Cancer

The two main classes of chromosomal abnormalities found in human cancer are shown.

- **Balanced chromosomal rearrangements** can be categorized into those that lead to the formation of a **chimeric fusion gene** and those that lead to the aberrant juxtaposition of gene regulatory elements to the coding sequence of a structurally intact gene. The formation of a **chimeric fusion gene** results in the expression of a chimeric protein with new or altered activity. In the majority of cases, only one of the two fusion genes generated and not the reciprocal counterpart contributes to cancer pathogenesis.
- **Chromosomal imbalances** can be categorized into **genomic gains and genomic losses**. Genomic **gains** include **complete or partial trisomies** and **intrachromosomal** or **extrachromosomal amplifications**, which can be identified cytogenetically as **homogeneously staining regions (HSR)** and **double-minute chromosomes (dmin)**, respectively. HSR are chromosomal regions that display no typical banding pattern; dmin are circular, acentric, autonomously replicating DNA strands of varying size; mRNA denotes messenger RNA. Genomic **losses** include **monosomies** and large-scale or **submicroscopical deletions**.

Chromosome shattering and reassembly by chromothripsis.

- a) One or multiple parts of one or a few chromosomes are shattered into pieces in a **one-off catastrophic** event. Chromosomes are subsequently stitched back together in a random order by **NHEJ**, with some fragments being incorporated into a **double-minute** chromosome and others getting lost to the cell.
- b) Chromothripsis typically leads to frequent oscillations between two copy number states in which the lower copy state shows loss of heterozygosity (LOH).
- **Chromothripsis** is a mutational process by which up to **thousands** of clustered chromosomal **rearrangements** occur in a **single event** in localized and confined genomic regions in one or a few chromosomes, and is known to be involved in both cancer and congenital diseases



Indications for Chromosome Microarray Analysis

Box 17.2

Indications for Chromosome Analysis

Multiple congenital abnormalities
The presence of dysmorphic features
Unexplained intellectual disability and neurodevelopmental disorders
Sexual ambiguity or disorder of sexual development
Infertility
Recurrent miscarriage
Unexplained stillbirth
Malignancy and chromosome breakage syndromes

More Power to You