الوراثة في طب الأطفال

Abdul Muttaleb Alsah (Ph.D, MBBCH, MA, AMRCPCH)

د. عبدالمطلب السح

كل الوسائط مسموحة:
تسجيل .. تصوير .. نسخ .. نقل الخ

(الفصل ٩ صفحة ١٢١)

Genetics

Features of the genetic basis of diseases are:

- the Human Genome Project resulted in the first publication of the human genome sequence in 2001
- it is now estimated that the human genome contains 20 000–25 000 genes, although the function of many of them remains unknown. Greater diversity and complexity at the protein level is achieved by alternative messenger RNA splicing and post-translational modification of gene products
- microarray techniques and high-throughput sequencing are increasing the volume and speed of genetic investigations and reducing their costs, leading to a greater understanding of the impact of genetics on health and disease

(٤٦,٨٣١)

20,000 – 300,000

- access to genome browser databases containing DNA sequence and protein structure has greatly enhanced progress in scientific research and the interpretation of clinical test results (Fig. 9.1)
- genetic databases are available on thousands of multiple congenital anomaly syndromes, on chromosomal variations and disease phenotypes, and on all Mendelian disorders
- clinical application of these advances is available to families through specialist genetic centres that offer investigation, diagnosis, counselling and antenatal diagnosis for an ever-widening range of disorders
- gene-based knowledge is entering mainstream medical and paediatric practice, especially in diagnosis and therapeutic guidance, such as for the treatment of malignancies.

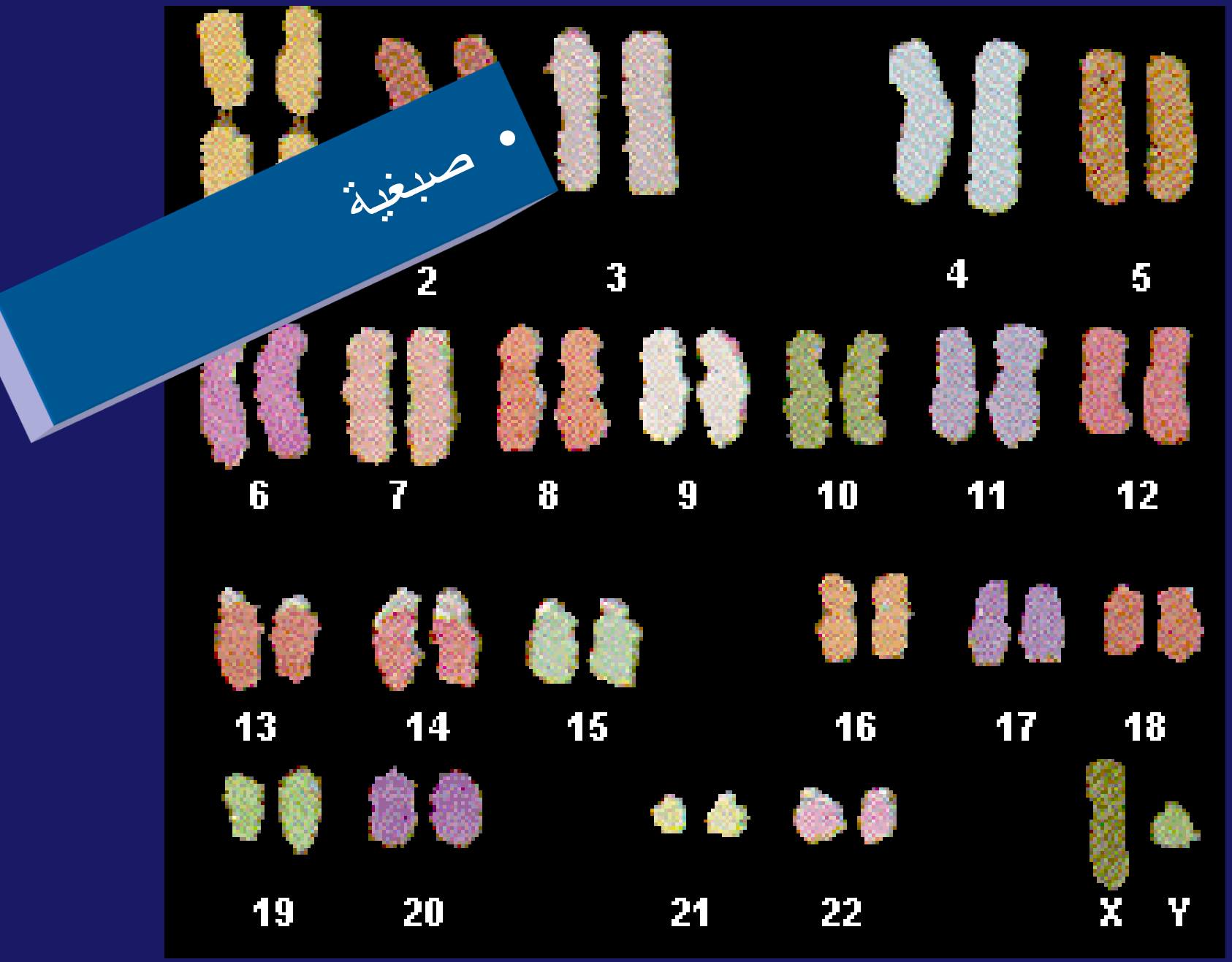
Genetic disorders are:

- common, with 2% of live-born babies having a significant congenital malformation and about 5% a genetic disorder
- burdensome to the affected individual, family, and society, as many are associated with severe and permanent disability.

Genetically determined diseases include those resulting from:

- chromosomal abnormalities
- the action of a single gene (Mendelian disorders)
- unusual genetic mechanisms
- interaction of genetic and environmental factors (polygenic, multifactorial, or complex disorders), which include epigenetic influences on gene expression from early in life.

Chromosomal abnormalities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Genes are composed of DNA that is wound around a core of histone proteins and packaged into a succession of supercoils to form the chromosomes. The human chromosome complement was confirmed as 46 in 1956. The chromosomal abnormalities in Down, Klinefelter, and Turner syndromes were recognized in 1959 and thousands of chromosome defects have now been documented.

Chromosomal abnormalities are either numerica or structural. They occur in approximately 10% of spermatozoa and 25% of mature oocytes and are a common cause of early spontaneous miscarriage. The estimated incidence of chromosomal abnormalities in live-born infants is about 1 in 150; they often cause multiple congenital anomalies and cognitive difficulties. Acquired chromosomal changes play a significant role in carcinogenesis and tumour progression.

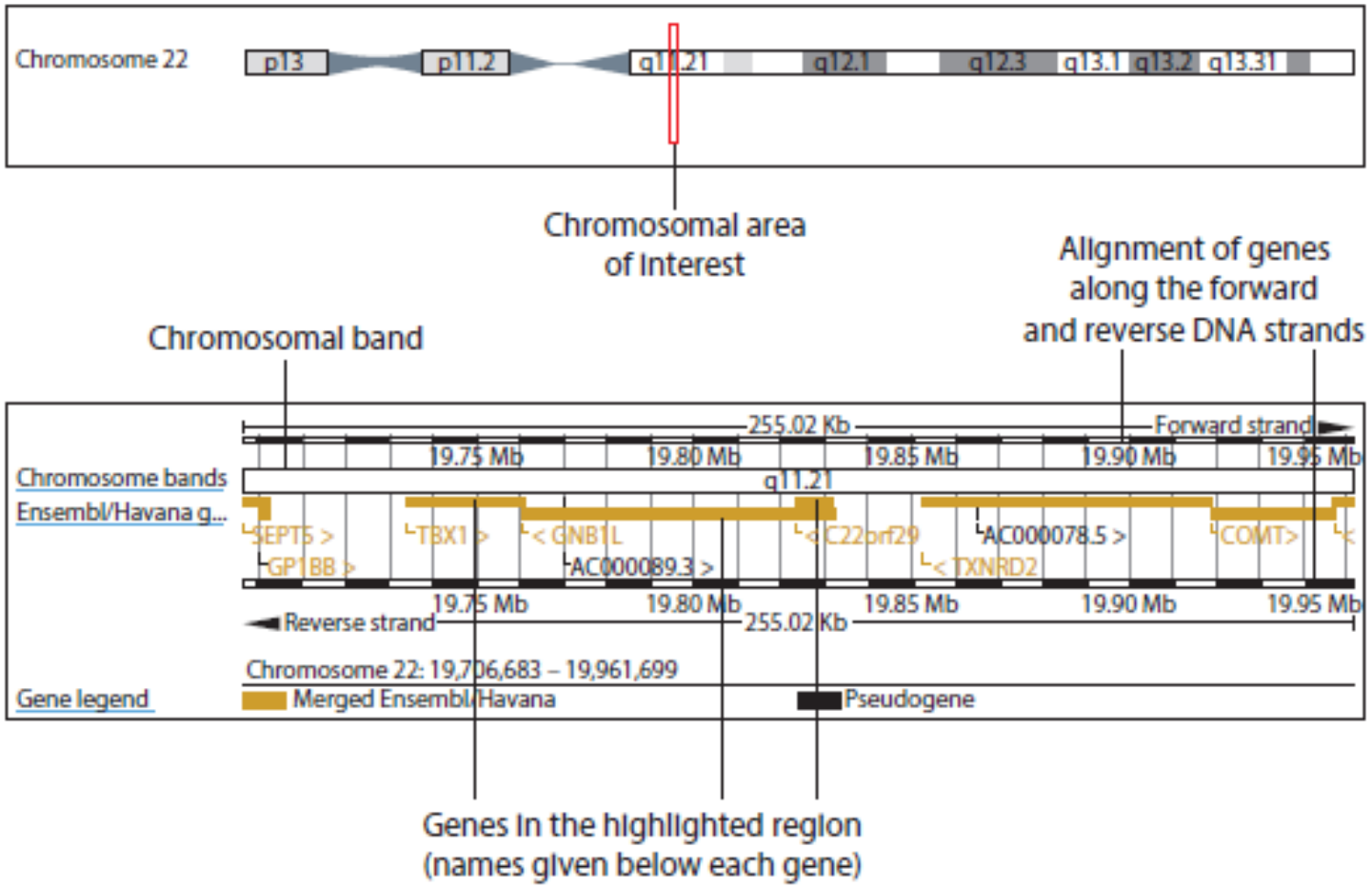

Figure 9.1 Ensembl genome browser. The image shows part of chromosome region 22q11, involved in 22q11 deletion syndrome (DiGeorge syndrome). Although only part of the commonly deleted region is shown, the image shows several genes that are deleted in 22q11 deletion syndrome. The online Ensembl browser can be used to 'zoom in' on specific areas, showing the genes present in different chromosome regions, and can also be used to show the gene sequence itself.

Disorders of chromosome number

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متلازمة داون - تثلث الصبغي ٢١

Synonyms and related keywords:

- Down syndrome
- Down's syndrome
- Mongolism
- Trisomy 21 تثلث الصبغي ٢١
- الطفل المنغولي
- متلازمة داون
- المنغولية

Down syndrome (trisomy 21)

This is the most common autosomal trisomy and the most common genetic cause of severe learning difficulties. The incidence (without antenatal screening) in live-born infants is about 1 in 650, and increases with maternal age.

Clinical features

If not diagnosed antenatally, Down syndrome is usually suspected at birth because of the baby's facial appearance. Most affected infants are hypotonic and other useful clinical signs include a flat occiput, single palmar creases, incurved fifth finger and wide 'sandal' gap between the big and second toes (Fig. 9.2a–c, Box 9.1). The diagnosis can be difficult to make when relying on clinical signs alone and a suspected diagnosis should be confirmed by a senior paediatrician. Before blood is sent for analysis, parents should be informed that a test for Down syndrome is being performed. The results may take 1–2 days, using real-time PCR (rtPCR) or rapid fluorescence in situ hybridization (FISH) techniques. Parents need information about the short-term and long-term implications of the diagnosis. They are also likely, at some stage in the future, to appreciate the opportunity to discuss how and why the condition has arisen, the risk of recurrence, and the possibility of antenatal diagnosis in future pregnancies.

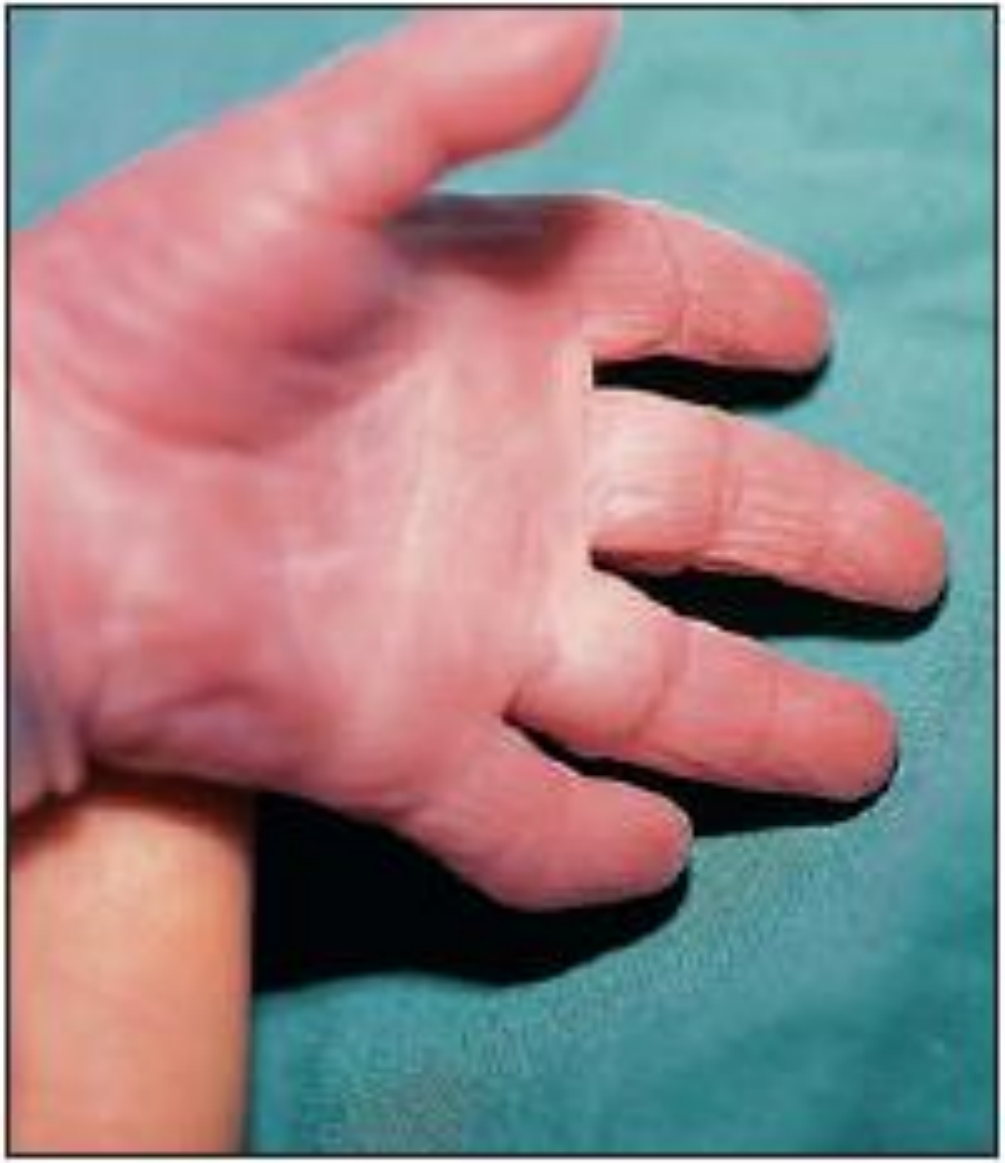
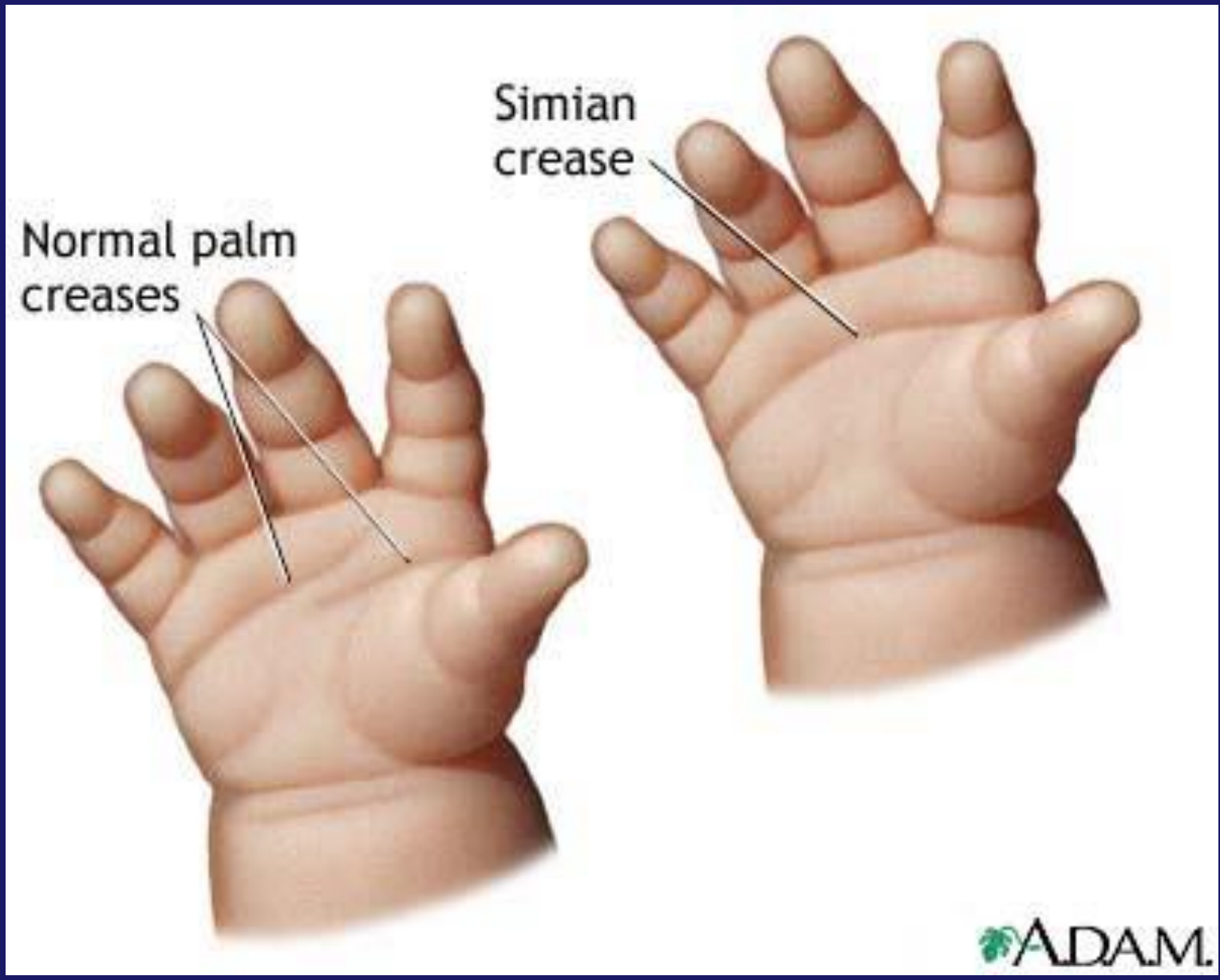


Figure 9.2b Single palmar crease.


Simian crease
Normal palm creases
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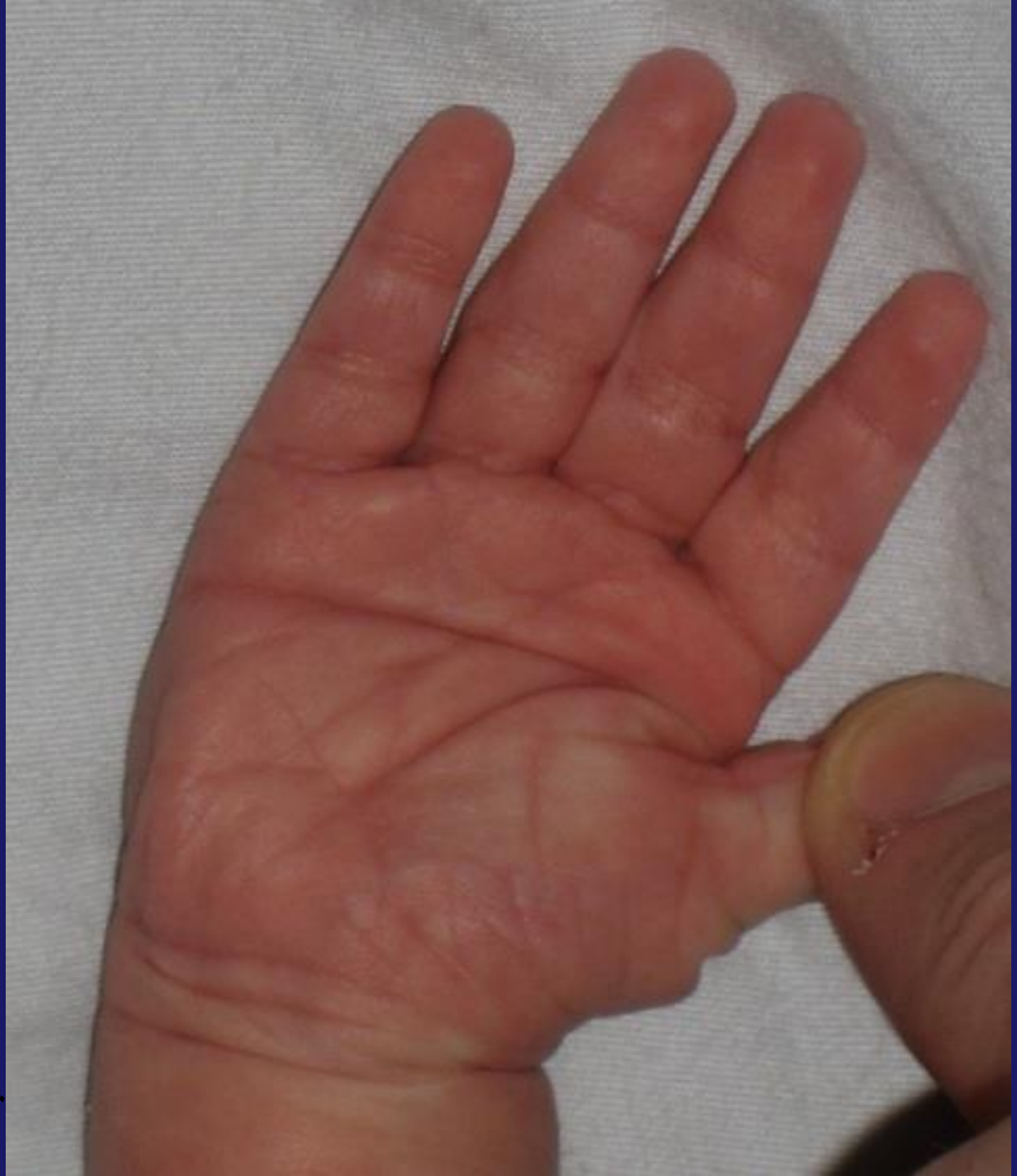
- Note the transverse palmar crease and clinodactyly of the 5th finger.



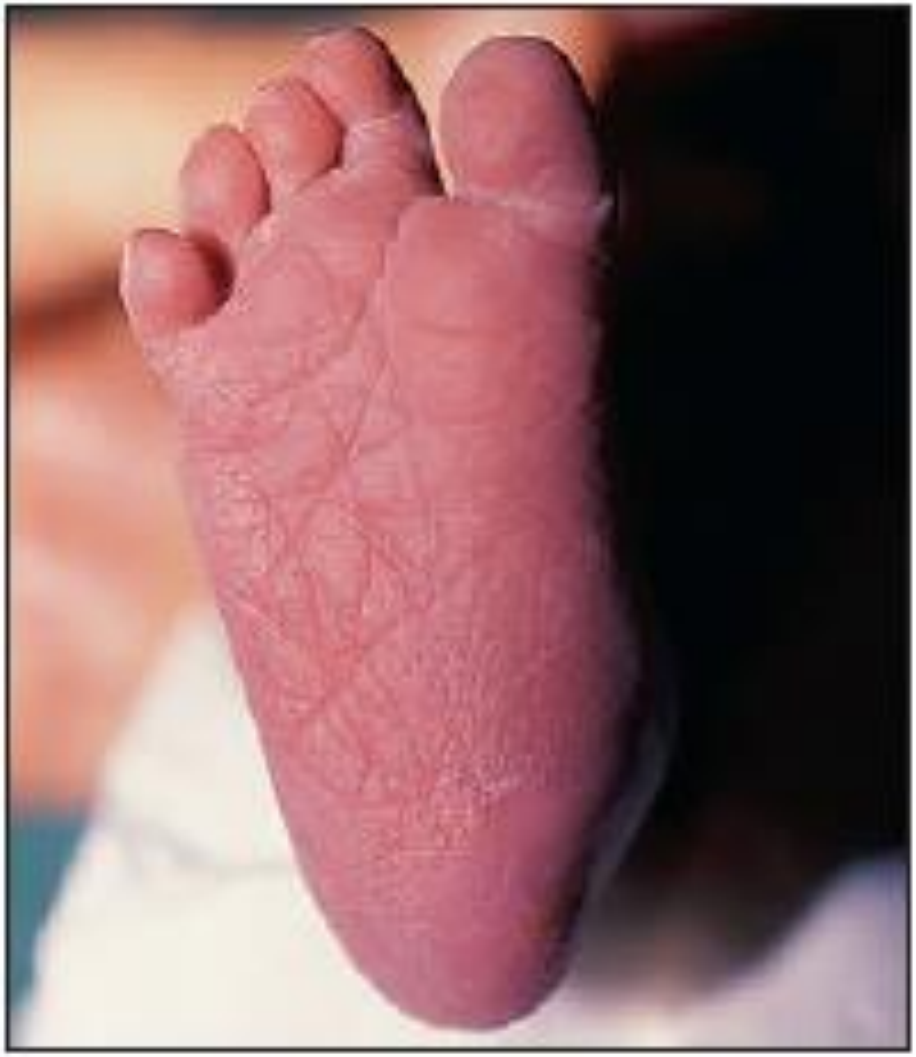


Figure 9.2c Pronounced 'sandal' gap with wide space and often a deep fissure between the big toe and second toe.


flattened nose and face, upward slanting eyes,
single palmer crease, short fifth finger that curves inward
widely separated first and second toes and increased skin creases
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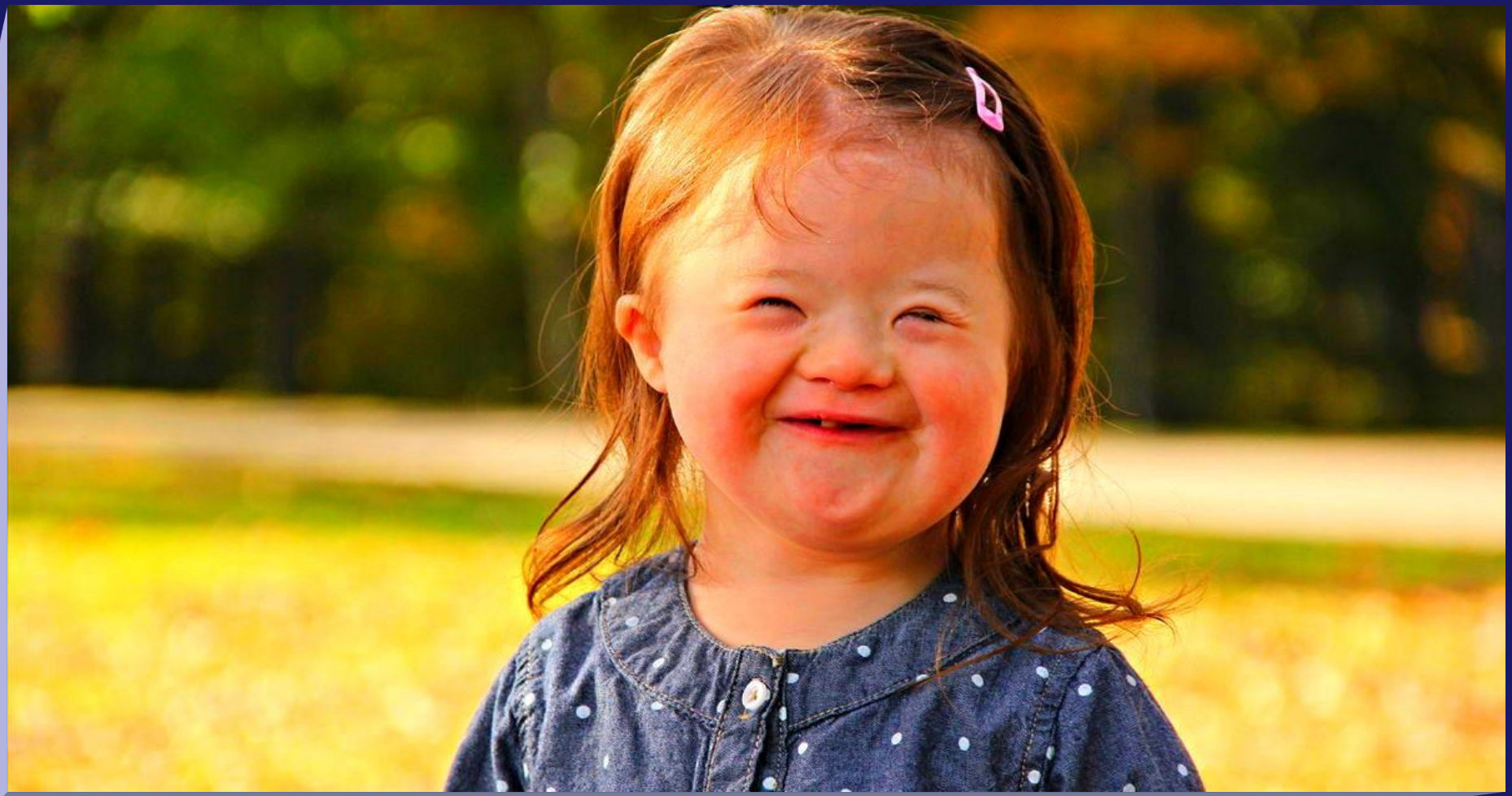
Figure 9.2a Characteristic facies seen in Down syndrome. Her posture is due to hypotonia.

السحنة المسطحة (داون)



It is difficult to give a precise long-term prognosis in the neonatal period, as there is great individual variation in the degree of learning difficulty and the development of complications. Over 85% of infants with trisomy 21 survive to 1 year of age. Congenital heart disease is present in about 40% and is a major cause of early mortality, particularly atrioventricular canal defects. Duodenal atresia is another problem in the newborn period. However, in the UK, at least 50% of affected individuals live longer than 50 years. Parents also need to know what assistance is available from both professionals and family support groups. Counselling may be helpful to assist the family to deal with feelings of grief, anger, or guilt.

Child development services will provide or co-ordinate care for the parents. This will include regular review of the child's development and health. Children with Down syndrome should be screened periodically for impairment of vision and hearing, hypothyroidism coeliac disease, and atlantoaxial instability.

Cytogenetics

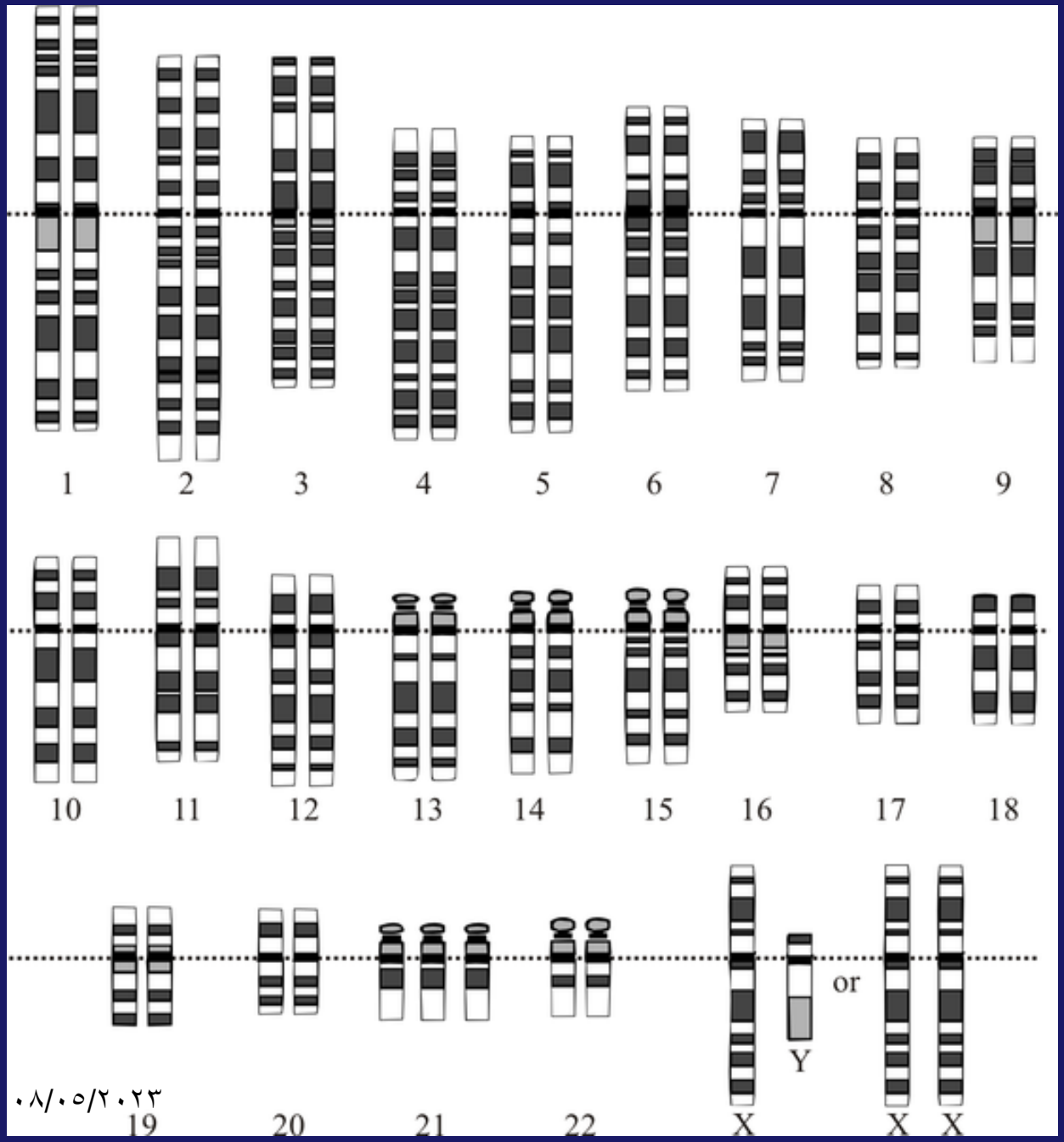
The extra chromosome 21 may result from meiotic nondisjunction, translocation, or mosaicism.

Meiotic nondisjunction (94%)

In nondisjunction trisomy 21:

- most cases result from an error at meiosis
- the chromosome 21 pair fails to separate, so that one gamete has two chromosome 21s and one has none (Fig. 9.3)

- fertilization of the gamete with two chromosome 21s gives rise to a zygote with trisomy 21
- parental chromosomes do not need to be examined.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The incidence of trisomy 21 due to nondisjunction is related to maternal age (Table 9.1). However, as the proportion of pregnancies in older mothers is small, most affected babies are born to younger mothers. Furthermore, meiotic nondisjunction can occur in spermatogenesis so that the extra copy of chromosome 21 can be of paternal origin. All pregnant women are now offered screening tests measuring biochemical markers in blood samples and nuchal thickening on ultrasound (thickening of the soft tissues at the back of the neck) to identify an increased risk of Down syndrome in the fetus. When an increased risk is identified, amniocentesis is offered to check the fetal karyotype. Noninvasive prenatal testing (NIPT) is now possible, in which cell-free fetal DNA is analyzed from maternal blood, and is becoming part of routine screening in the UK. After having one child with trisomy 21 due to nondisjunction, the risk of recurrence of Down syndrome is given as 1 in 200 for mothers under the age of 35 years, but remains similar to their age-related population risk for those over the age of 35 years.

Inheritance of Down syndrome

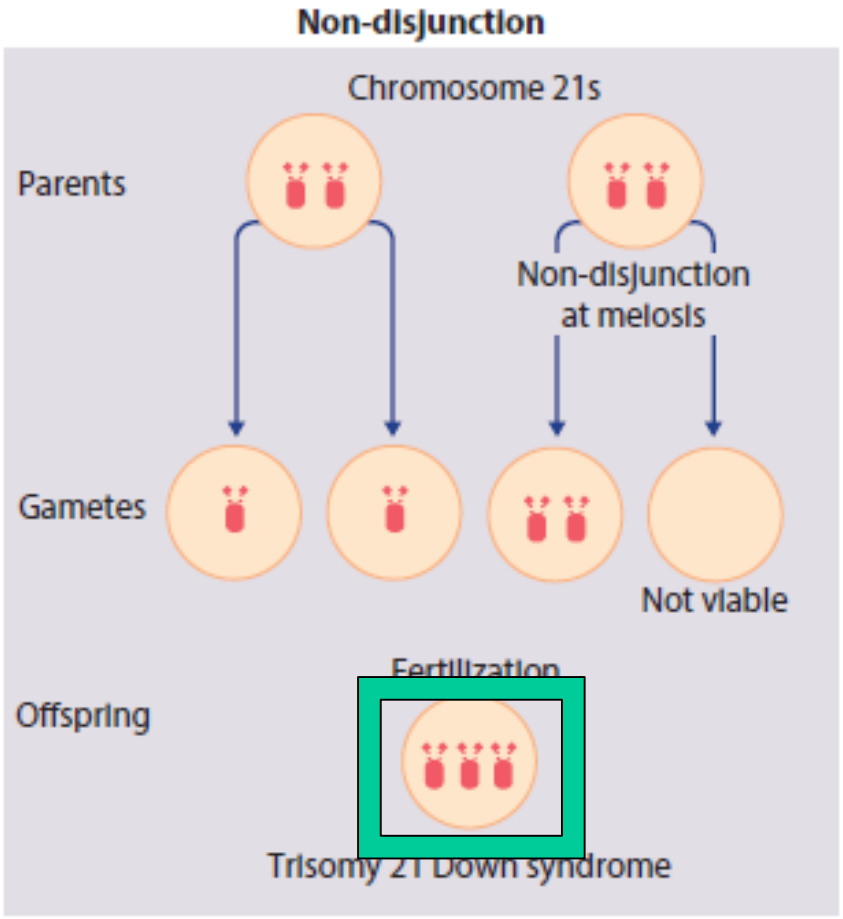

Figure 9.3 Nondisjunction Down syndrome.

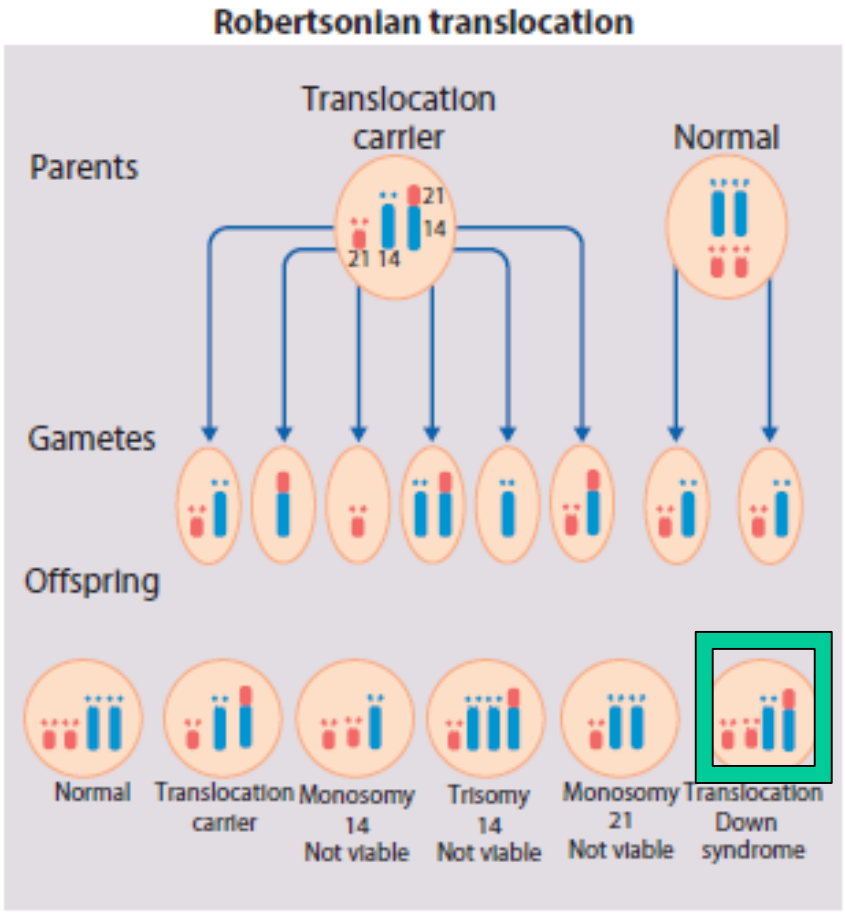

Figure 9.4 Translocation Down syndrome. There is a Robertsonian translocation involving chromosomes 21 and 14, which has been inherited from a parent.

Translocation (5%)

When the extra chromosome 21 is joined onto another chromosome (usually chromosome 14, but occasionally chromosome 15, 22, or 21), this is known as a Robertsonian translocation. This may be present in a phenotypically normal carrier with 45 chromosomes (two being 'joined together') or in someone with Down syndrome and a set of 46 chromosomes but with three copies of chromosome 21 material. In this situation, parental chromosomal analysis is recommended, because one of the parents may well carry the translocation in balanced form (in 25% of cases; Fig. 9.4).

Table 9.1 Risk of Down syndrome (live births) with maternal age at delivery, prior to screening in pregnancy

Maternal age (years)	Risk of Down syndrome
All ages	1 in 650
20	1 in 1530
30	1 in 900
35	1 in 385
37	1 in 240
40	1 in 110
44	1 in 37

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In translocation Down syndrome:

- the risk of recurrence is 10–15% if the mother is the translocation carrier and about 2.5% if the father is the carrier
- if a parent carries the rare 21:21 translocation, all the offspring will have Down syndrome
- if neither parent carries a translocation (75% of cases), the risk of recurrence is less than 1%.

Mosaicism (1%)

In mosaicism, some of the cells are normal and some have trisomy 21. This usually arises after the formation of the chromosomally normal zygote by nondisjunction at mitosis but can arise by later mitotic nondisjunction in a trisomy 21 conception. The phenotype is sometimes milder in Down syndrome mosaicism.

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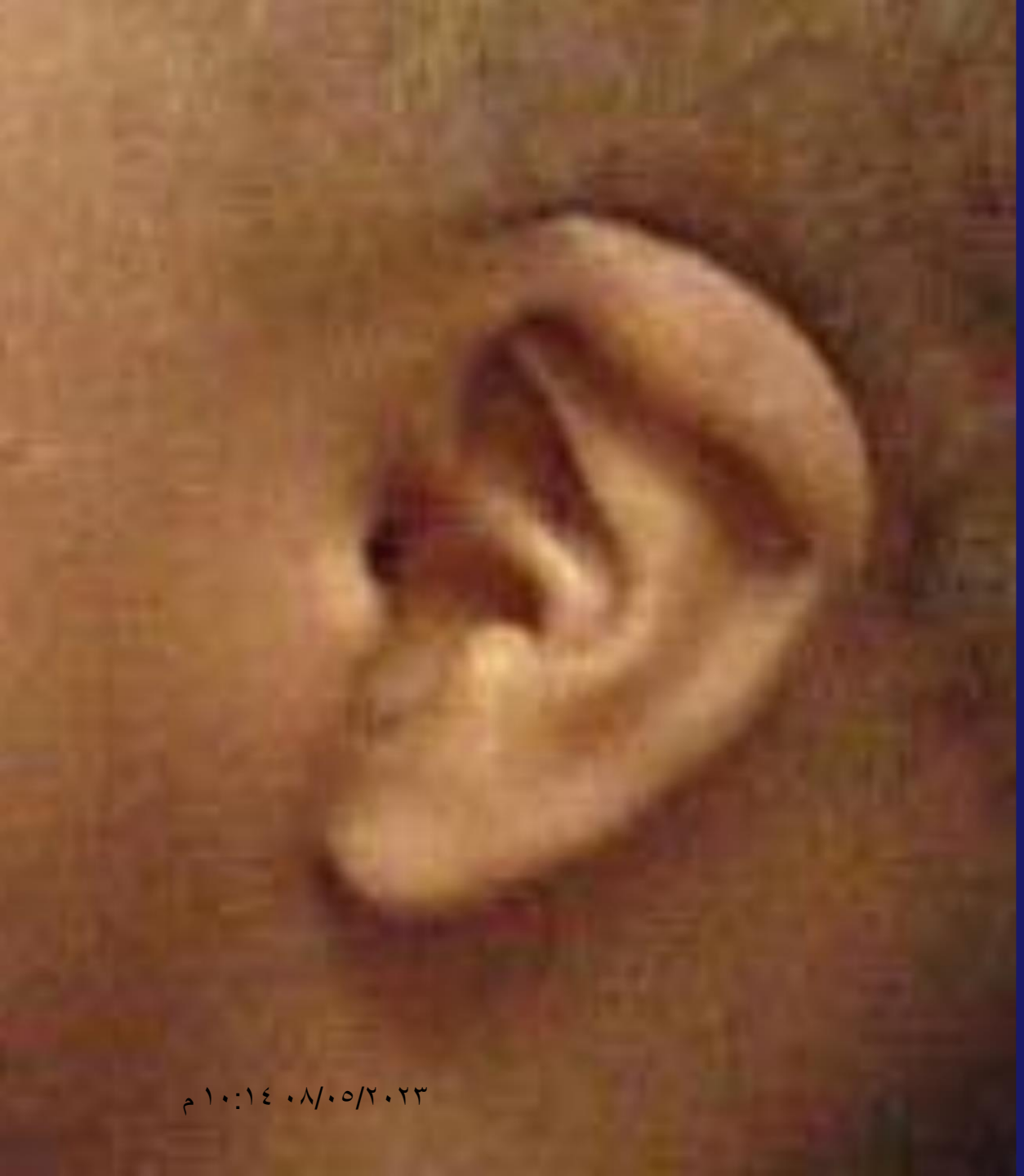
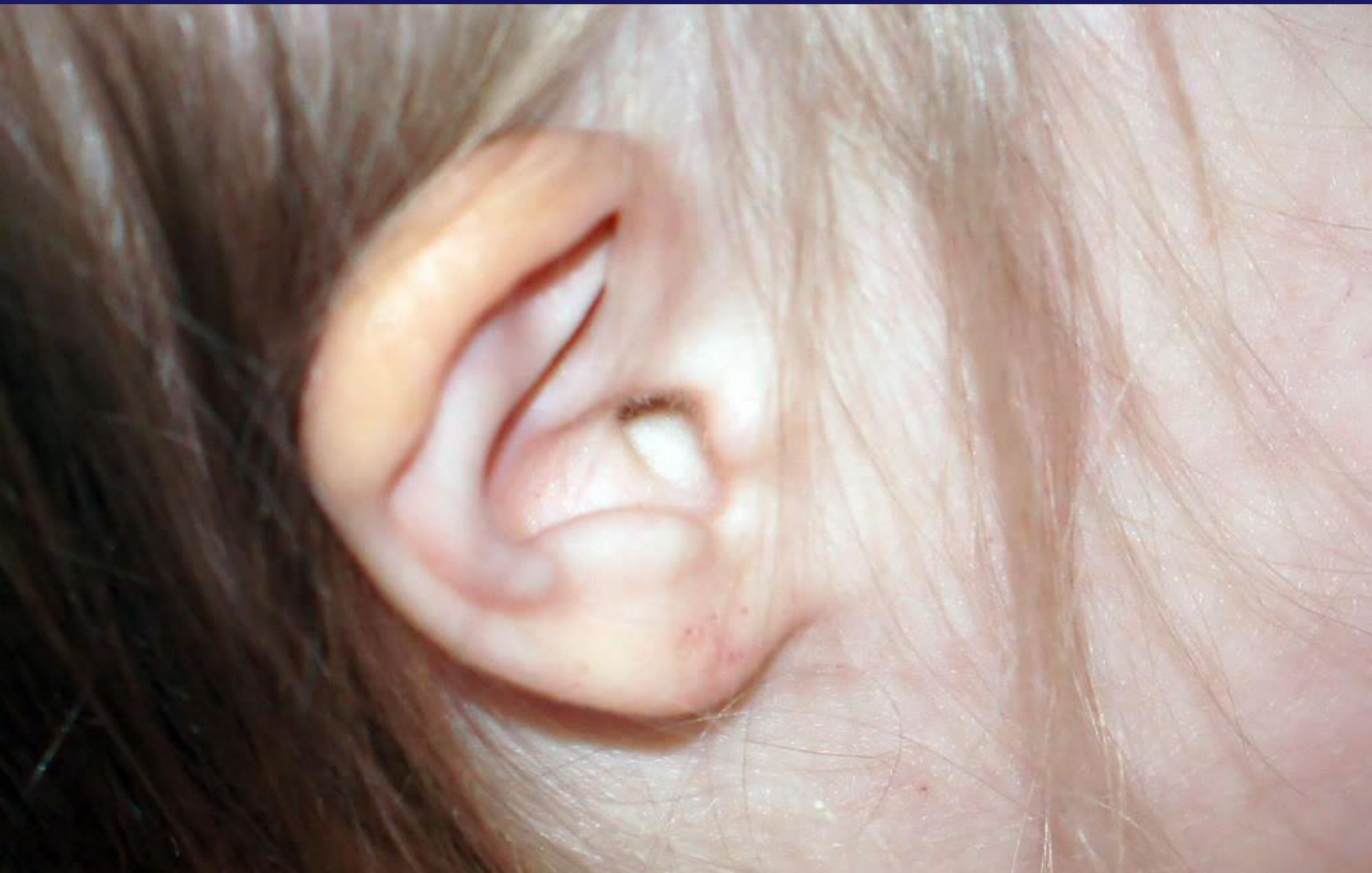
Trisomy 21 food corner



- Note the characteristic small ear with overfolded helix.



Eyes

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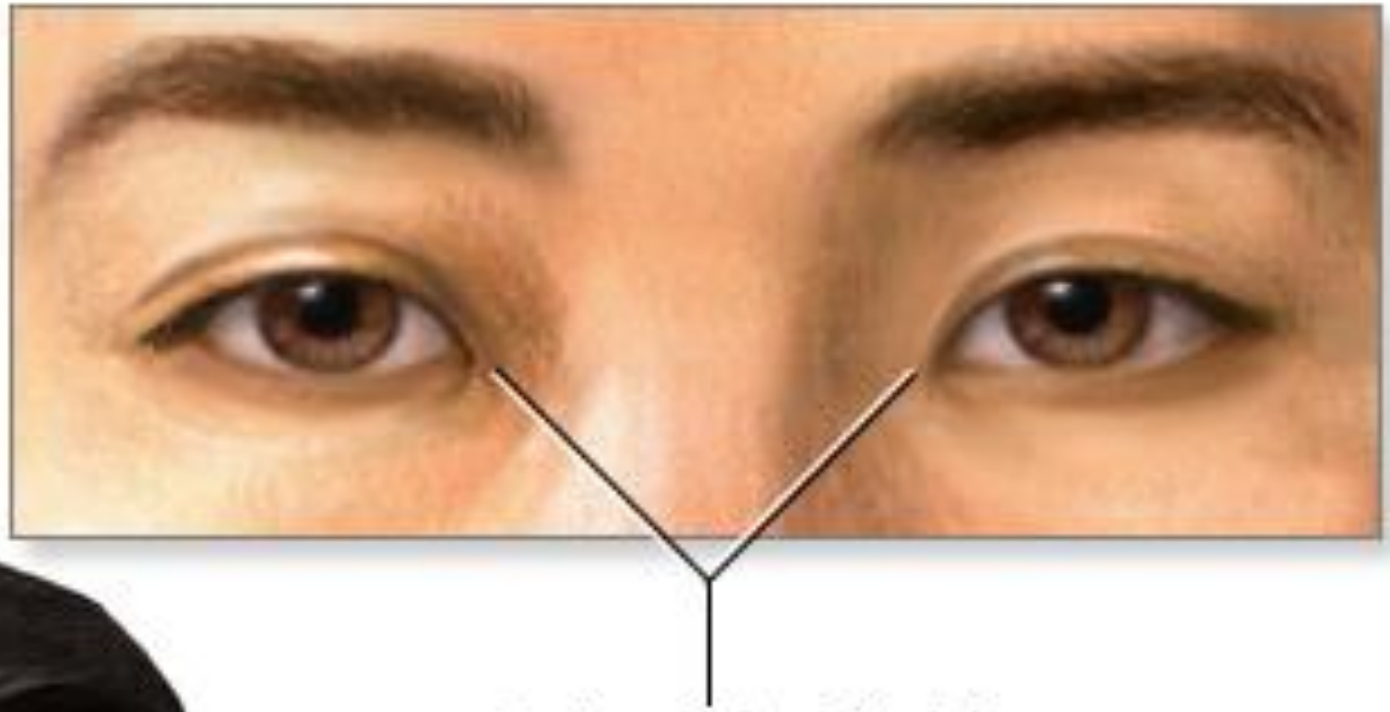
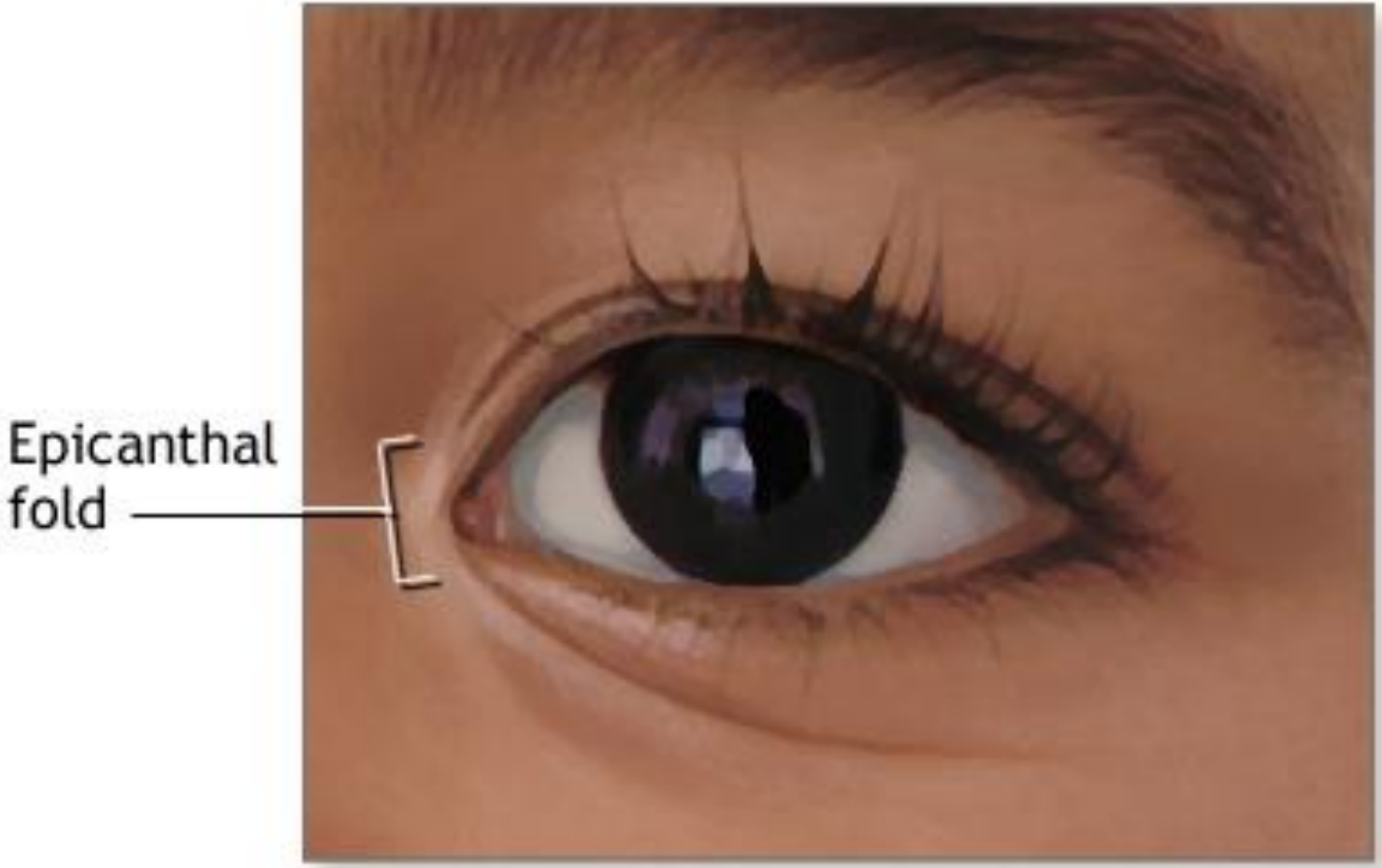


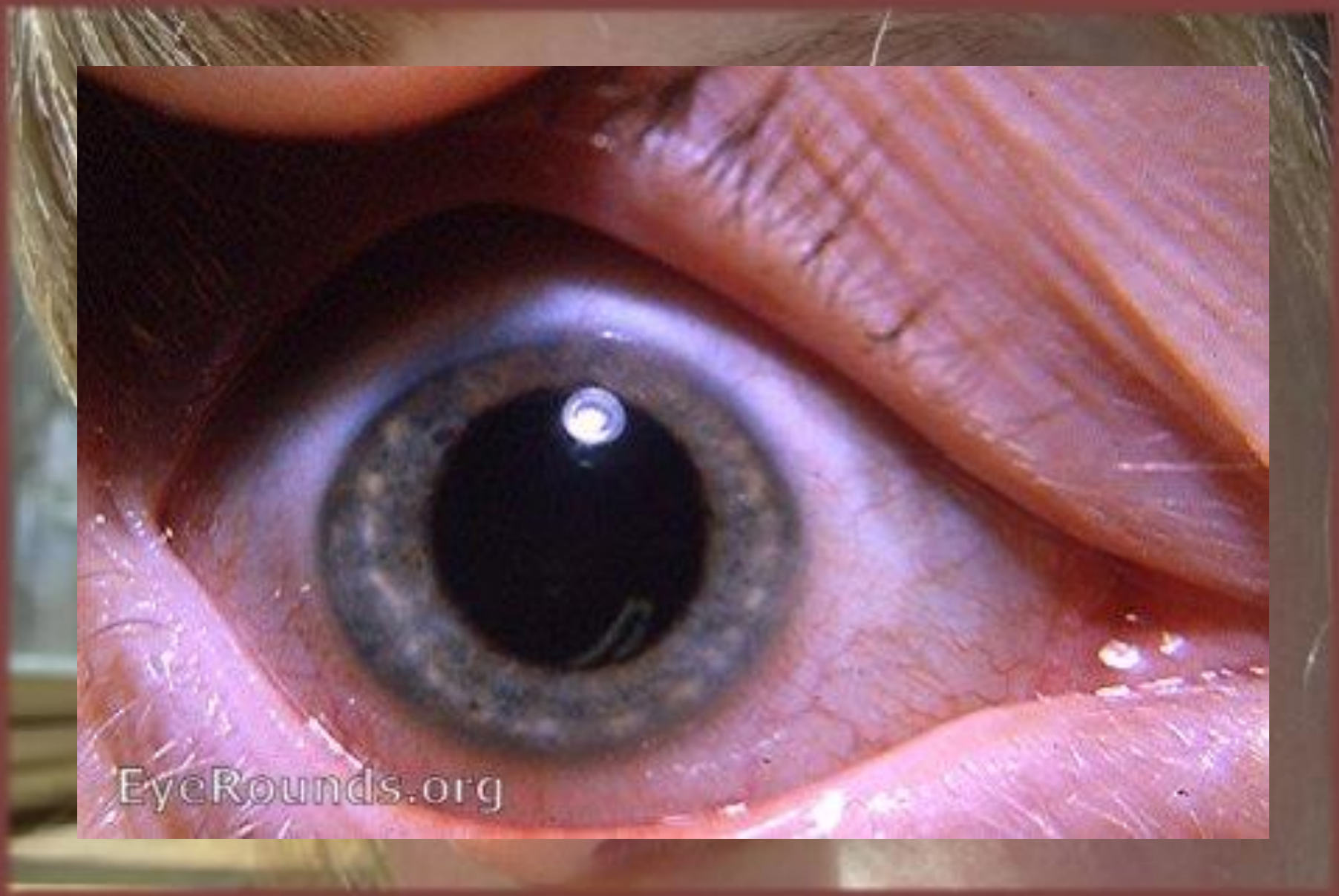
Epicanthal folds

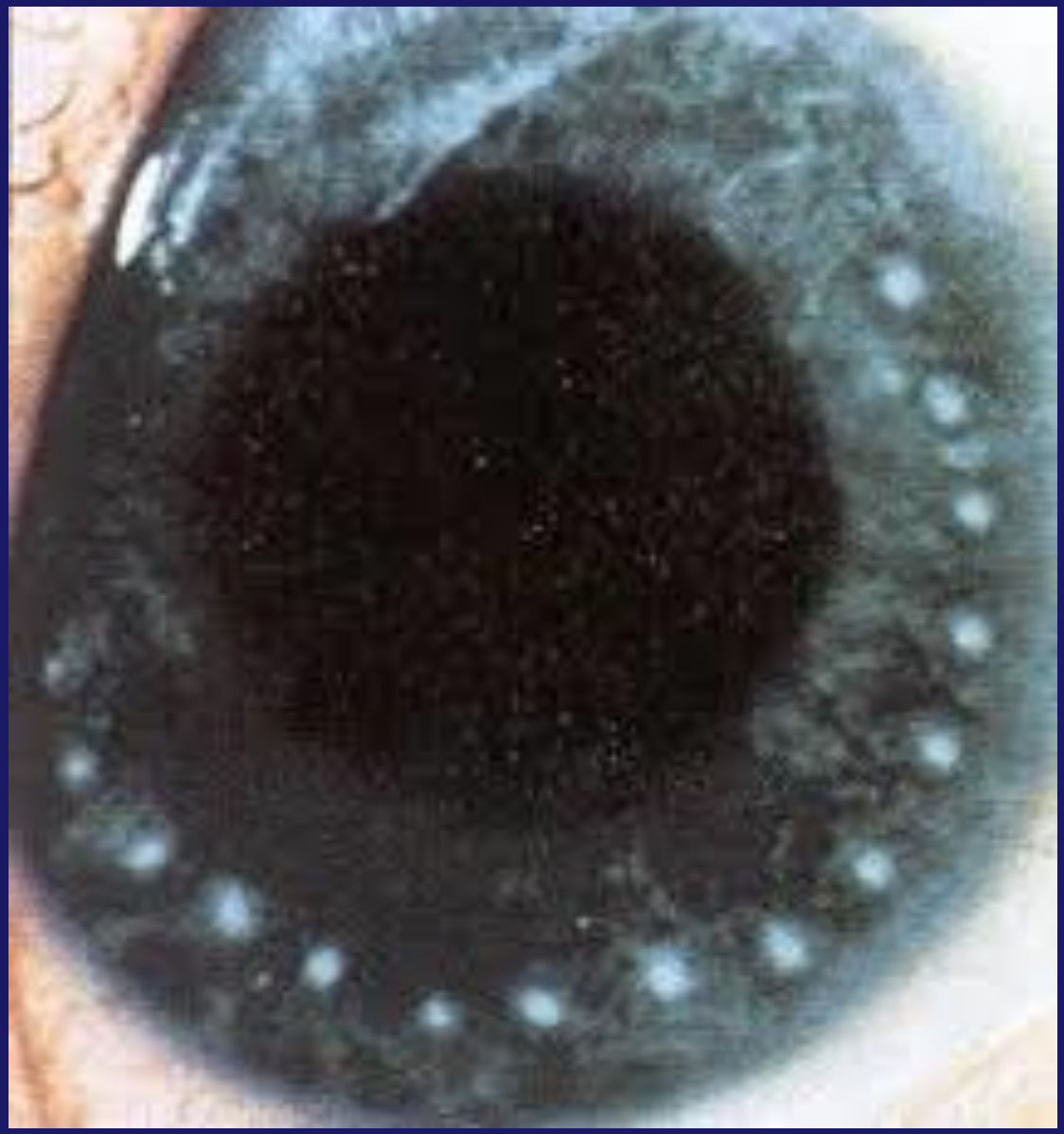
A.D.A.M.



Brushfield spots

- White specks in a linear pattern around the circumference of the iris
  - Suggests Down syndrome


EyeRounds.org



Mongolian spots

- Irregular areas of deep blue pigmentation usually in sacral and gluteal regions
  - *Seen predominantly in African, Native American, Asian or Latin descent

البقع الزرقاء

Typical craniofacial appearance:

- round face and flat nasal bridge
- upslanted palpebral fissures
- epicanthic folds (a fold of skin running across the inner edge of the palpebral fissure)
- Brushfield spots in iris (pigmented spots)
- small mouth and protruding tongue
- small ears
- flat occiput and third fontanelle.

Other anomalies:

- short neck
- single palmar creases, incurved and short fifth finger, and wide 'sandal' gap between first and second toes
- hypotonia
- congenital heart defects (in 40%)
- duodenal atresia
- Hirschsprung disease (<1%).

Later medical problems:

- delayed motor milestones
- learning difficulties – severity is variable, usually mild to moderate but may be severe
- short stature
- increased susceptibility to infections
- hearing impairment from secretory otitis media (75%)
- visual impairment from cataracts (15%), squints, myopia (50%)
- increased risk of leukaemia and solid tumours (<1%)
- acquired hip dislocation and atlantoaxial instability
- obstructive sleep apnoea (50% to 75%)
- increased risk of hypothyroidism (15%) and coeliac disease
- epilepsy
- early-onset Alzheimer disease.

Summary

Down syndrome (trisomy 21)

- Natural incidence – about 1.5 per 1000 infants.
- Cytogenetics – nondisjunction (most common, related to maternal age), translocation (one parent may carry a balanced translocation), or mosaicism (rare).
- Presentation – antenatal screening, prenatal diagnosis, or clinical presentation; confirmed on chromosome analysis.
- Immediate medical complications – increased risk of duodenal atresia, congenital heart disease.
- Clinical manifestations – see Box 9.1.

Edwards syndrome and Patau syndrome

متلازمة إدوارد - تثلث الصبغي ١٨

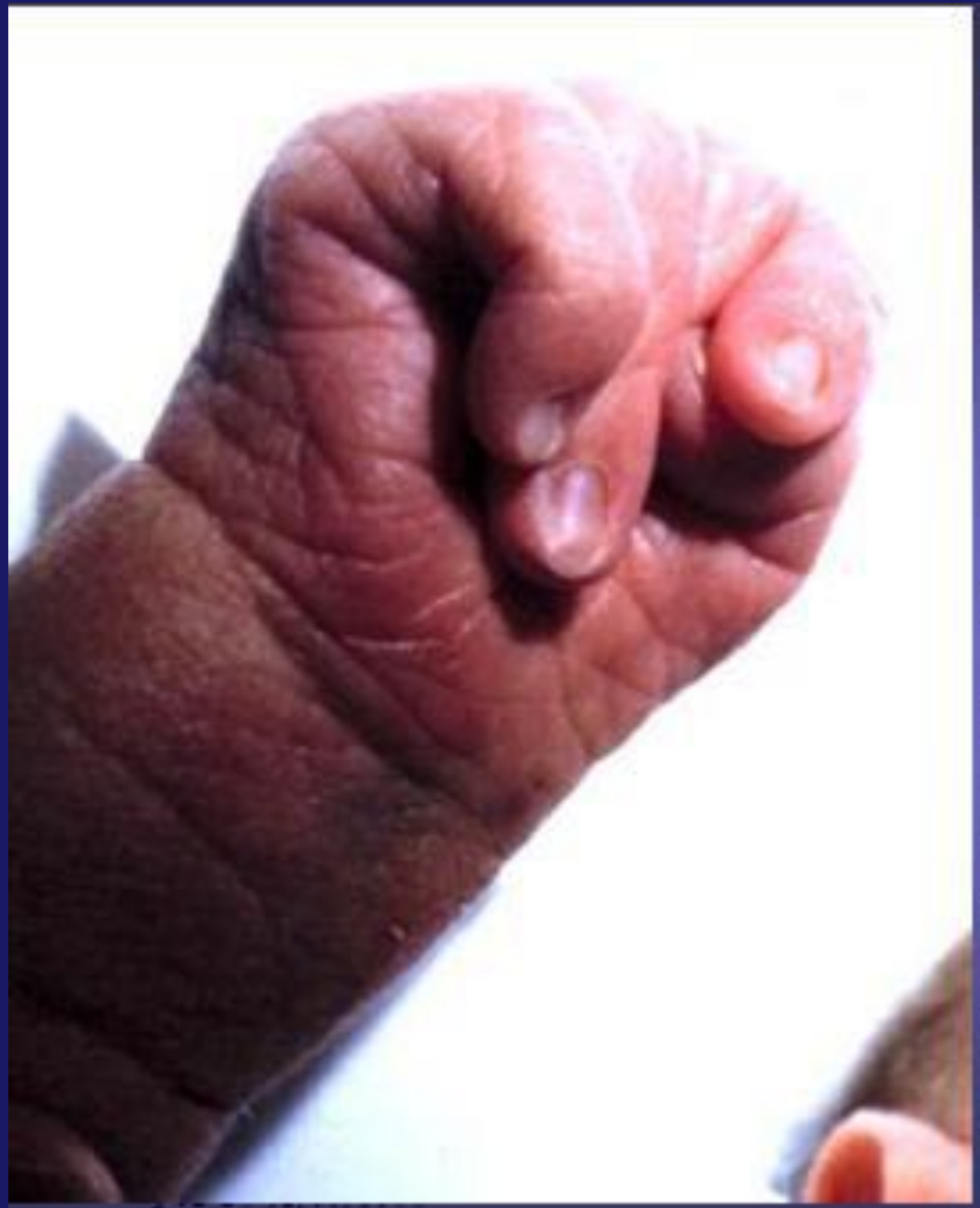
Box 9.2 Clinical features of Edwards syndrome (trisomy 18)

- Low birthweight
- Prominent occiput
- Small mouth and chin
- Short sternum
- Flexed, overlapping fingers (Fig. 9.5)
- 'Rocker-bottom' feet
- Cardiac and renal malformations

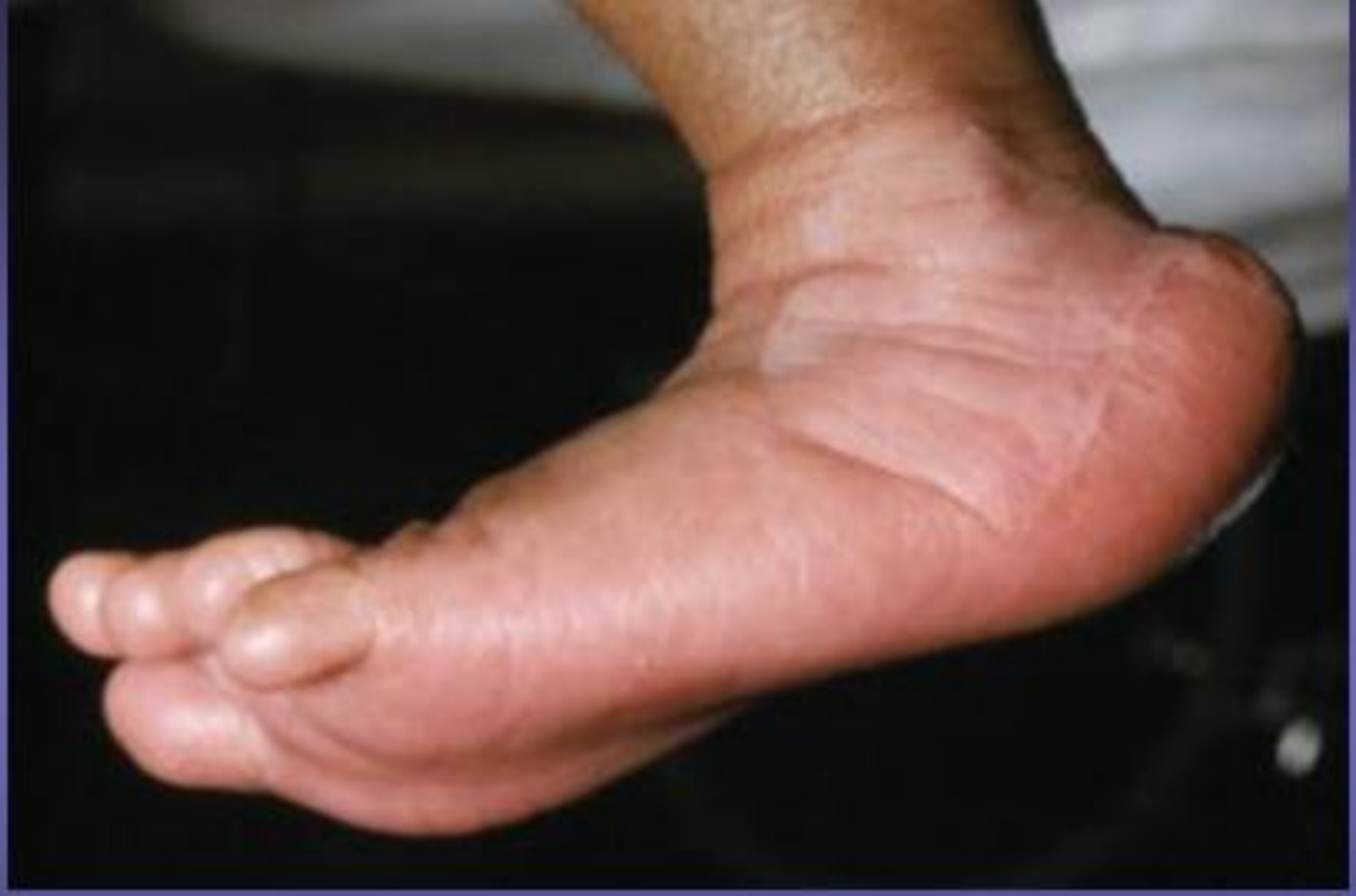
Trisomy 18 (Edward's Syndrome)

- unusually small head
- back of the head is prominent
- ears are malformed and low-set
- mouth and jaw are small (may also have a cleft lip or cleft palate
- hands are clenched into fists, and the index finger overlaps the other fingers
- Clubfeet (or rocker bottom feet) and toes may be webbed or fused

Figure 9.5 Overlapping of the fingers in Edwards syndrome.



Note the characteristic clenched hand of trisomy 18 (Edwards syndrome) with the index finger overriding the middle finger and the fifth finger overriding the fourth finger.



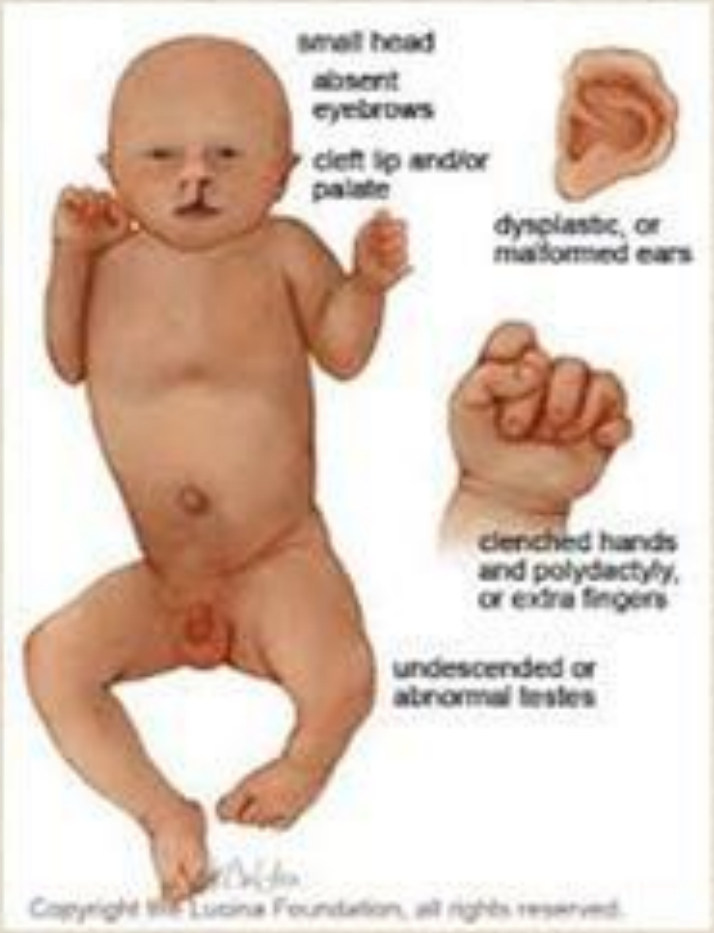
Note the rocker-bottom foot with a prominent calcaneus in an infant with trisomy 18 (Edwards syndrome).

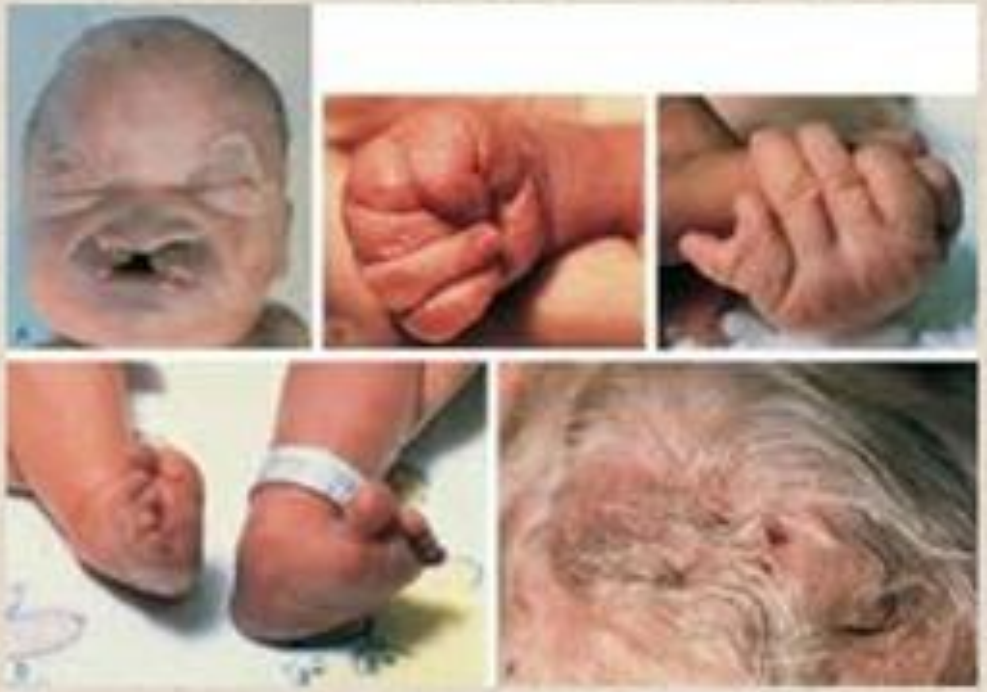
متلازمة باتاو - تثلث الصبغي ١٣

Box 9.3 Clinical features of Patau syndrome (trisomy 13)

- Structural defect of brain
- Scalp defects
- Small eyes (microphthalmia) and other eye defects
- Cleft lip and palate
- Polydactyly
- Cardiac and renal malformations.

Patau, Trisomy 13





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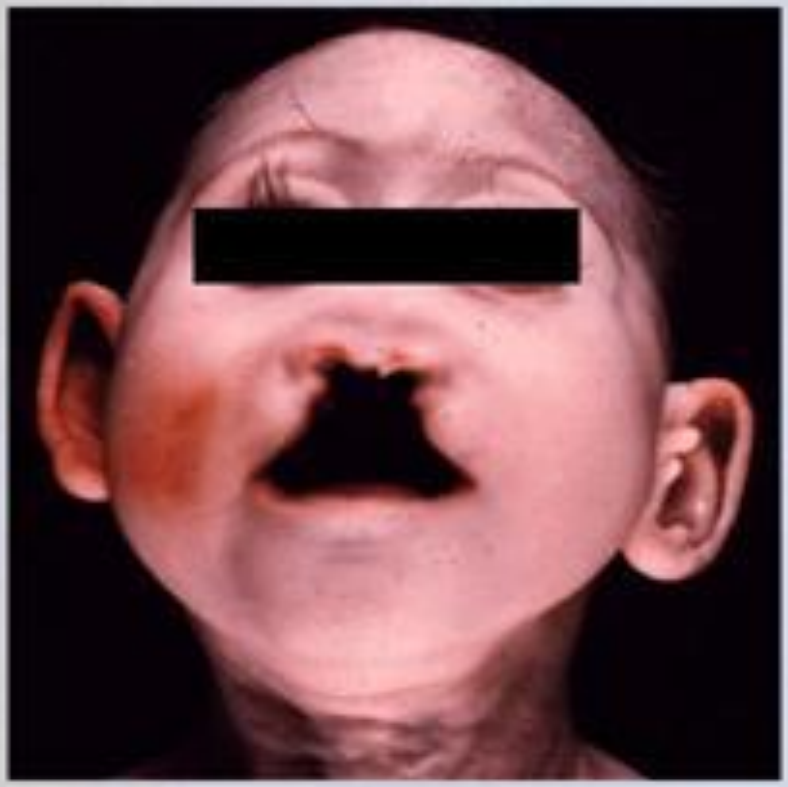
Trisomy 13 – Patau Syndrome

Extra Chromosome 13

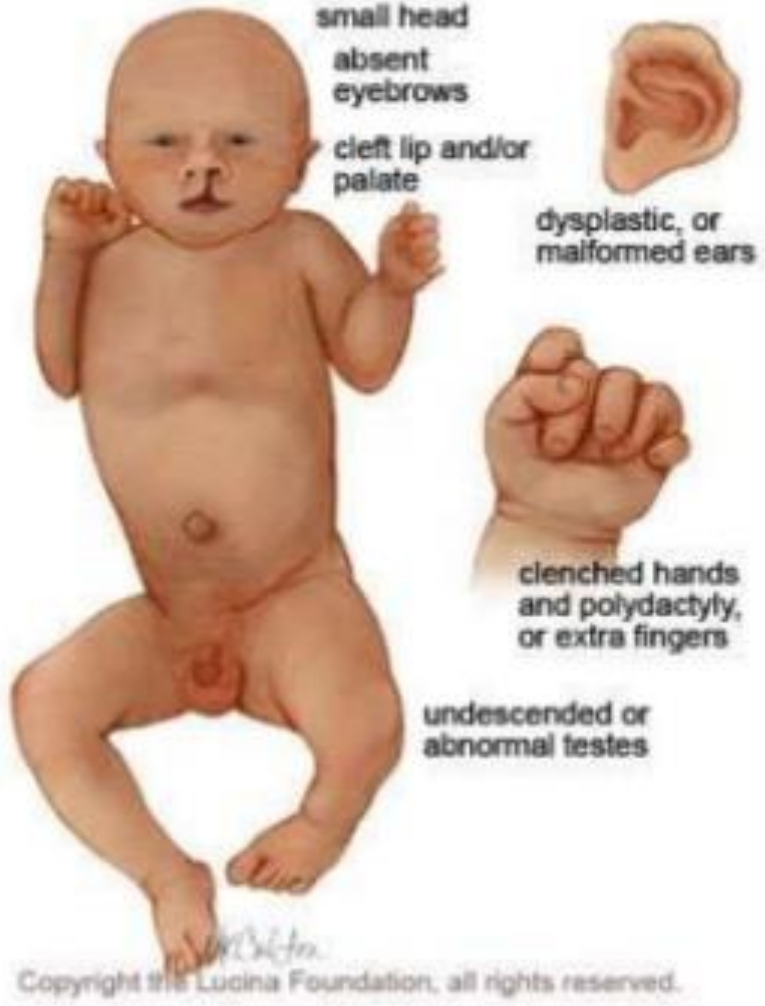


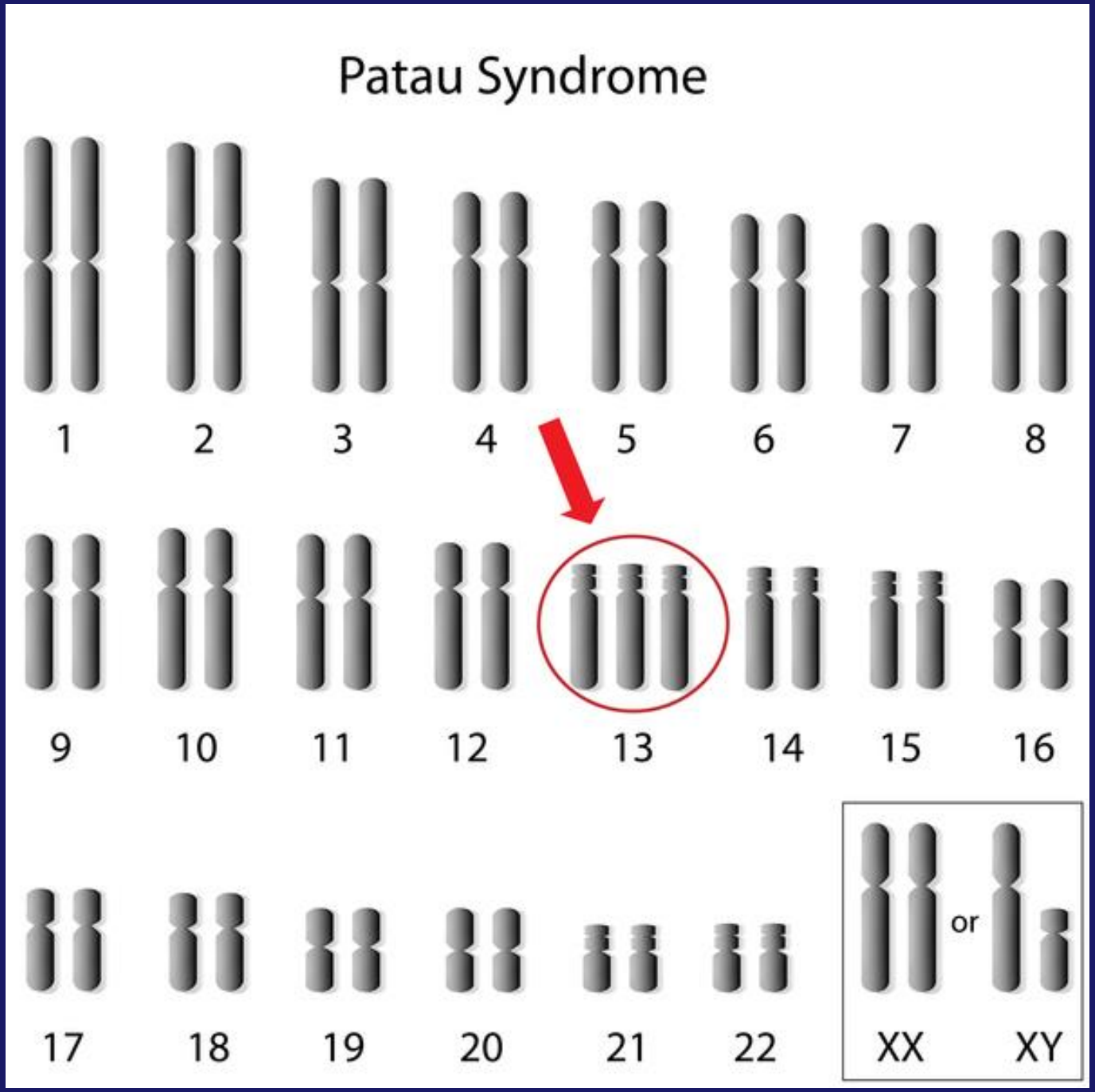
Symptoms can include

- Cleft lip or palate
- Close-set eyes -- eyes may actually fuse together into one
- Decreased muscle tone
- Extra fingers or toes
- Hernias
- Hole, split, or cleft in the iris
- Low-set ears
- Mental retardation
- Scalp defects (absent skin)
- Seizures
- Single palmar crease
- Skeletal (limb) abnormalities
- Small eyes
- Small head
- Small lower jaw
- Undescended testicle

سحنة باتاو

Patau's syndrome. (Trisomy 13)

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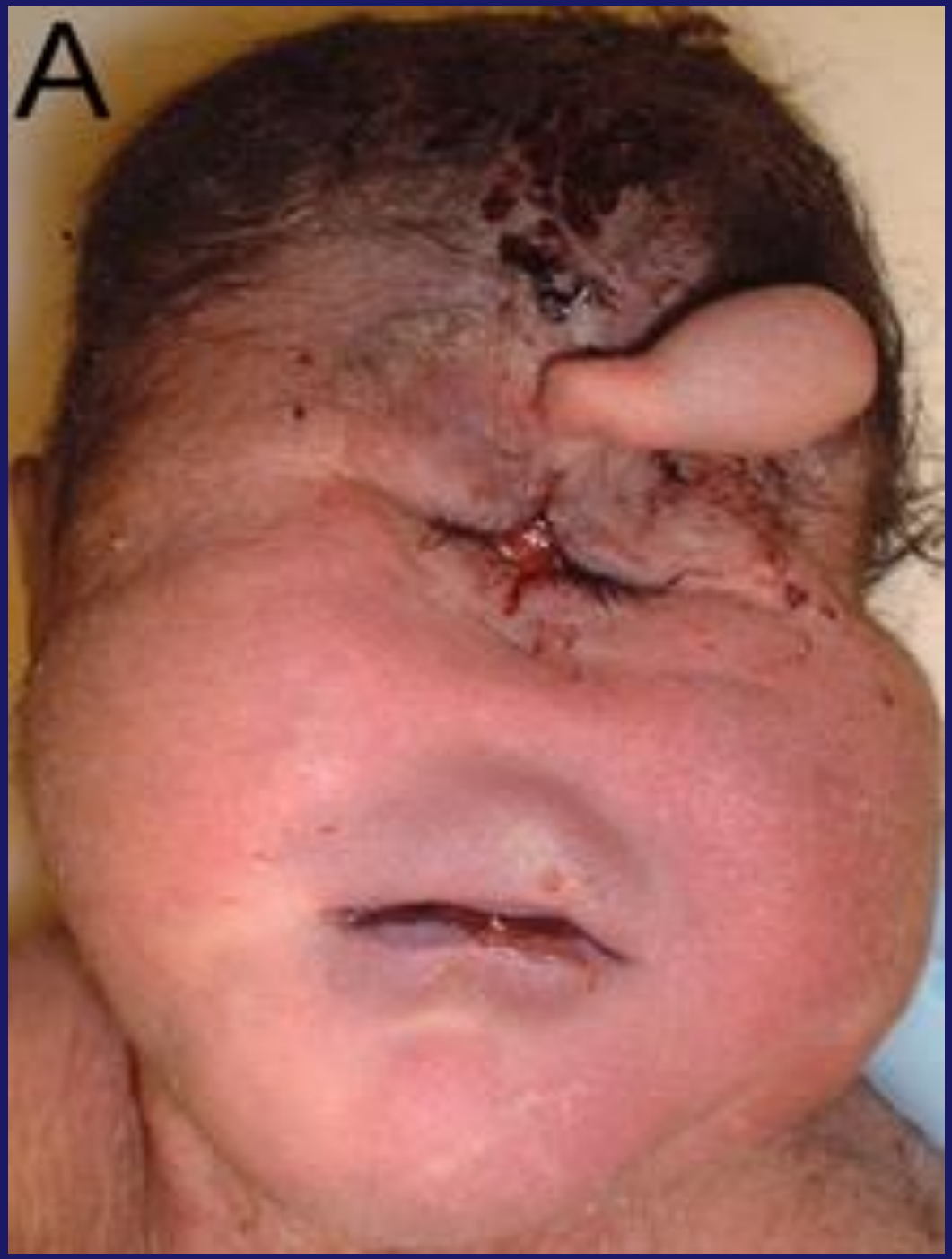
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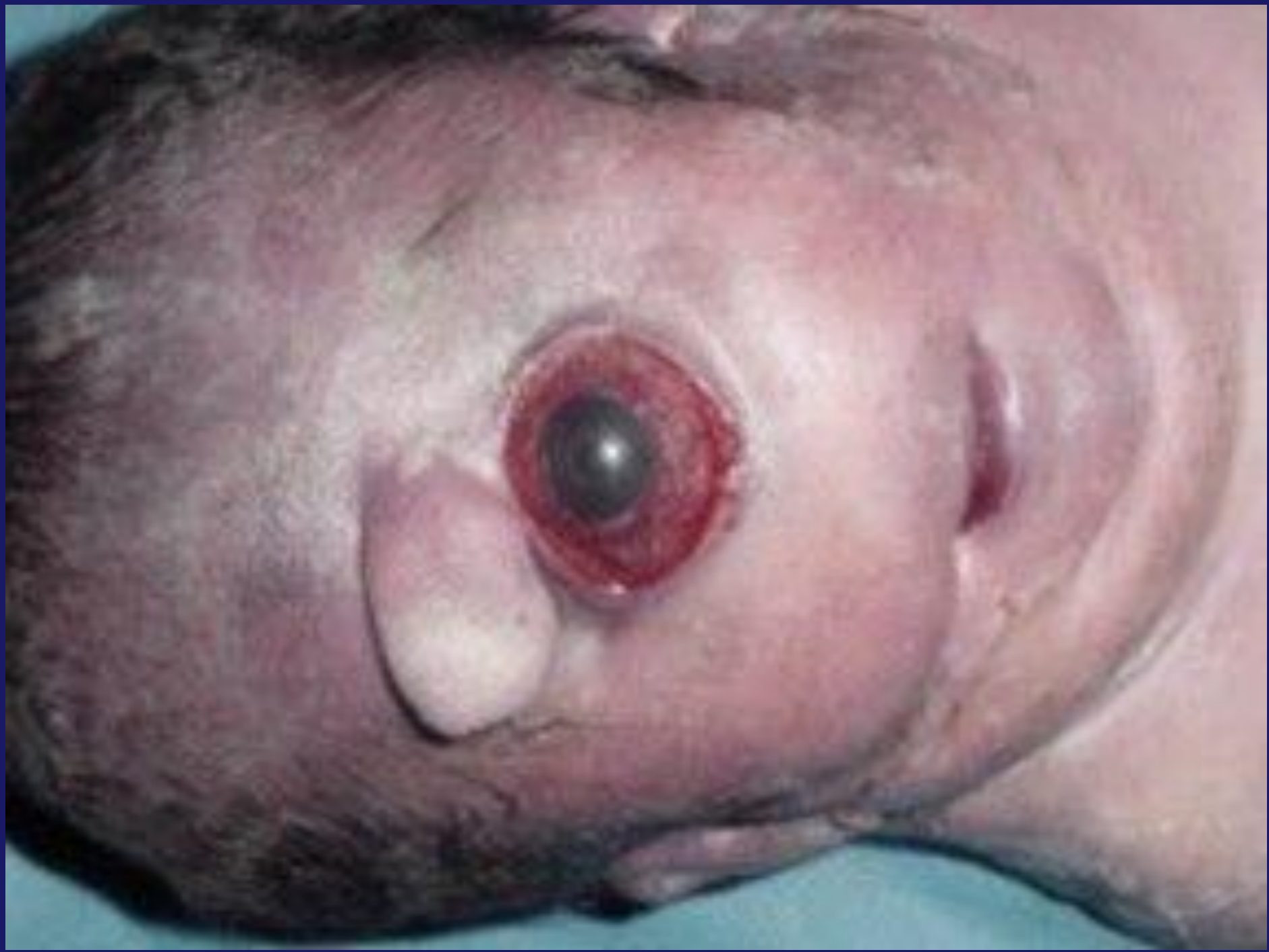


Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13)

Although rarer than Down syndrome (1 in 8000 and 1 in 14 000 live births respectively), particular constellations of severe multiple abnormalities suggest these diagnoses at birth; most affected babies die in infancy (Fig. 9.5, Boxes 9.2 and 9.3) but extended survival is possible. The diagnosis is confirmed by chromosome analysis. Many affected fetuses are detected by ultrasound scan during the second trimester of pregnancy and diagnosis can be confirmed antenatally by amniocentesis and chromosome analysis. Can also be diagnosed on non-invasive prenatal testing (NIPT). Recurrence risk is low, except when the trisomy is due to a balanced chromosome rearrangement in one of the parents.

متلازمة تورنر - أحادية الصبغي

X

Turner syndrome (45, X)

Turner syndrome usually results in early miscarriage (>95%) and is increasingly detected by ultrasound antenatally when fetal oedema of the neck, hands, or feet or a cystic hygroma may be identified. In live-born females, the incidence is about 1 in 2500. Fig. 9.6 and Box 9.4 show the clinical features of Turner syndrome, although short stature may be the only clinical abnormality in children.

Box 9.4 Clinical features of Turner syndrome

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

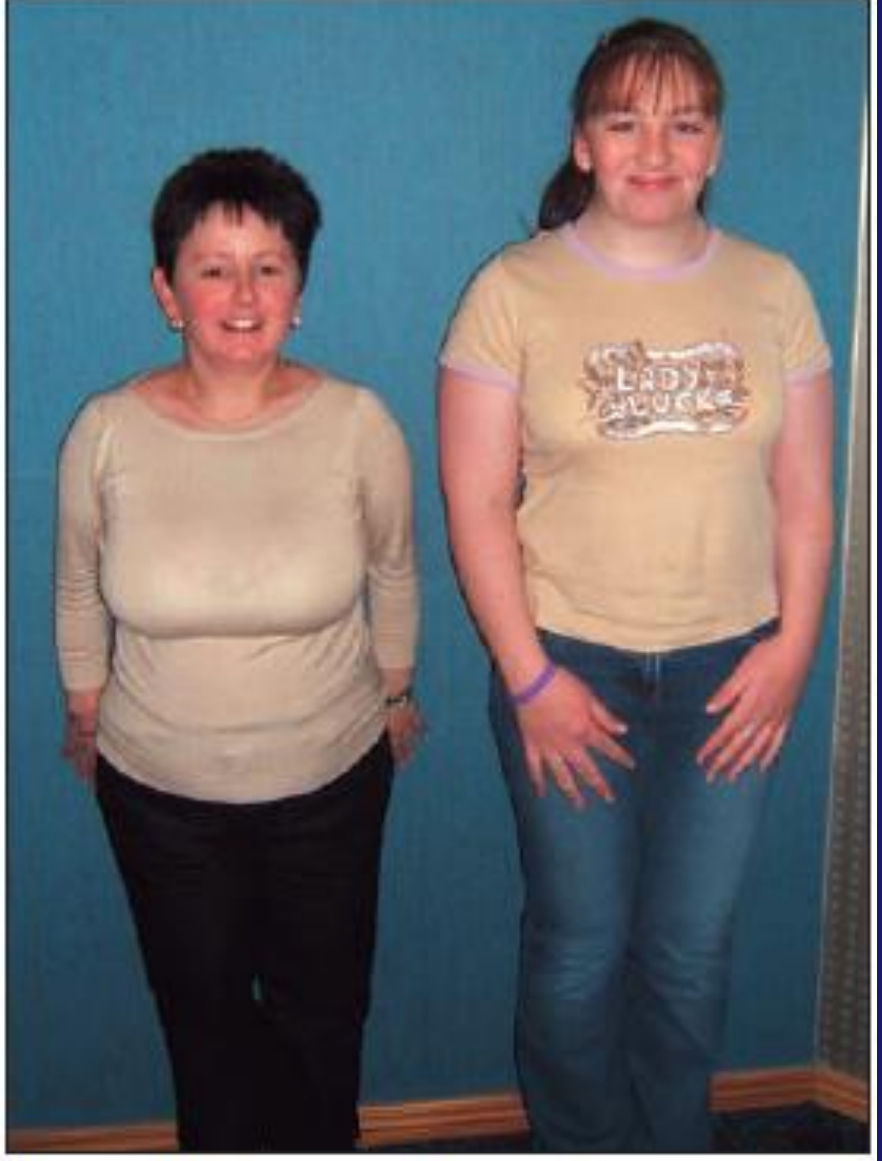
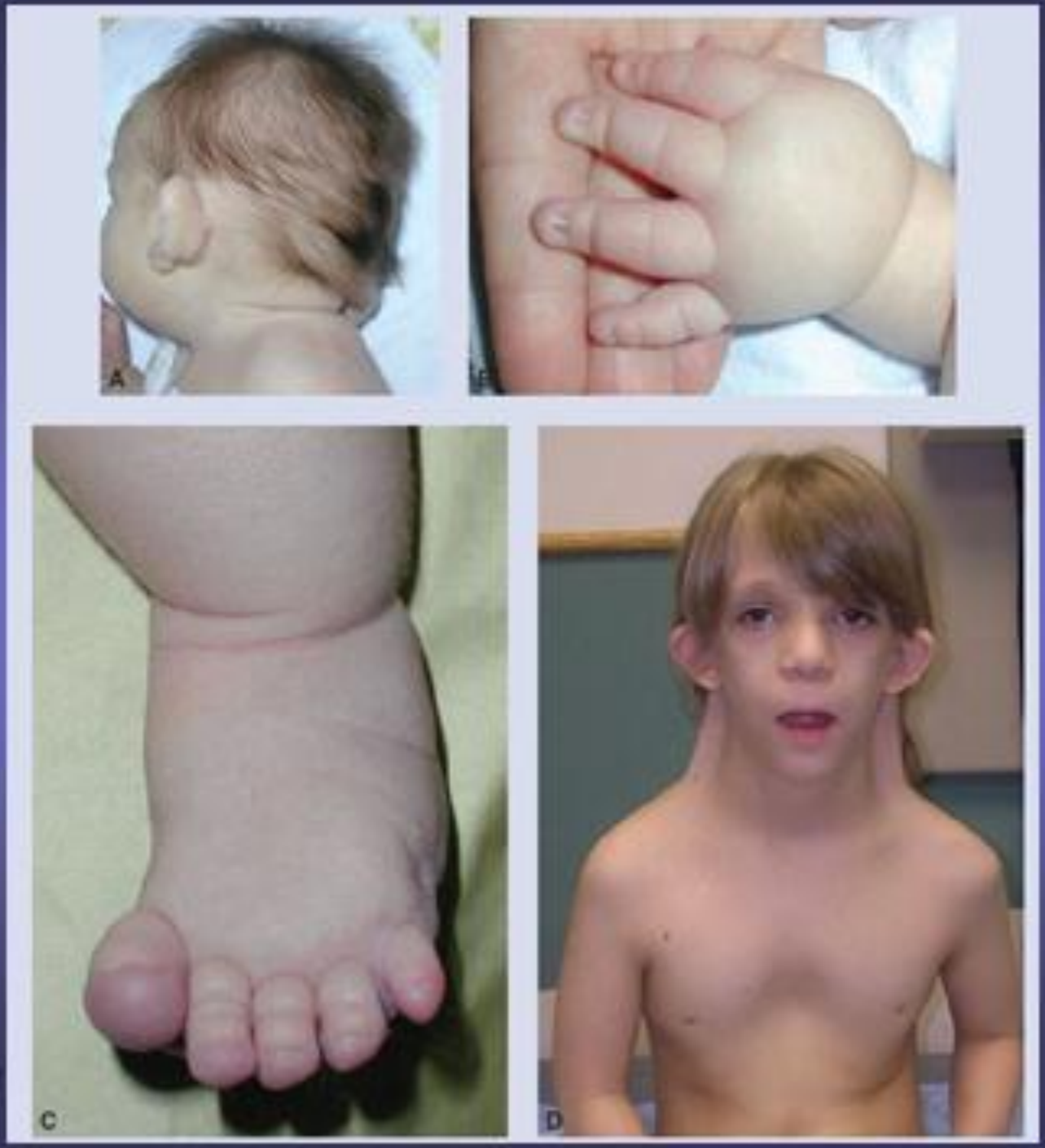
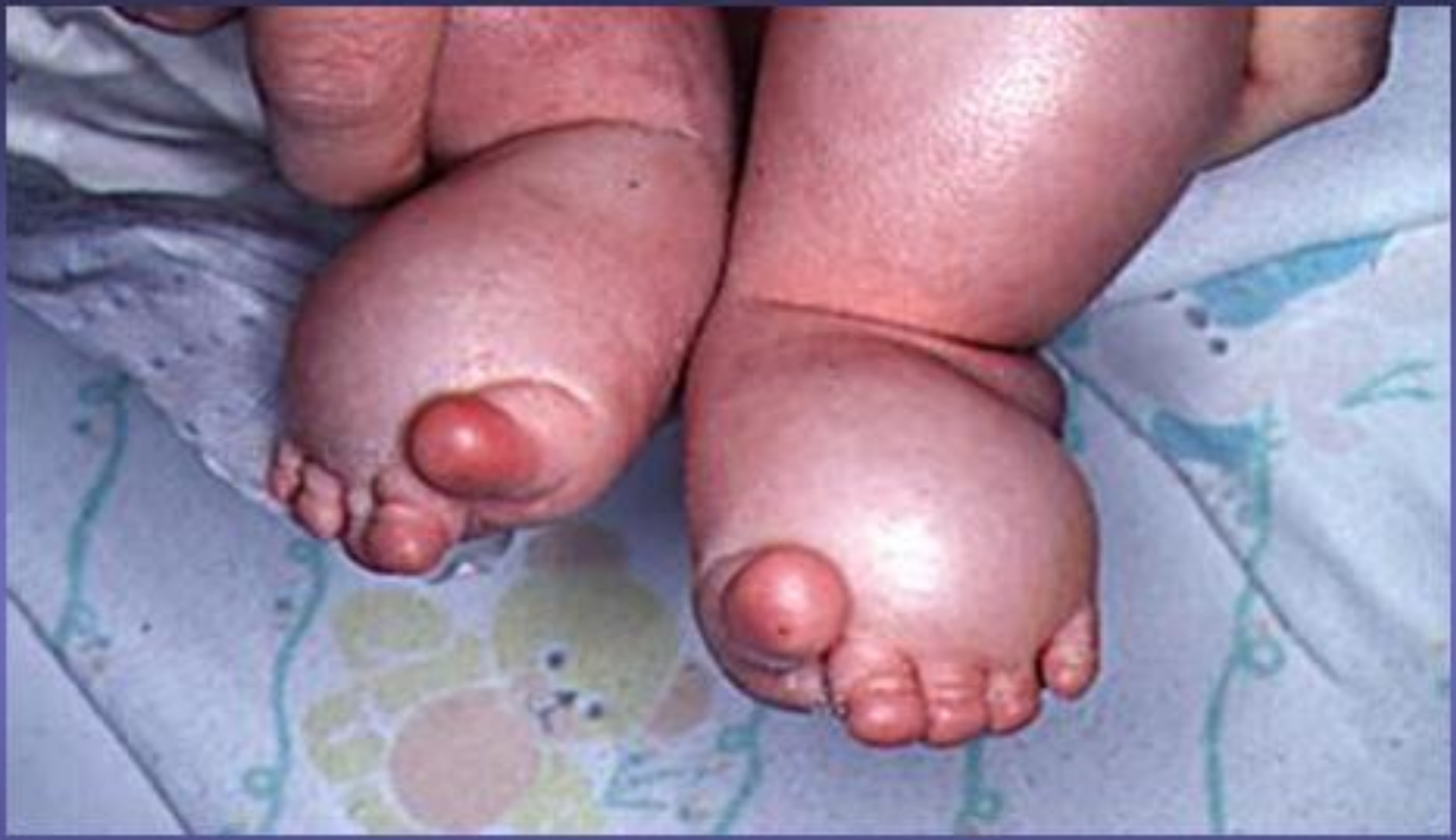
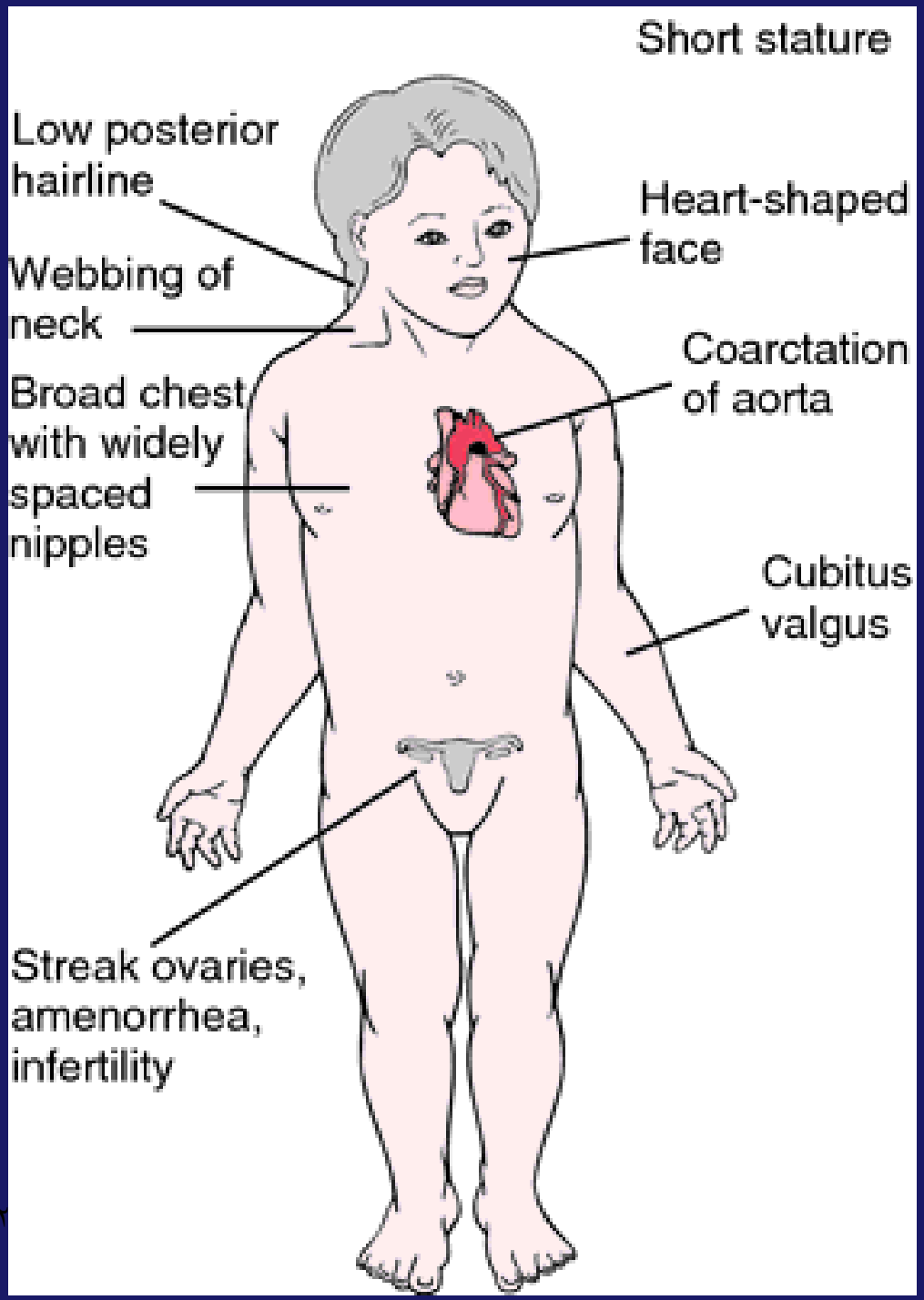


Figure 9.6 Turner syndrome. The woman on the left has marked short stature but no other clinical features; the adolescent female on the right has neck webbing and has received growth hormone and is 150 cm in height.


A
C
D



Lymphedema of the feet in an infant is shown. The toes have the characteristic sausagelike appearance


Short stature
Low posterior hairline
Heart-shaped face
Webbing of neck
Coarctation of aorta
Broad chest with widely spaced nipples
Cubitus valgus
Streak ovaries, amenorrhea, infertility

Treatment is with:

- growth hormone therapy
- oestrogen replacement for development of secondary sexual characteristics at the time of puberty (but infertility persists).

In about 50% of girls with Turner syndrome, there are 45 chromosomes, with only one X chromosome. The other cases have a deletion of the short arm of one X chromosome, an isochromosome that has two long arms but no short arm, or a variety of other structural defects of one of the X chromosomes. The presence of a Y chromosome sequence may increase the risk of gonadoblastoma. The incidence does not increase with maternal age and risk of recurrence is very low.

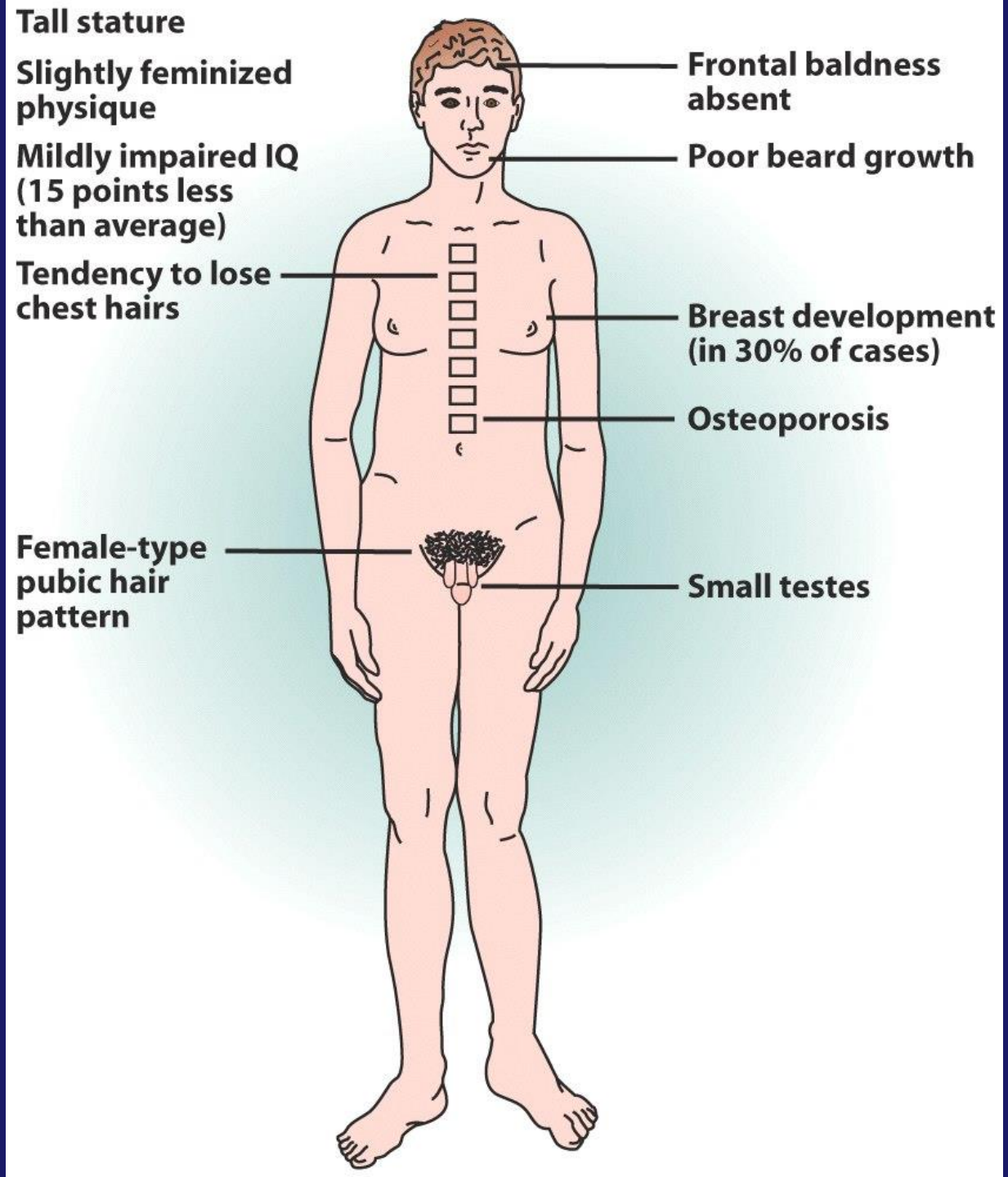
متلازمة كلاينفلتر

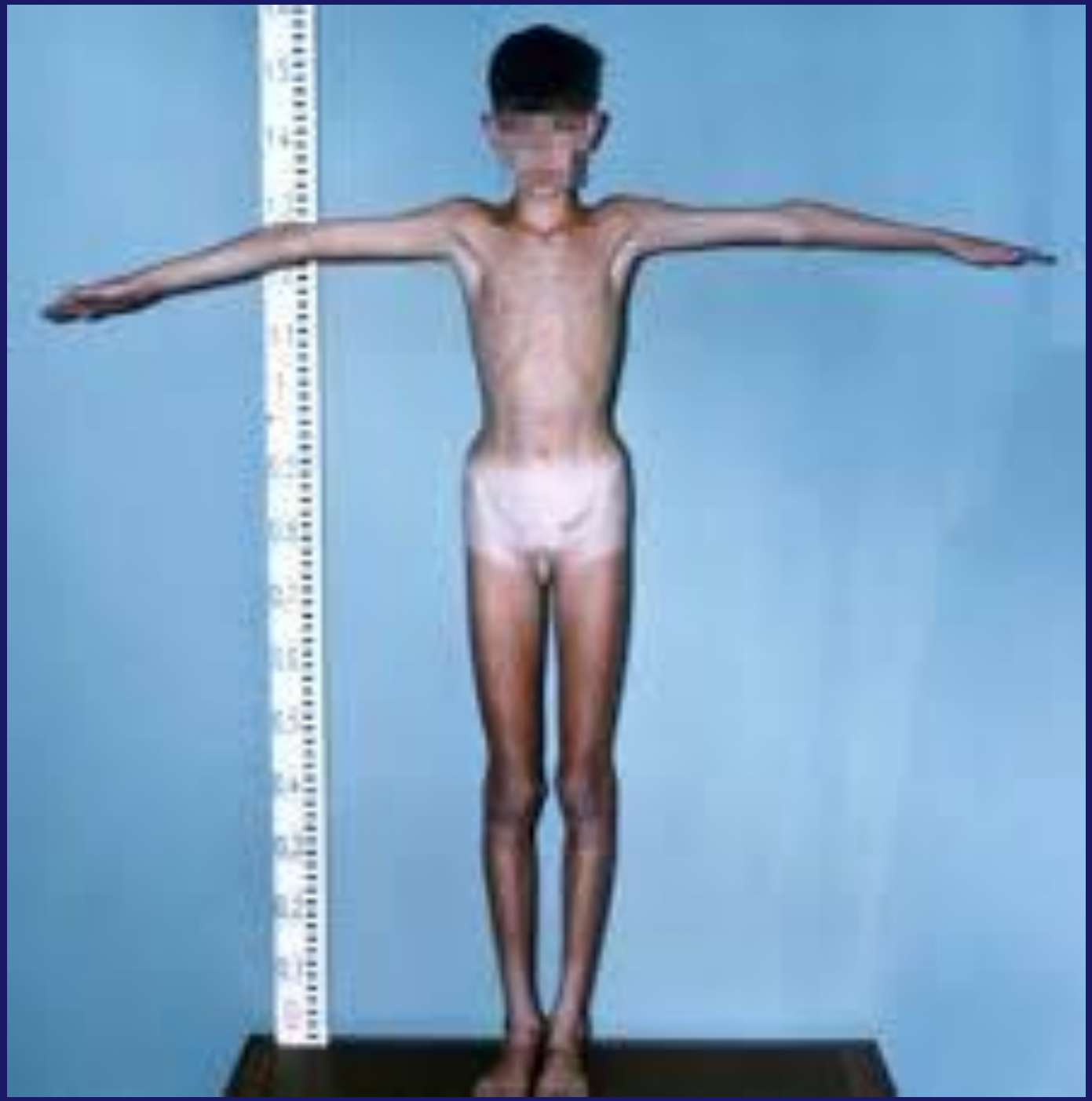
XXY أو KS

هذه المُتلازِمة شائِعةٌ كثيراً، وتُصِيبُ حوالي ١ من كل ٦٦٠ ذكرا (١-٢: ١٠٠٠).

Klinefelter syndrome (47, XXY)

This disorder occurs in about 1–2 per 1000 live-born males. For clinical features, see Box 9.5. Recurrence risk is very low.


Tall stature
Slightly feminized physique
Mildly impaired IQ (15 points less than average)
Tendency to lose chest hairs
Female-type pubic hair pattern
Frontal baldness absent
Poor beard growth
Breast development (in 30% of cases)
Osteoporosis
Small testes



Box 9.5 Clinical features of Klinefelter syndrome

- Infertility – most common presentation
- Hypogonadism with small testes
- Pubertal development may appear normal (some males benefit from testosterone therapy)
- Gynaecomastia in adolescence
- Tall stature
- Intelligence usually in the normal range, but some have educational and psychological problems

Structural chromosome anomalies

Reciprocal translocations

An exchange of material between two different chromosomes is called a reciprocal translocation. When this exchange involves no loss or gain of chromosomal material, the translocation is 'balanced' and usually has no phenotypic effect. Balanced reciprocal translocations are relatively common, occurring in 1 in 500 of the general population. A translocation that appears balanced on conventional chromosome analysis may still involve the loss of a few genes or the disruption of

الإزفاءات المتبادلة (تبادلات الموضع)

cognitive difficulties. Studying the break points in such individuals has been one way of identifying the location of specific genes.

Unbalanced reciprocal translocations contain an 'incorrect' amount of chromosomal material and often impair both physical and cognitive development, leading to dysmorphic features, congenital malformations, developmental delay, and learning difficulties. When recognized in a newborn baby, the prognosis is difficult to predict but the effect is usually severe. The parents' chromosomes should be checked to determine whether the abnormality has arisen de novo, or as a consequence of a parental rearrangement. Finding a balanced translocation in one parent indicates a recurrence risk for future pregnancies, so that antenatal diagnosis by chorionic villus sampling or amniocentesis should be offered as well as testing relatives who might be carriers.

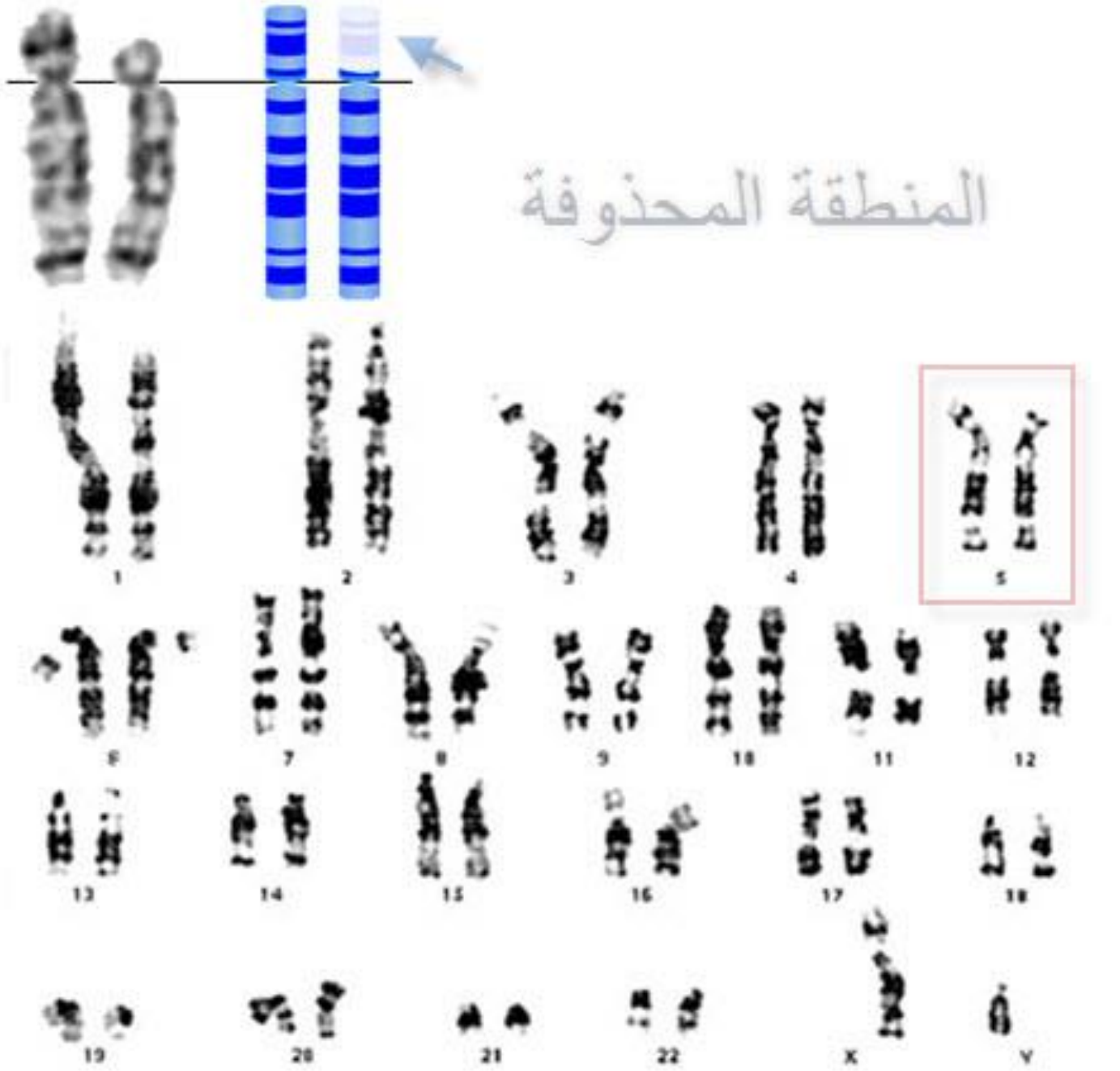
Deletions

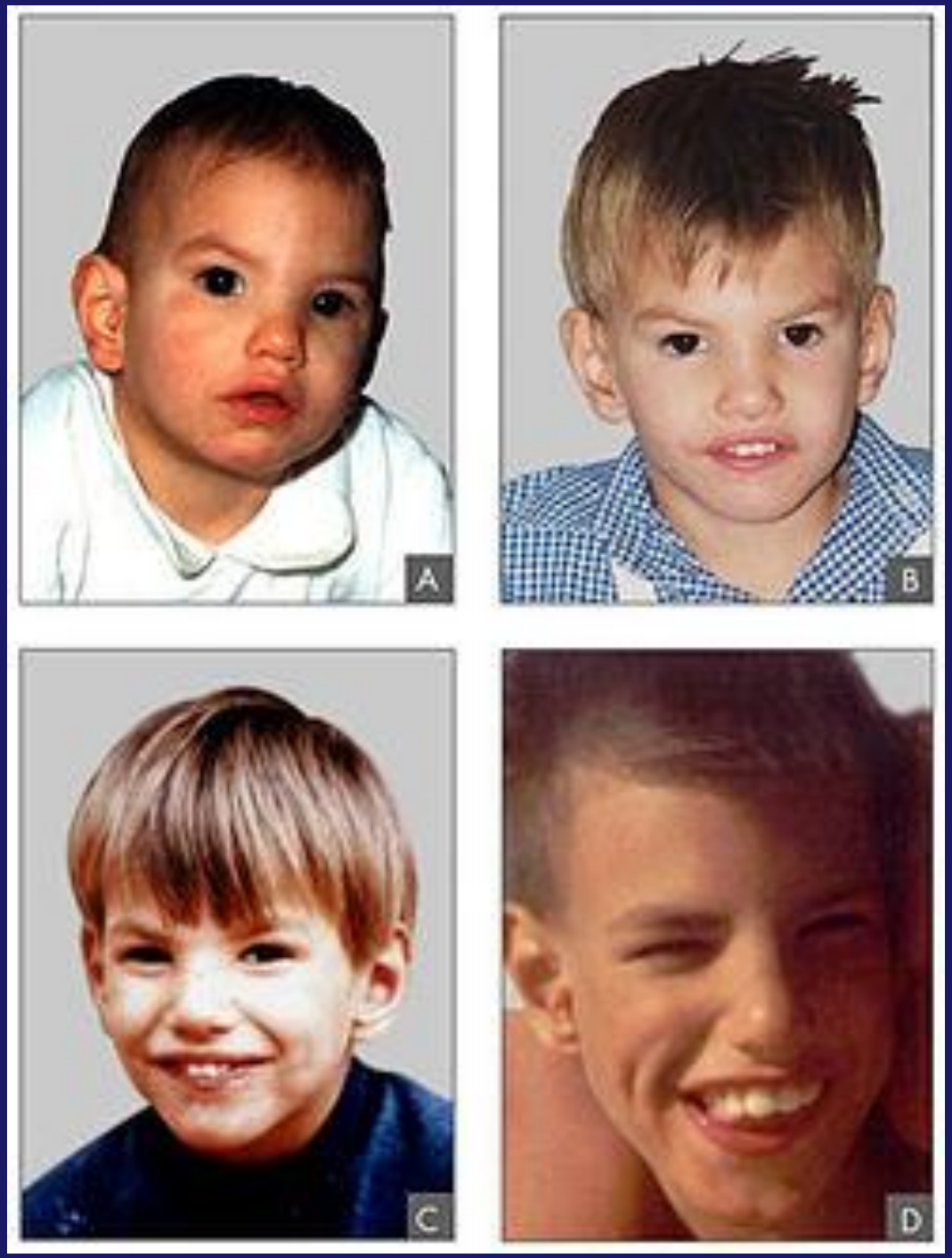
Deletions are another type of structural abnormality. Loss of part of a chromosome usually results in physical abnormalities and cognitive impairment. The deletion may involve loss of the terminal or an interstitial part of a chromosome arm.

الخبون (الشطب) (الحذف)

متلازمة مواء القطة

An example of a deletion syndrome involves loss of the tip of the short arm of chromosome 5, hence the name 5p- or monosomy 5p. Because affected babies have a high-pitched mewing cry in early infancy, it is also known as cri-du-chat syndrome. Parental chromosomes should be checked to see if one parent carries a balanced chromosomal rearrangement. The clinical severity varies greatly, depending on the extent of the deletion. It is now possible to specify the genes involved in chromosomal deletions as molecular methods are replacing standard cytogenetic investigations.


المنطقة المحذوفة


A
B
C
D


قصر القامة + صغر حجم الرأس

A deletion of band q11 on chromosome 22 (i.e. 22q11) can be associated with a range of phenotypes including both the DiGeorge syndrome (Fig. 15.27) and the velocardiofacial syndrome. Williams syndrome is another example of a microdeletion syndrome due to loss of chromosomal material at band q11 on the long arm of chromosome 7 (i.e. 7q11; Fig. 9.18, see also Box 9.12).

Duplications

Gain of structural material can also lead to congenital malformations and intellectual impairment, although duplications are often better tolerated than deletions.

An example of a duplication syndrome is partial trisomy of 17p. The duplication can range from being submicroscopic to being large enough to be visible on a karyotype. If it involves duplication of the *PMP22*

الترفيلات (التضاعفات)

pathy) in addition to other features resulting from the abnormality.

Testing for submicroscopic copy number variants

An increasing number of syndromes are now known to be due to chromosome deletions (or duplications) too small to be seen by conventional cytogenetic analysis. Submicroscopic deletions can be detected by FISH studies using DNA probes specific to particular chromosome regions. FISH studies are useful when a specific chromosome deletion is suspected.

Newer techniques are beginning to supersede the karyotype and FISH (Table 9.2, Fig. 9.7a). Array comparative genomic hybridization (microarray) can be used to check the chromosomes for structural rearrangements larger than 150 kB in size (Fig. 9.7b).

The advantage of microarrays is that no specific target is required for the test to be effective. Many of the newly emerging submicroscopic copy number variants have overlapping clinical features, and non-targeted testing is the most effective way to identify these.

One disadvantage of array comparative genomic hybridization is that the information provided can be unhelpful if the test reveals a copy number variant of uncertain significance. In addition, microarrays only provide quantitative data, and cannot be used to check for structural rearrangements, e.g. Robertsonian translocations. The information provided by microarray often requires discussion with a clinical geneticist.

Table 9.2 Cytogenetic analysis techniques

	Resolution	Microscopic	Submicroscopic	Rearrangements
Karyotype	3 Mb	+	–	+
Fluorescence in situ hybridization (FISH)	Specific to target	+	+	+
Comparative genomic hybridization array (microarray)	150 kB	+	+	–

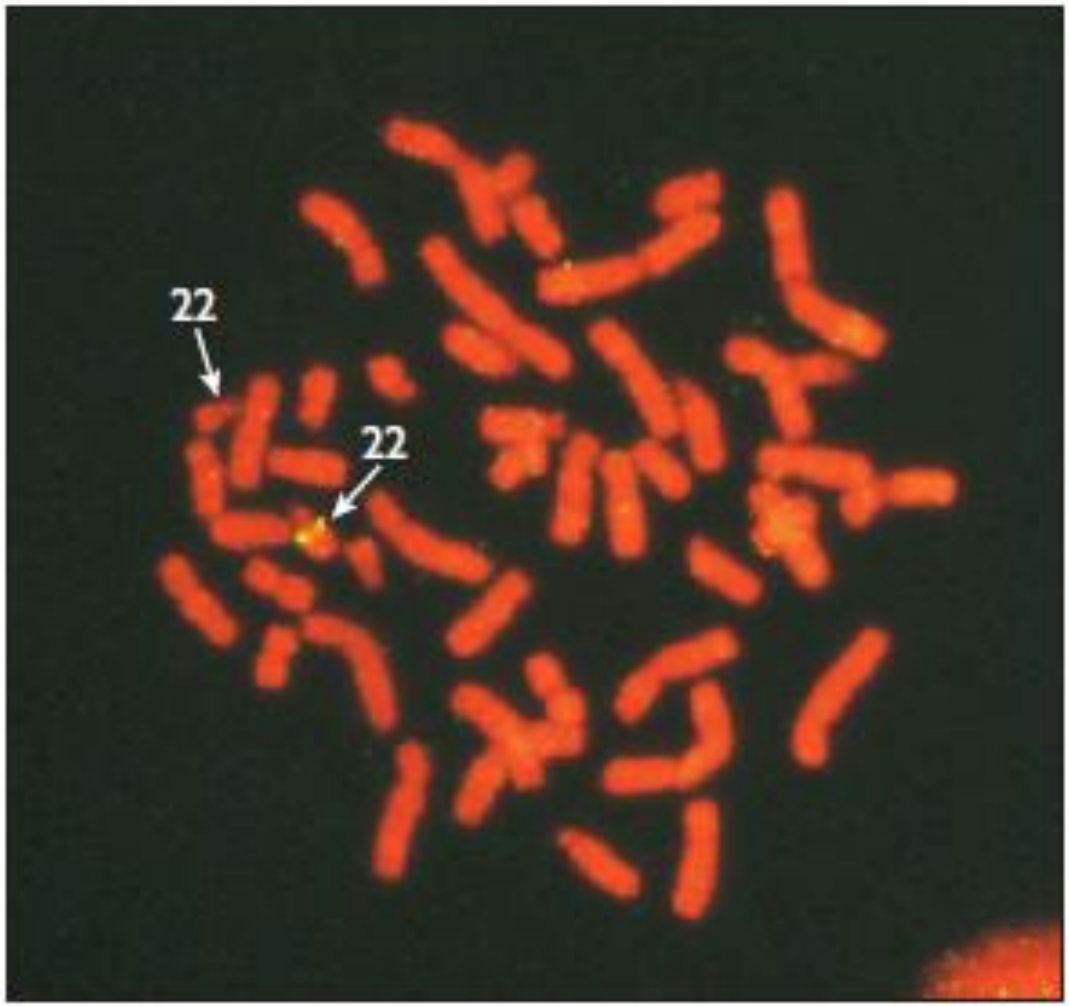


Figure 9.7a Fluorescence in situ hybridization (FISH) demonstrating a microdeletion on chromosome 22 associated with DiGeorge syndrome. Hybridization signals are seen on one chromosome 22 but not on the other because of the presence of a deletion (Courtesy of L. Gaunt, St Mary's Hospital, Manchester, UK.)

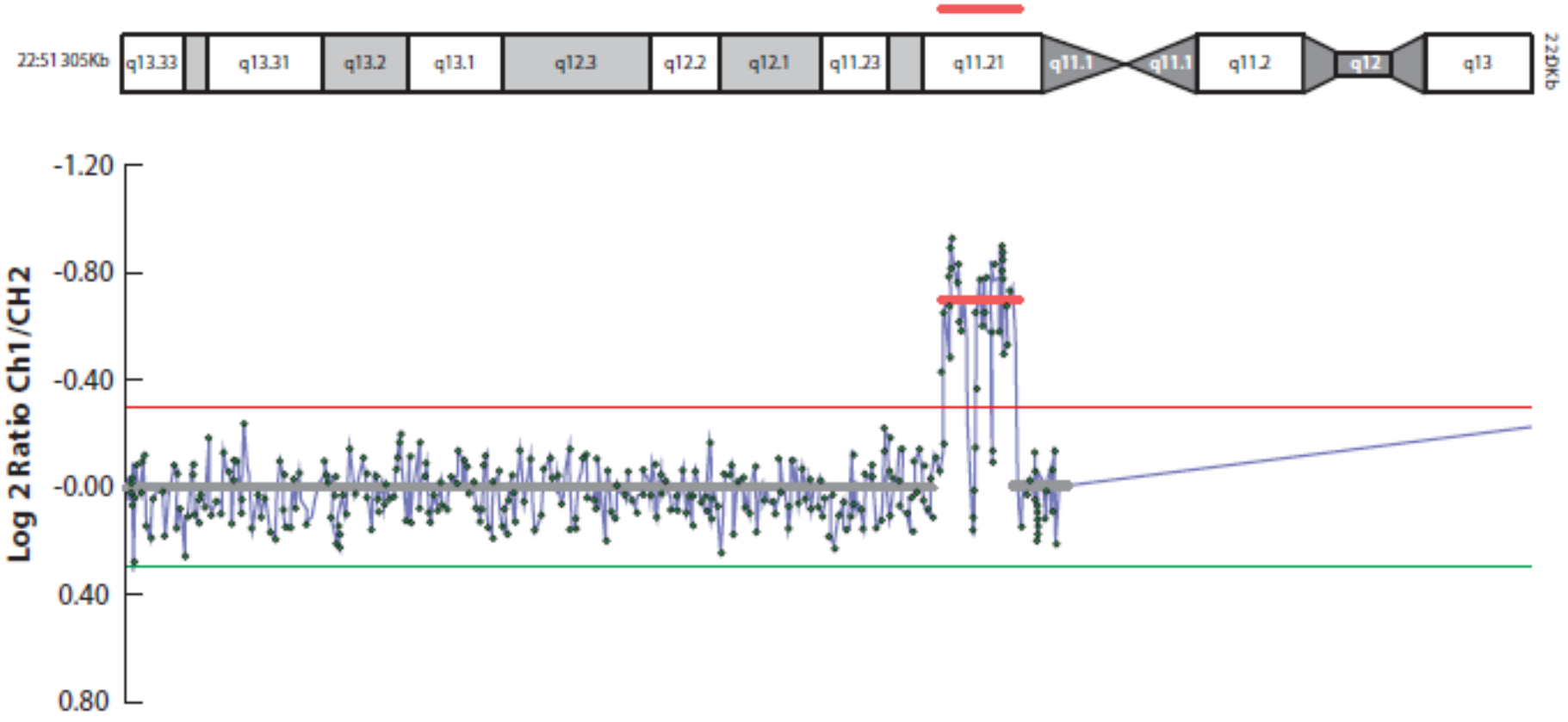


Figure 9.7b Array comparative genomic hybridization (microarray) result for a patient with 22q11 deletion. There is a reduction in the ratio of patient:control sequences from within band 22q11 on the long arm of chromosome 22.

Mendelian inheritance

Mendelian inheritance, described by Mendel in 1866 from work on garden peas, is the transmission of inherited traits or diseases caused by variation in a single gene in a characteristic pattern. These Mendelian traits or disorders are individually rare but collectively numerous and important: over 6000 have been described so far. For many disorders, the Mendelian pattern of inheritance is known. If the diagnosis of a condition is uncertain, its pattern of inheritance may be evident on drawing a family tree (pedigree), which is an essential part of genetic evaluation (Fig. 9.8).

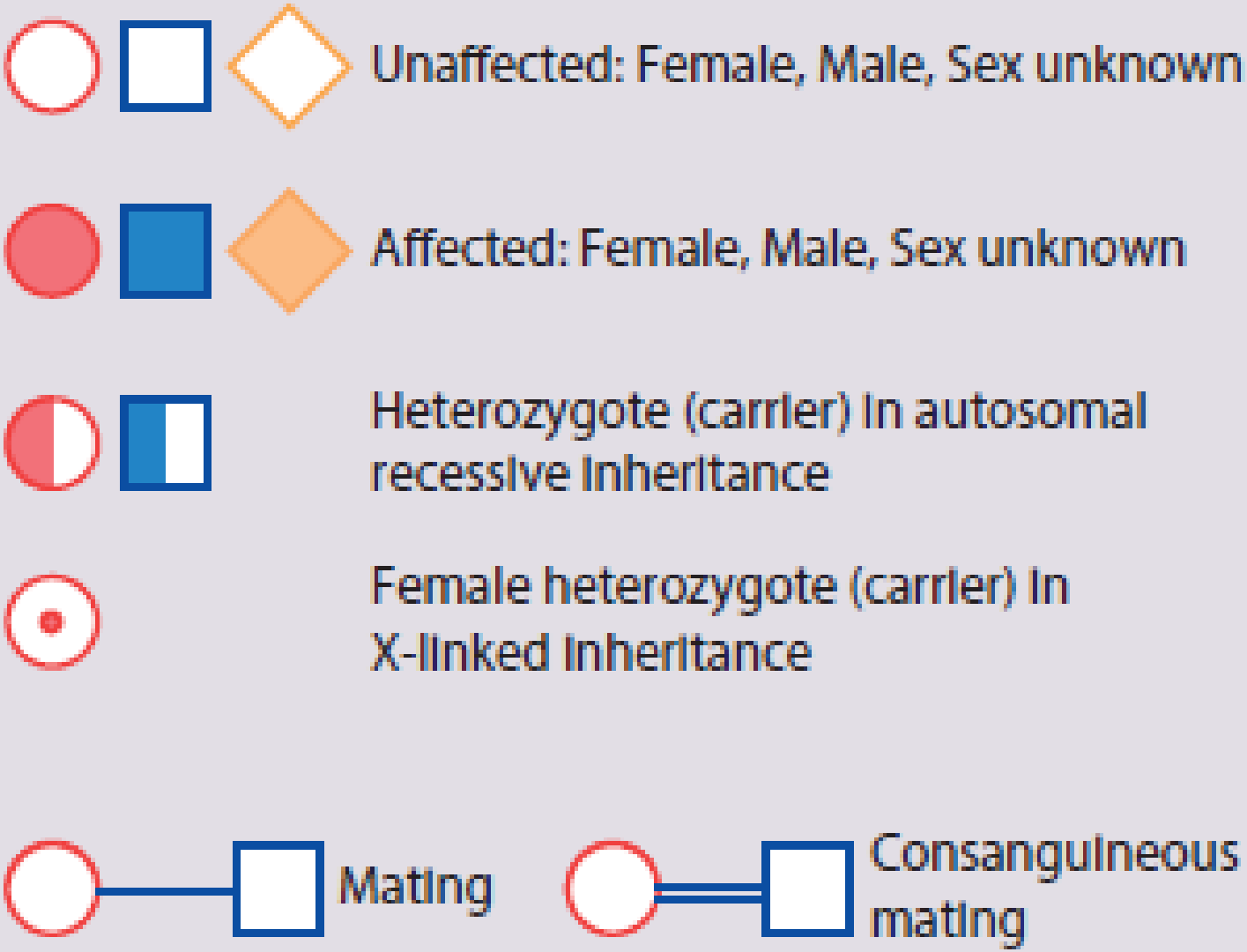
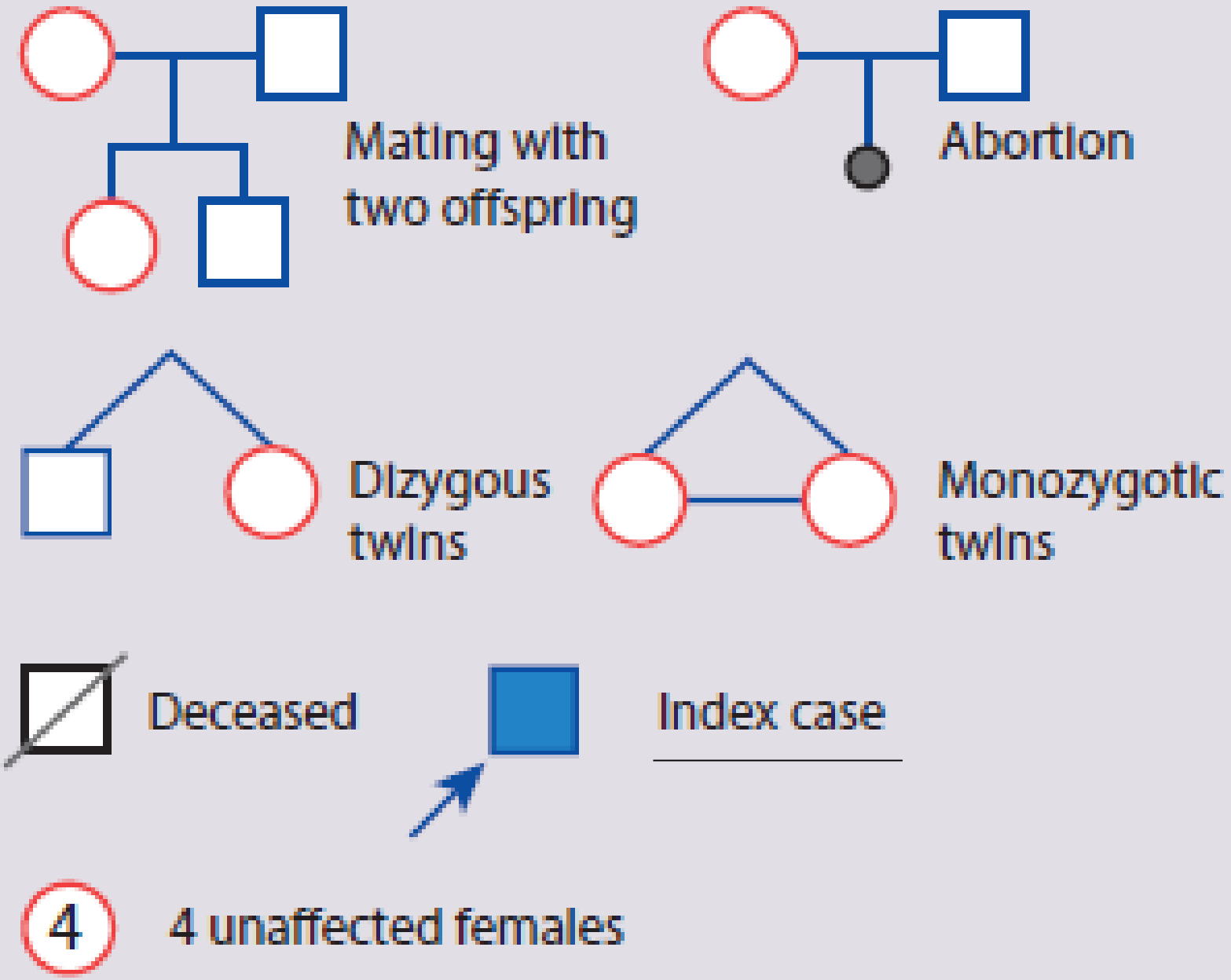


Figure 9.8 Examples of pedigree symbols.


Mating with
two offspring
Abortion
Dizygous
twins
Monozygotic
twins
Deceased
Index case
4
4 unaffected females

الوراثات العشرة:

نمط الوراثة الصاغرة (المقهورة) الجسمية	• الوراثة متعددة العوامل
نمط الوراثة السائدة (القاهرة) الجسمية	• وراثة المتقدرات (الوراثة الميتوكوندرية)
الوراثـــة المرتبطة بالجنس الصاغرة (المقهورة)	• الوراثات الأخرى
الوراثـــة المرتبطة بالجنس الســـائدة (القاهرة)	• الطفرات
الوراثة المرتبطة بالجنس والمتعلقة بالصبغي (٧)	• الاضطرابات الصبغية

Autosomal dominant inheritance

This is the most common mode of Mendelian inheritance (Box 9.6). Autosomal dominant conditions are caused by alterations in only one copy of a gene pair, i.e. the condition occurs in the heterozygous state despite the presence of an intact copy of the relevant gene. Autosomal dominant genes are located on the autosomes (chromosomes 1–22), and so males and females are equally affected. Each child from an affected parent has a 1 in 2 (50%) chance of inheriting the abnormal gene (Fig. 9.9a,b). This appears to be straightforward, but complicating factors include the following factors.

- التفاوت في التعبير

Variation in expression

Within a family, some affected individuals may manifest the disorder mildly and others more severely. This may be the result of variation at other genes, environmental effects, or sheer chance.

- عدم الانتفاذ

Non-penetrance

Refers to the lack of clinical signs and symptoms in an individual who has inherited the abnormal gene. An example of this is otosclerosis, in which only about 40% of gene carriers develop deafness (Fig. 9.10).

De novo mutation

• الطفرة الجديدة

A mutation is classed as de novo if it does not affect either parent. It may be due to:

- a new mutation in one of the gametes leading to the conception of the affected person. This is the most common reason for absence of a family history in dominant disorders, e.g. about 80% of individuals with achondroplasia have unaffected parents. The risk of new single-point mutations increases with paternal age

- parental mosaicism – very occasionally a healthy parent harbours the mutation only in some of their cells, e.g. in their gonads. This can account for recurrences of autosomal dominant disorders in siblings born to apparently unaffected parents. It has been described in congenital lethal osteogenesis imperfecta
- non-paternity – if the apparent father is not the biological father.

- تماثل الألائل

Homozygosity

In the rare situation where both parents are affected by the same autosomal dominant disorder, there is a 1 in 4 risk that a child will be homozygous for the altered gene. This usually causes a more severe phenotype, which may be lethal, as with achondroplasia.

Knudson two-hit hypothesis

Some autosomal dominant conditions related to cancer susceptibility follow Knudson two-hit hypothesis. Both copies of the gene n
a malignancy to occur. If a pe
one working copy of the gene in every cell in his/her body, then only one further mutation event needs to occur for both copies of the gene to be inactivated. The chance of this happening is much greater than the chance of two successive mutations occurring in someone who starts life with two functional copies of the gene. The susceptibility to cancer is therefore inherited in a dominant fashion but the development of cancer within a cell can be thought of as a local event within the individual, so that not every person who inherits the susceptibility will necessarily develop a malignancy.

- فرضية الضربتين لنودسون

An example in paediatrics is mutation in the retinoblastoma (*Rb*) gene. If a child inherits the susceptibility, i.e. a mutation in one copy of the *Rb* gene, then a tumour will occur if a second hit occurs on the working copy in a cell of the relevant type, so that the child inheriting a mutation will often have a tumour in both eyes, but approximately 10% will escape with neither eye affected.

Box 9.6 Examples of autosomal dominant disorders

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

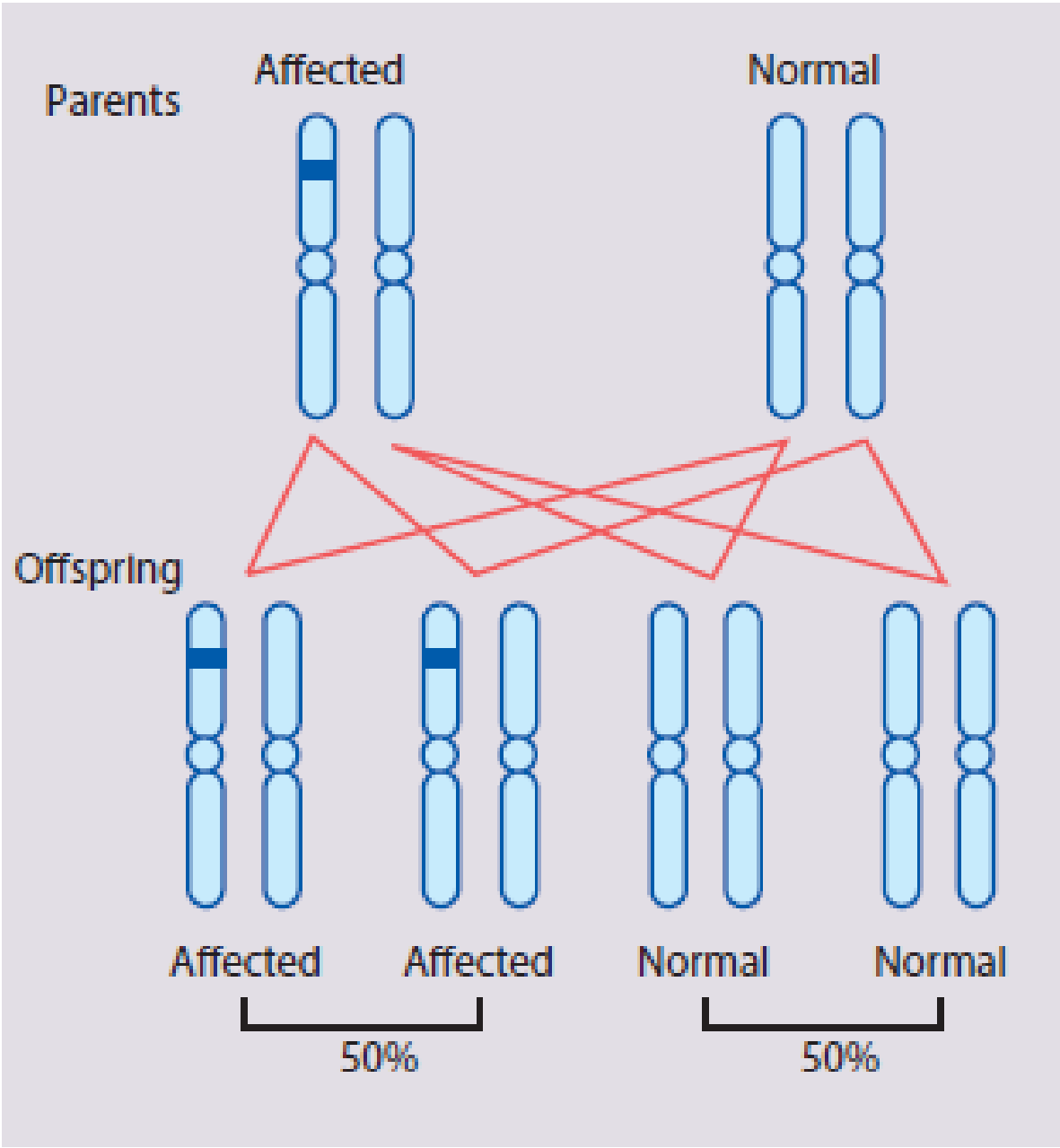


Figure 9.9a Autosomal dominant inheritance.

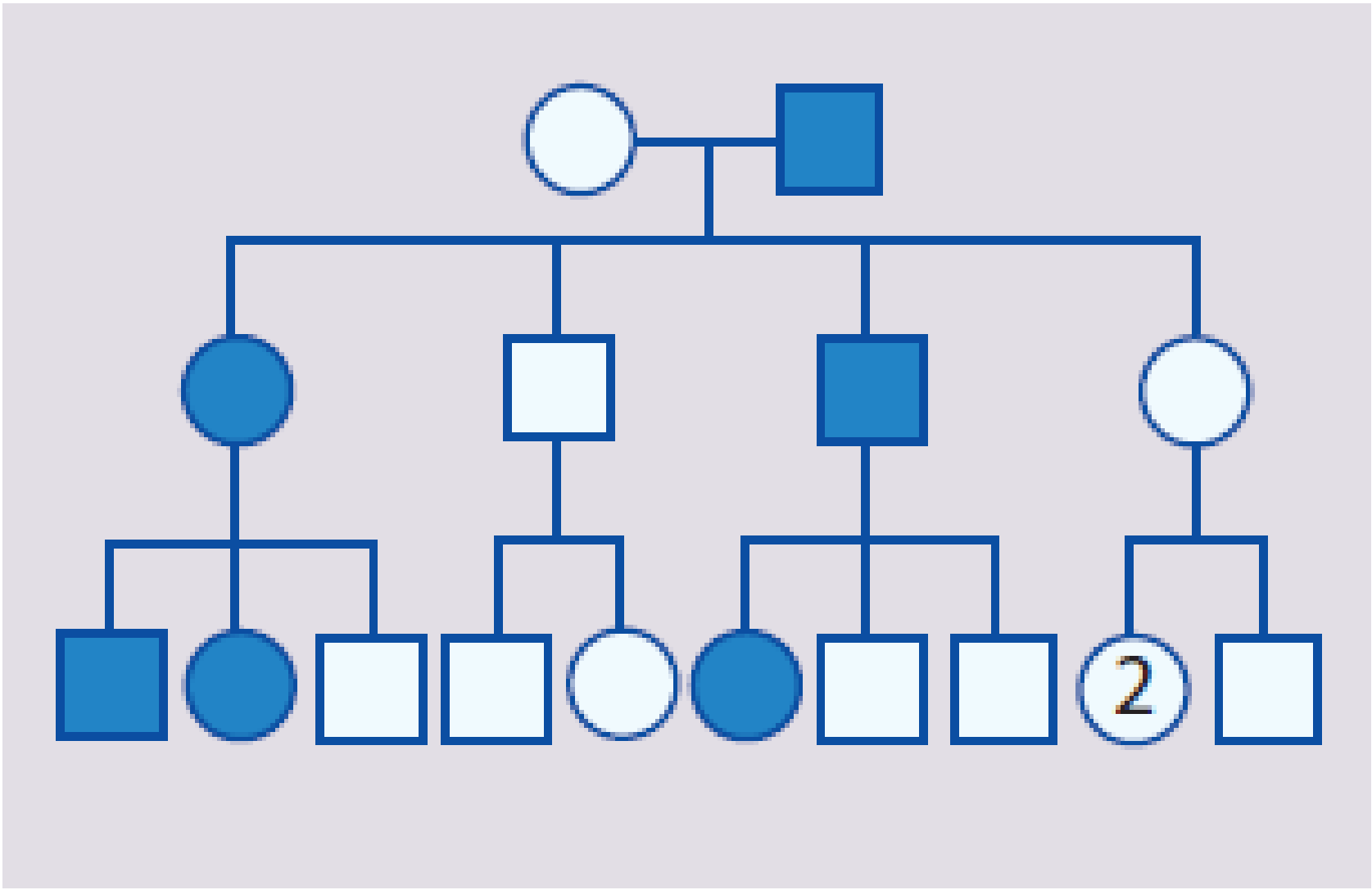


Figure 9.9b Typical pedigree of an autosomal dominant disorder.

Summary

Autosomal dominant inheritance:

- Most common mode of Mendelian inheritance.
- Affected individual carries the abnormal gene on one of a pair of autosomes.
- There is 1 in 2 chance of inheriting the abnormal gene from affected parent, but there may be variation in expression, non-penetrance, no family history (new mutation, parental mosaicism, non-paternity), or homozygosity (rare).

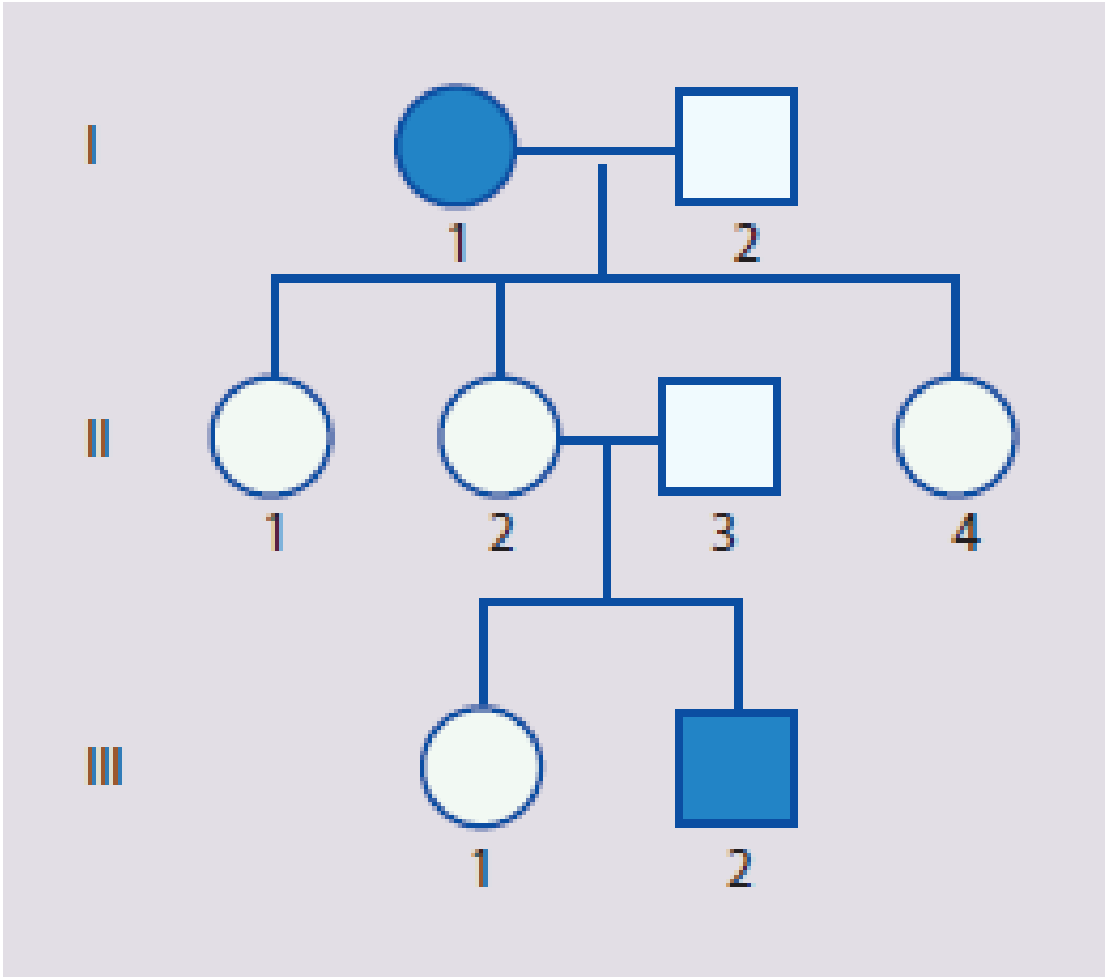


Figure 9.10 Example of nonpenetrance. I1 and III2 have otosclerosis. II2 has normal hearing but must have the gene (a new mutation event is most unlikely to arise independently for a second time in the family). The gene is nonpenetrant in II2.

Autosomal recessive inheritance

An affected individual is homozygous for the mutant allele in the gene. Sometimes, there is a different mutation on each copy of the gene, for example cystic fibrosis, and the affected individual is a compound heterozygote. In either situation, they will have inherited an abnormal allele from each parent, both of whom will usually be unaffected heterozygous carriers (Box 9.7). For a couple with both parents being carriers, the risk of any child being affected, male or female, is 1 in 4 (25%; Fig. 9.11a,b). All offspring of an affected individual will carry the condition. If an affected individual has children with an unaffected carrier, then each has a 50% chance of being affected.

Consanguinity

It is thought that we all carry six to eight abnormal recessive genes. Fortunately, our partners usually carry different ones. Marrying a cousin or another relative increases the chance of both partners carrying the same autosomal recessive gene mutation. Cousins who marry have a modest in
child with a serious rece
discussion with families i
as it may trigger feeling
cultural disrespect.

The frequencies of disease alleles at recessive gene loci vary between population groups. When the gene occurs sufficiently often and the gene or its effects can be detected, population-based carrier screening can be performed and antenatal diagnosis can be offered for high-risk pregnancies where both parents are carriers. Disorders that have been screened for in this way for many years include sickle cell disease in black Africans and African Americans, the thalassaemias in those from Mediterranean or Asian populations, and Tay–Sachs disease in Ashkenazi Jews. With developments in DNA-sequencing technologies, it is becoming

possible for the range of disorders being screened to increase dramatically. Wealthy countries that practise customary consanguineous marriage are beginning to use these technologies to identify the genetic basis of the recessive disorders prevalent in their communities and to screen for a broad range of conditions.

Box 9.7 Examples of autosomal recessive disorders

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

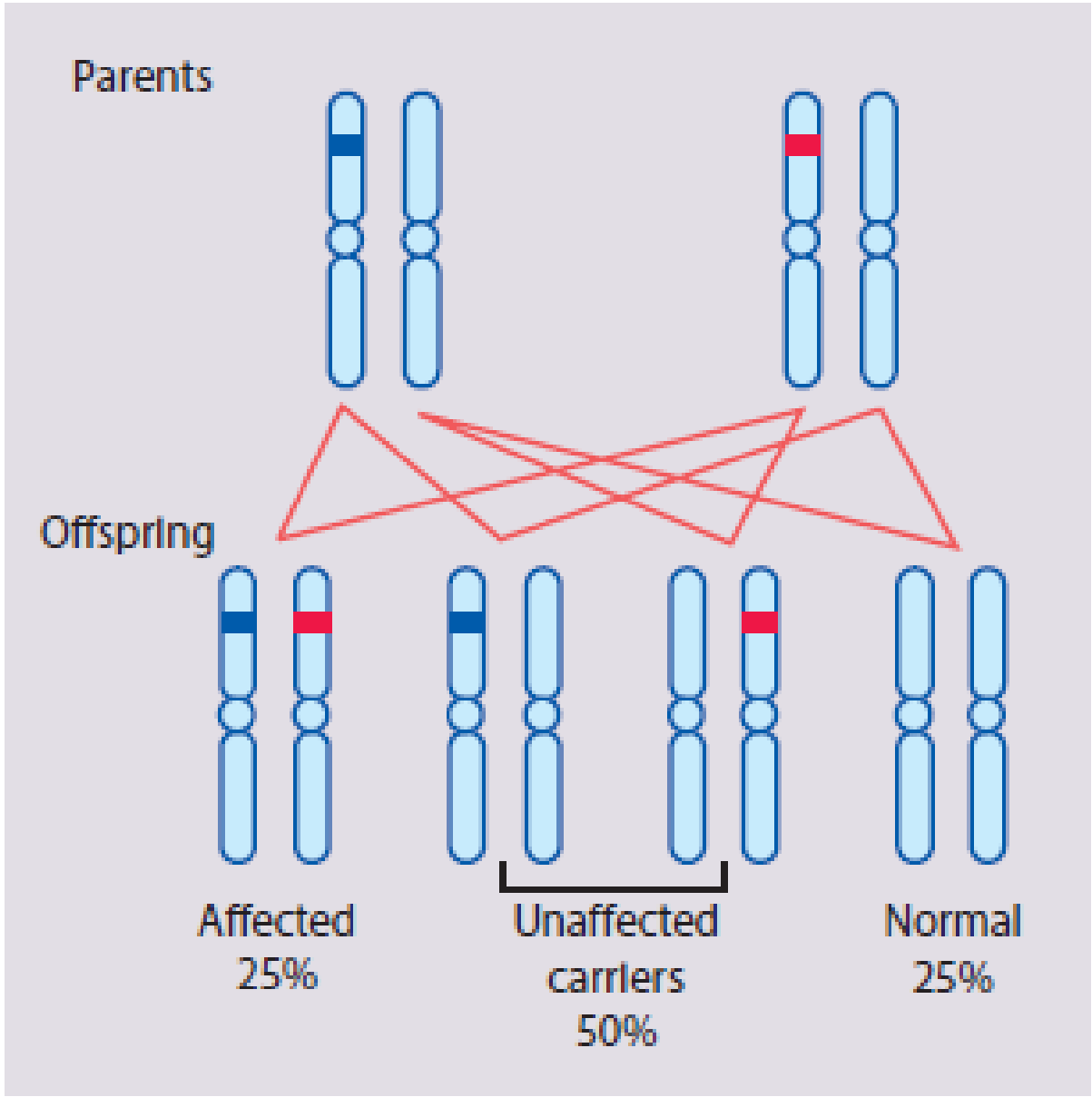


Figure 9.11a Autosomal recessive inheritance.

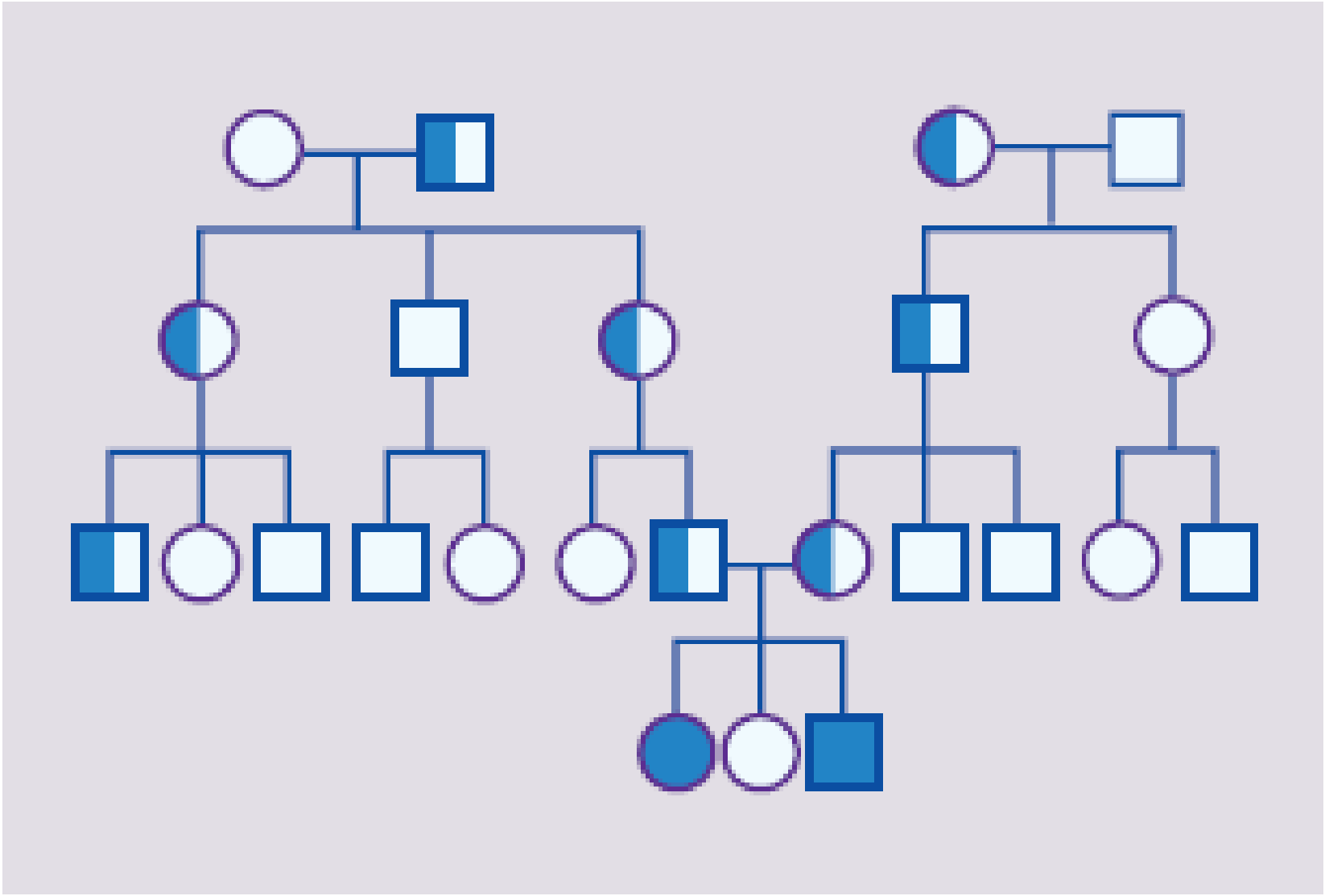


Figure 9.11b Pedigree to show autosomal recessive inheritance.

Summary

Autosomal recessive inheritance

- Affected individuals are usually homozygous for the abnormal gene; each unaffected parent will be a heterozygous carrier.
- Two carrier parents have a 1 in 4 risk of having an affected child.
- Risk of these disorders varies between populations and is increased by consanguinity.
- Autosomal recessive disorders often affect metabolic pathways, whereas autosomal dominant disorders often affect structural proteins.

X-linked inheritance

X-linked conditions are caused by alterations in genes found on the X chromosome. These may be inherited as X-linked recessive or X-linked dominant traits but the distinction between these is much less clear than in autosomal traits because of the variable pattern of X chromosome inactivation in females.

In X-linked recessive inheritance (Box 9.8, Fig. 9.12a,b):

- males are affected
- female carriers are usually healthy
  - occasionally a female carrier shows features of the disease
  - each son of a female carrier has a 1 in 2 (50%) risk of being affected
  - each daughter of a female carrier has a 1 in 2 (50%) risk of being a carrier
  - daughters of affected males will all be carriers
  - sons of affected males will not be affected, because a man passes a Y chromosome to his sons.

The family history may be negative, because new mutations and (gonadal) mosaicism are fairly common in some conditions. Identification of carrier females in a family requires interpretation of the pedigree, the search for mild clinical manifestations, and the identification of carriers through specific biochemical or molecular tests. Identifying carriers is important because a female carrier has a 50% risk of having an affected son regardless of who her partner is and X-linked recessive disorders can be very severe.

X-linked dominant disorders, where both males and females are affected, are unusual. An example is hypophosphataemic (vitamin D-resistant) rickets. In some other X-linked dominant disorders, a female carrying the mutation will be affected while the mutation-carrying males have an even more serious condition. Thus, a mutation that causes Rett syndrome (a neurodegenerative disorder) in a girl will cause a lethal, neonatal-onset encephalopathy in males. Another reason why a sex-linked condition may predominantly affect females is because it usually arises through mutations at spermatogenesis (e.g. Rett syndrome). As male offspring must inherit a Y chromosome from their father, they will not inherit any mutations on the X chromosome that arise during spermatogenesis.

Box 9.8 Examples of X-linked recessive disorders

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

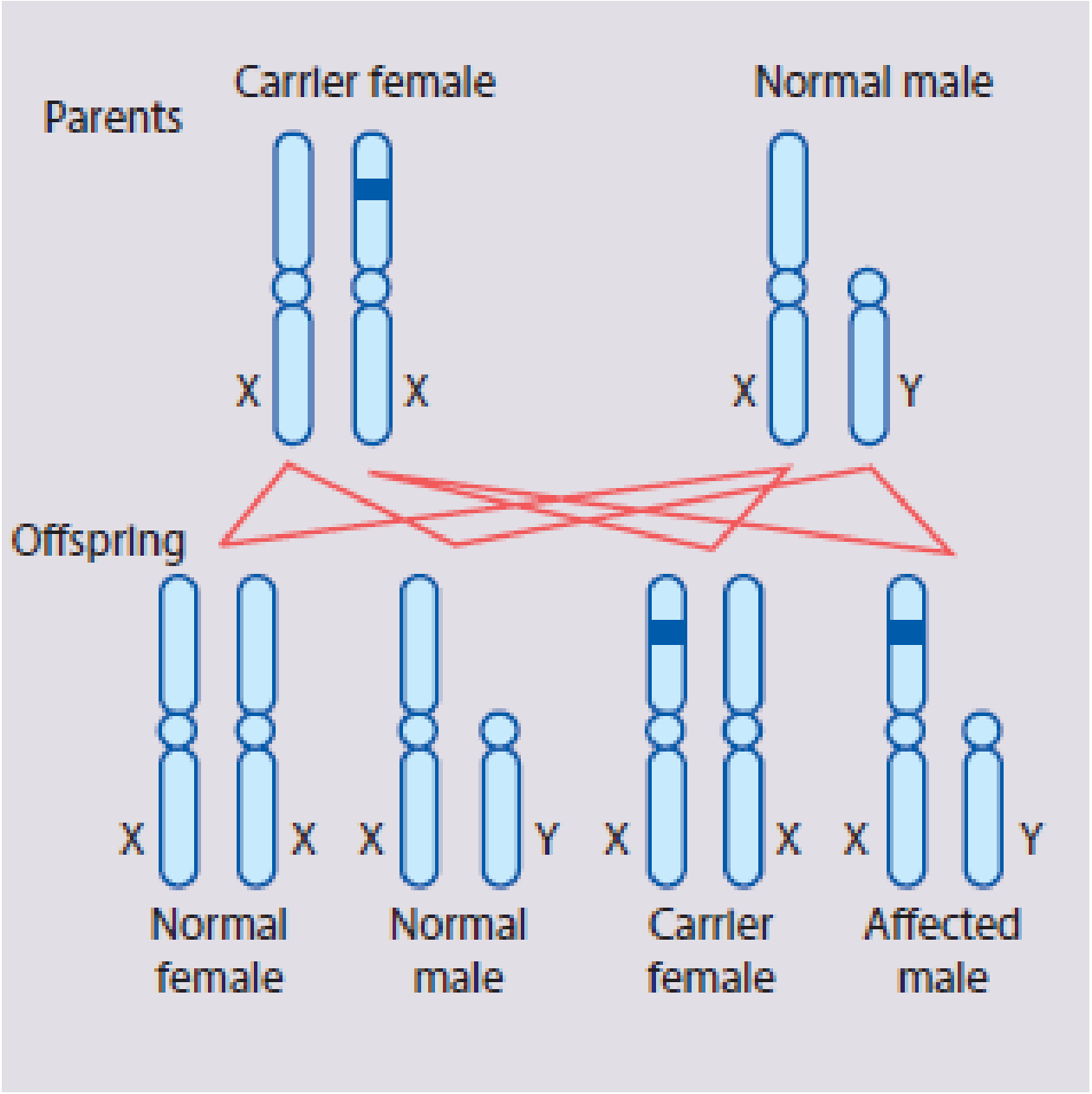
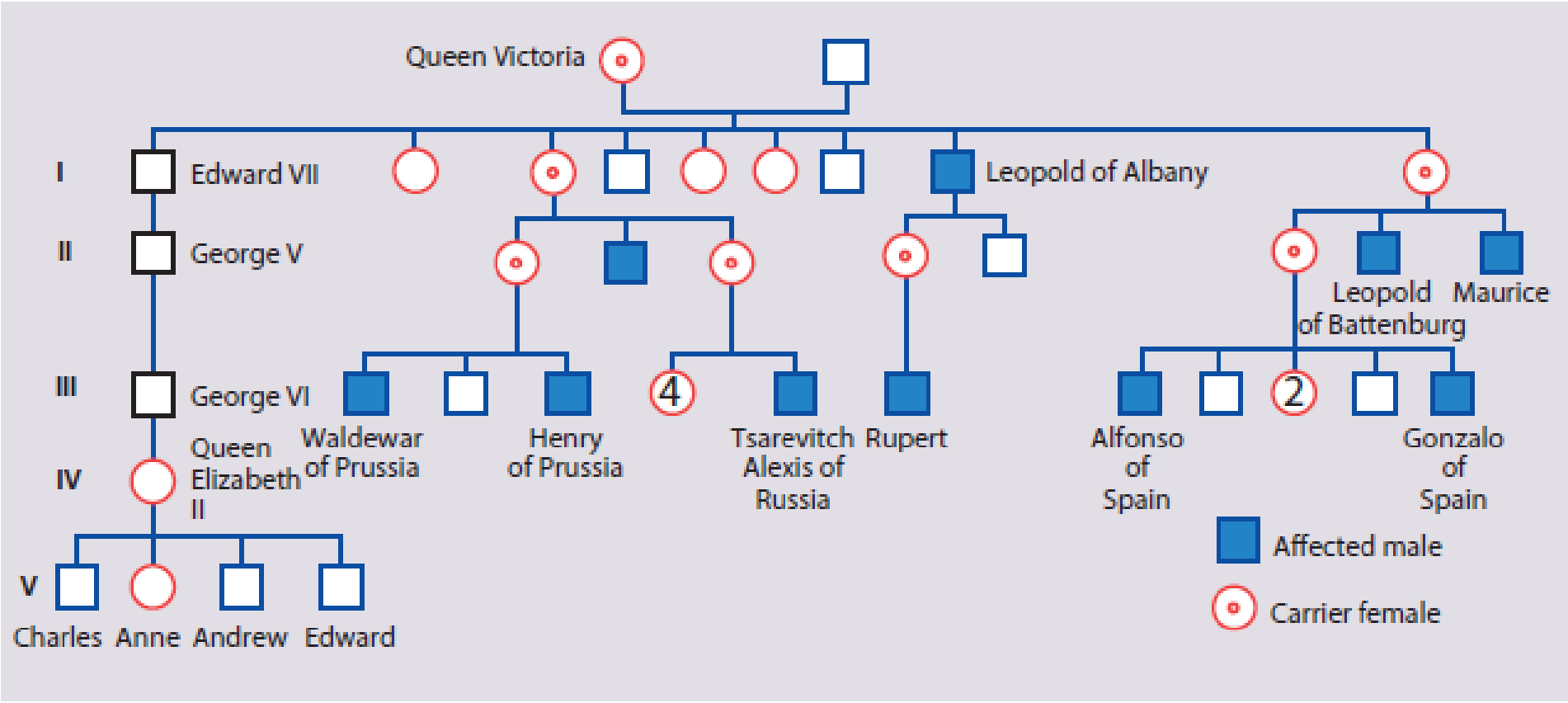


Figure 9.12a X-linked (recessive) inheritance.

Figure 9.12b Typical pedigree for X-linked (recessive) inheritance, showing Queen Victoria, a carrier for haemophilia A, and her family. It shows affected males in several generations, related through females, and that affected males do not have affected sons (contrast with autosomal dominant inheritance).


Queen Victoria
I
Edward VII
II
George V
III
George VI
IV
Queen Elizabeth II
V
Charles
Anne
Andrew
Edward
Waldewar of Prussia
Henry of Prussia
4
Tsarevitch Alexis of Russia
Rupert
Leopold of Albany
Alfonso of Spain
Leopold of Battenburg
Maurice
2
Gonzalo of Spain
Affected male
Carrier female

Summary

X-linked recessive inheritance:

- Males are affected; females can be carriers but are usually healthy or have mild disease.
- Family history may be negative – many arise from new mutations or gonadal mosaicism.
- Identifying female carriers is important to be able to provide genetic counselling.
- All the female offspring of affected males will be carriers, but none of the male offspring can inherit the mutation.
- Half of the male offspring of a female carrier will be affected and half of the female offspring will be carriers.

Y-linked inheritance

Y-linked traits are extremely rare. Y-linked inheritance would result in only males being affected, with transmission from an affected father to all his sons. Y-linked genes determine sexual differentiation and spermatogenesis, and mutations are associated with infertility and so are rarely transmitted.

Unusual genetic mechanisms

Trinucleotide repeat expansion mutations

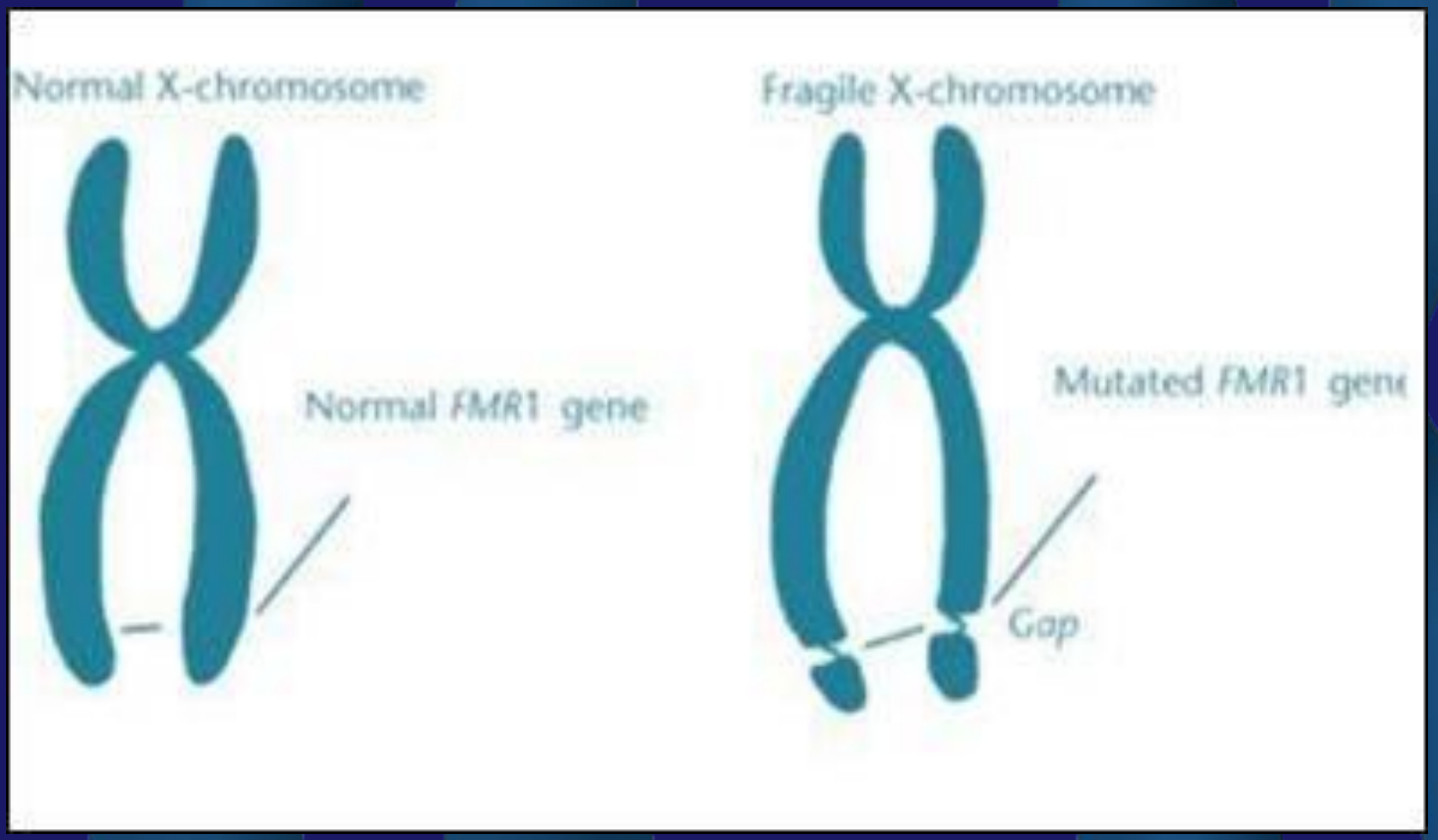
This is a class of unstable mutations that consist of expansions of trinucleotide repeat sequences inherited in Mendelian fashion. Fra
dystrophy, and Huntingto
known of these disorders. They follow different patterns of inheritance but share certain unusual properties due to the nature of the underlying mutation. Trinucleotide repeat disorders exhibit a phenomenom known as anticipation. The triplet repeat mutation is unstable and can expand between subsequent generations. In general, a larger expansion causes a more severe form of the disease. This means that these conditions can become more severe in successive generations of the same family.

- طفرات توسع المكررة ثلاثية النووية

There are two major categories of triplet repeat disorder, depending on whether or not the triplet repeat is in the coding sequence of the gene. When the triplet repeat expansion is in the coding sequence, as in Huntington disease (and in a number of other neurodegenerative disorders), proteins containing an excess of the amino acid, glutamine, are produced. Glutamine can damage the cells in the central nervous system when present in excess, leading to neurodegeneration. When the triplet repeat expansion is in other regions of the gene, reduced quantities of the protein are produced. In these cases, the reduction in the amount of the available protein leads to the symptoms of the condition. One such example is myotonic dystrophy, which is described further in Chapter 29. Neurological disorders.

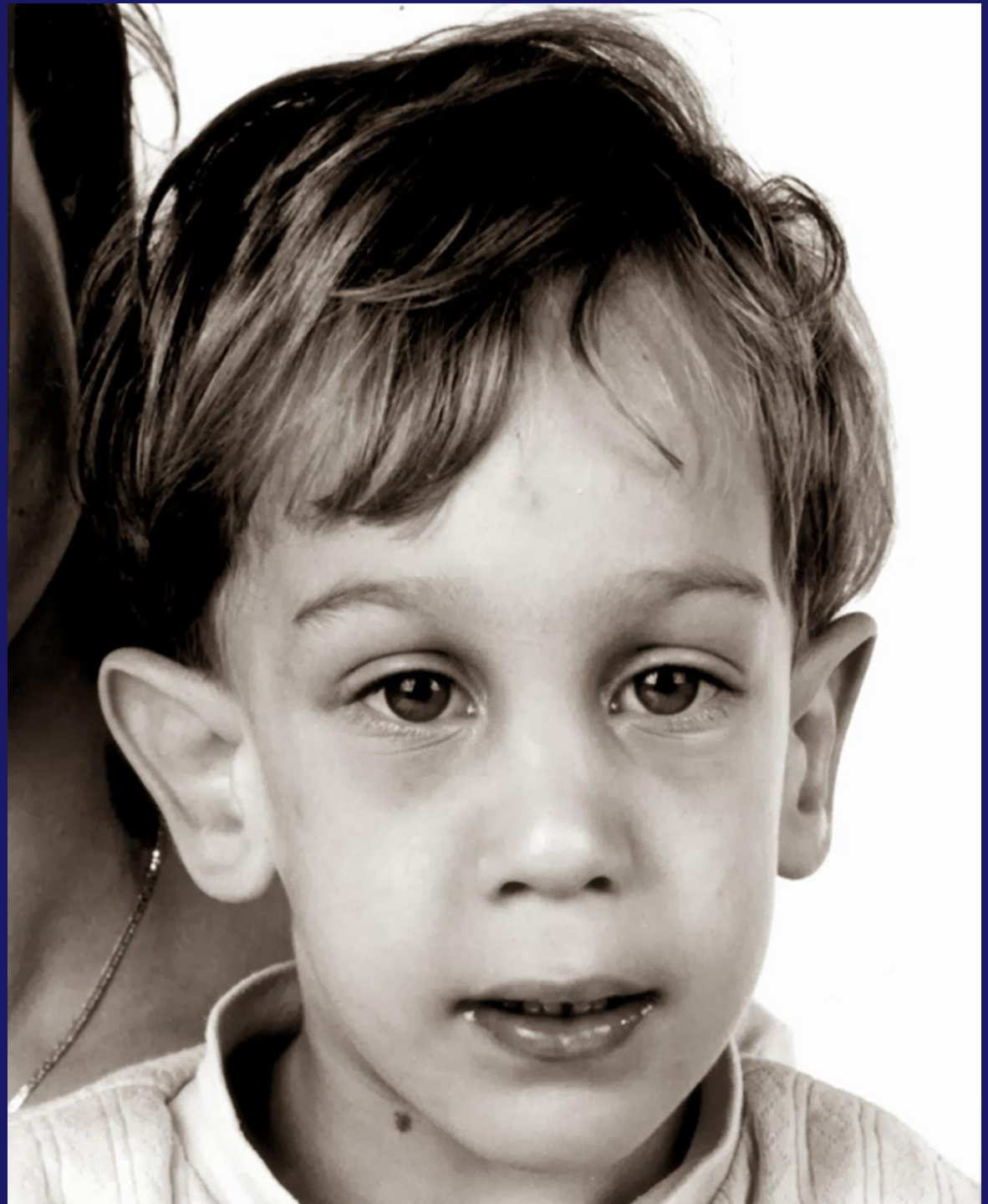
Most of the triplet repeat disorders are autosomal dominant but there is one autosomal recessive disorder, Friedreich ataxia, and fragile X syndrome, which is X linked.

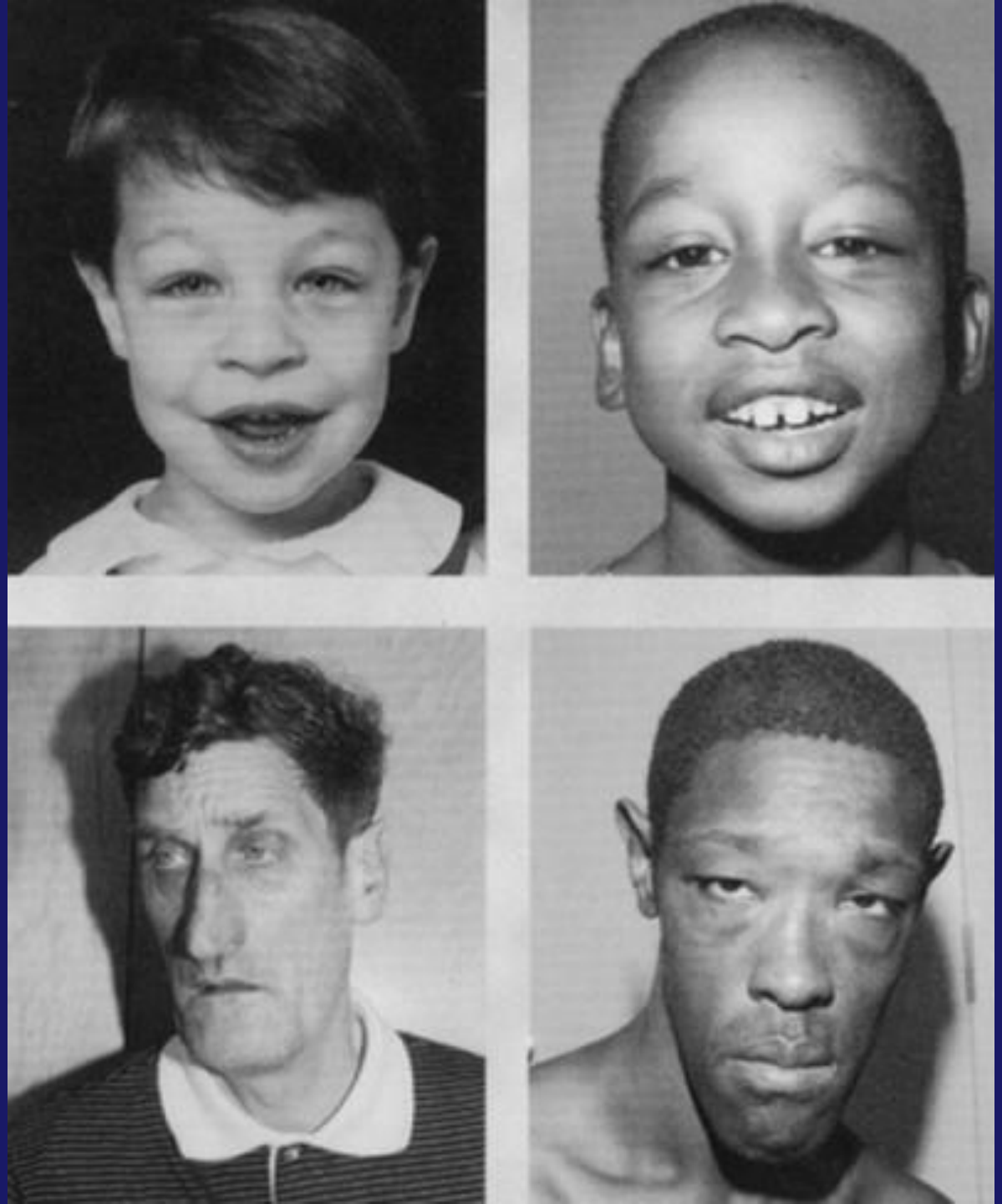
متلازمة الصبغي الهش



Normal X-chromosome

Fragile-X chromosome



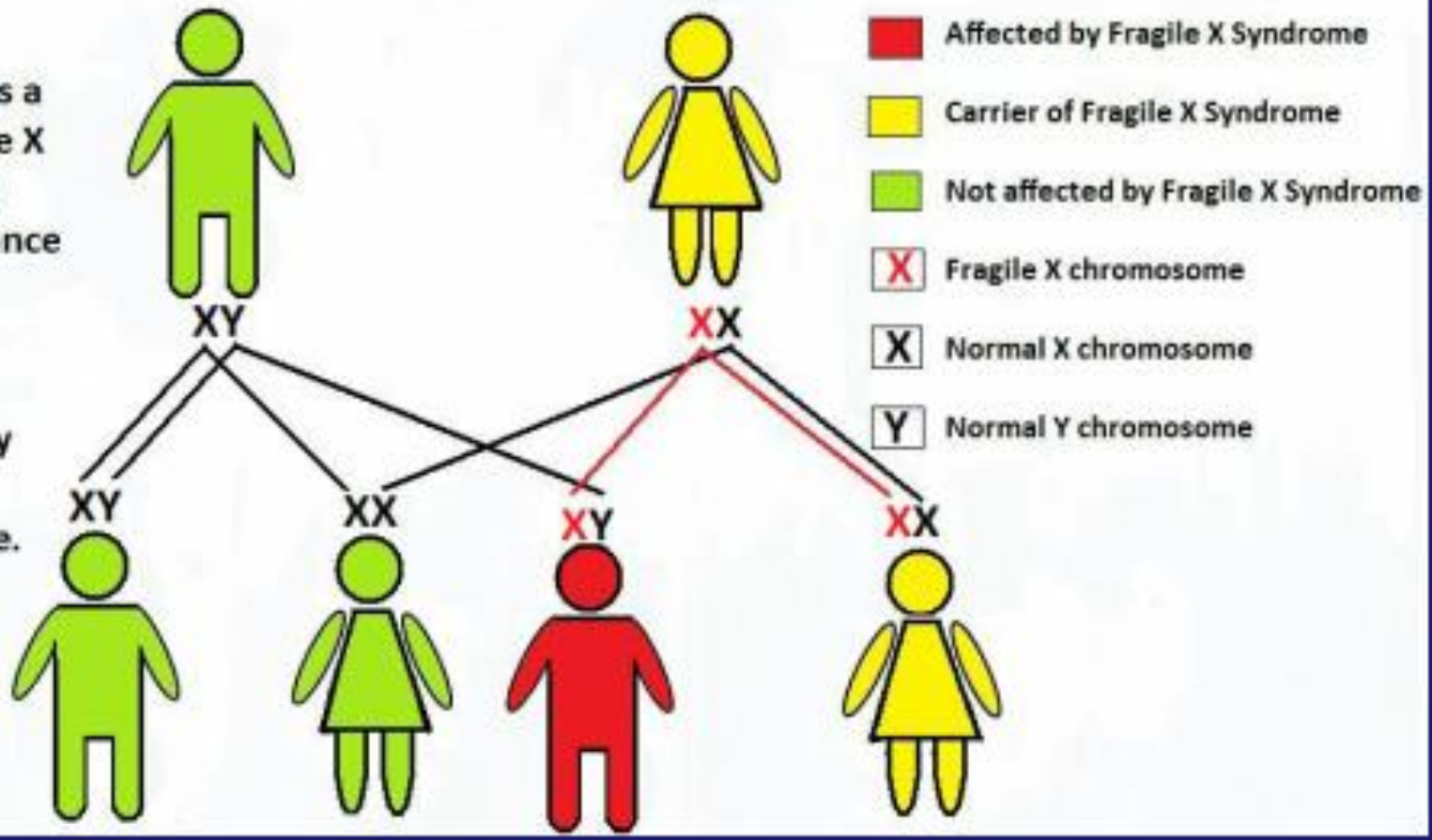


- normal structure
- broad forehead
- elongated face
- large prominent ears
- strabismus (crossed eyes)
- highly arched palate
- hyperextensible joints
- hand calluses
  (from self-abuse)
- pectus excavatum
  (indentation of chest)
- mitral valve prolapse
  (benign heart condition)
- enlarged testicles
- hypotonia (low muscle tone)
- soft, fleshy skin
- flat feet
- seizures (in about 10 percent)

Fragile X Syndrome Inheritance for Non-symptomatic Parents

When the mother is a carrier of the fragile X chromosome, each child has a 50% chance of inheritance.

Since girls have 2 X chromosomes, they are less severely affected as boys are.



Fragile X syndrome

The prevalence of significant learning difficulties in males due to fragile X syndrome is about 1 in 4000 (Fig. 9.13 and Box 9.9). This condition was initially diagnosed on the basis of the cytogenetic appearance of an apparent break (a fragile site) in the distal part of the long arm of the X chromosome. Diagnosis is now achieved by molecular analysis of the trinucleotide repeat expansion in the relevant gene.

Although it is inherited as an X-linked disorder, some 40% to 50% of female carriers have learning difficulties (usually mild to moderate). More puzzling is the observation that males can be unaffected but transmit the condition through their daughters to their grandsons. This is not possible in haemophilia or Becker muscular dystrophy, for example, where a male cannot inherit the condition from his family and transmit the condition to his children without himself being affected. This can occur in fragile X because the triplet repeat expansion varies in its nature with its size. The normal range of repeat numbers is up to about 45 repeats; when larger than that the block of repeats becomes increasingly unstable but continues to permit fragile X gene expression until a 'full mutation' is reached at about 200 repeats. From 55 repeats to 200 repeats is known as the 'premutation' range, and a male can inherit a premutation and transmit it to his daughters (who will all be carriers) while being intellectually normal and without the physical features of fragile X.

Because these full mutations always arise from expansion of premutations, and never directly from normal genes, the mothers of affected males have to be carriers of a premutation or full mutation. Offering referral for genetic counselling is therefore appropriate for all fragile X families, especially as there can be associated disorders for premutation carriers in adult life.

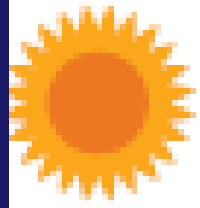
Figure 9.13 A child with fragile X syndrome. At this age, the main physical feature is often the prominent ears.

Box 9.9 Clinical findings in males in fragile X syndrome

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

FXS: Common Physical Features

- Elongated face & Broad forehead
- Large, prominent ears
- High arched palate
- Prominent jaw, Dental crowding
- Macro-orchidism (post-pubertal)
- Strabismus (squint)
- Murmur, Mitral valve prolapse, cardiomegaly, dilation of aorta
- Hypotonia & joint laxity
- Flat feet, Hollow chest, Scoliosis



Fragile X syndrome is the second most common genetic cause of severe learning difficulties after Down syndrome

Mitochondrial or cytoplasmic inheritance

Mitochondria are cytoplasmic organelles that function as a cellular compartment within which many different metabolic pathways are located, including most prominently the production of energy by oxidative phosphorylation. They contain their own DNA (mtDNA), but most of the proteins involved in mitochondrial metabolic reactions are encoded in the nuclear genome. The mtDNA encodes proteins involved in oxidative phosphorylation together with the RNA and proteins necessary for mitochondrial protein synthesis.

Each cell contains thousands of copies of the mitochondrial genome. Inherited disorders of mitochondrial function may result from mutations in the nuclear genome or, less often, from mutations in the mitochondrial genome (mtDNA). In disorders of the mtDNA, the mutation may be present in all or only some of the mitochondria, so that the tissues affected and the severity of the condition can be highly variable. Mutations in mtDNA cause overlapping clusters of disease phenotypes, with high-energy tissues such as muscle, brain, the heart, and the retina being more commonly affected (e.g. Leber hereditary optic neuropathy and various mitochondrial myopathies and encephalopathies, such as MERFF, MELAS, NARP). These conditions are described in more detail in Chapter 27 – Inborn errors of metabolism. Diseases caused by mutations in mtDNA show only maternal transmission, because only the egg contributes mitochondria to the zygote.

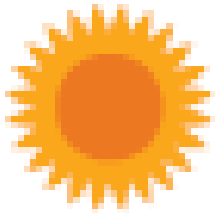
الختم وثنائية الصبغي أحادية الوالد

Imprinting and uniparental disomy

In the past, it was assumed that the activity of a gene is the same regardless of whether it is inherited from the mother or father. It has been shown that the expression of some genes is influenced by the sex of the parent who transmitted it. This phenomenon is called 'imprinting'. If one copy of a gene is said to be imprinted, that copy is switched off in at least some tissues.

An example involves Prader–Willi syndrome (PWS; hypotonia, developmental delay, hyperphagia, and obesity). The PWS chromosomal region is found at 15q11–13 (i.e. at bands 11 to 13 on the long arm of chromosome 15). Both the paternal and the maternal copies of this chromosomal region have to function for normal development. In the absence of a (functioning) paternal copy of this region, a child will develop PWS, as some genes are maternally imprinted. By contrast, the failure to inherit a (functioning) maternal copy of this chromosomal region results in an entirely different condition, Angelman syndrome, leading to severe cognitive impairment, a characteristic facial appearance, ataxia, and epilepsy because of a lack of expression of the *UBE3A* gene and the paternal copy being imprinted. There are two main ways that a child can develop one or other condition:

- deletion de novo (Fig. 9.14) – parental chromosomes are normal, and a deletion occurs as a new mutation in the child. If the deletion occurs on the paternal chromosome 15, the child has PWS. If the deletion affects the maternal chromosome 15, the child has Angelman syndrome
- uniparental disomy (Fig. 9.15) – this is when a child inherits two copies of a chromosome from one parent and none from the other parent. In PWS the affected child has no paternal (but two maternal) copies of chromosome 15q11–13. In Angelman syndrome the affected child has no maternal (but two paternal) copies of chromosome 15q11–13. This can be detected with DNA analysis
- there exist other, less common mechanisms that can lead to these conditions.



Imprinting is the unusual property of some genes that express only the copy derived from the parent of a given sex

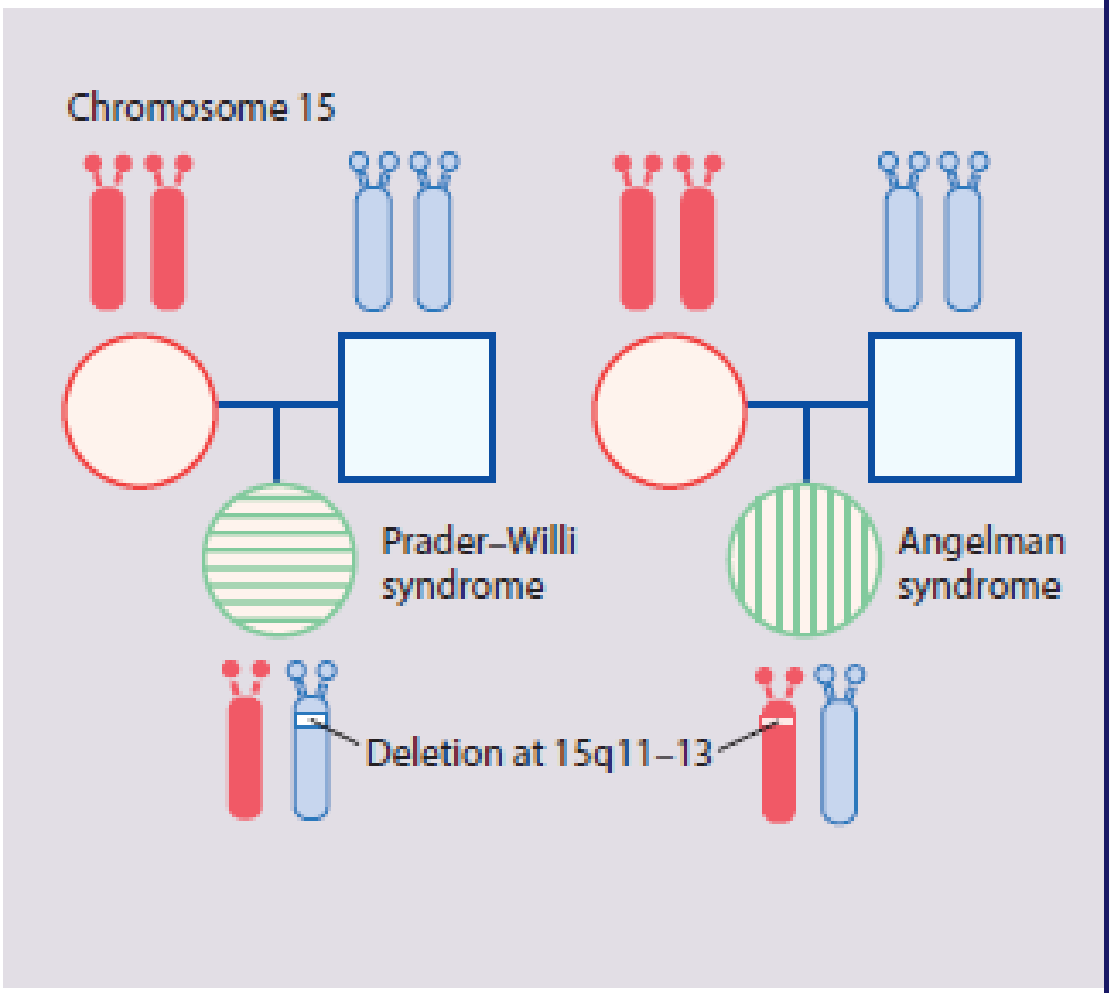


Figure 9.14 Genetic disorder resulting from deletion of an imprinted gene. If the deletion occurs on chromosome 15 inherited from the father, the child has Prader–Willi syndrome. If the deletion occurs on chromosome 15 from the mother, the child has Angelman syndrome.

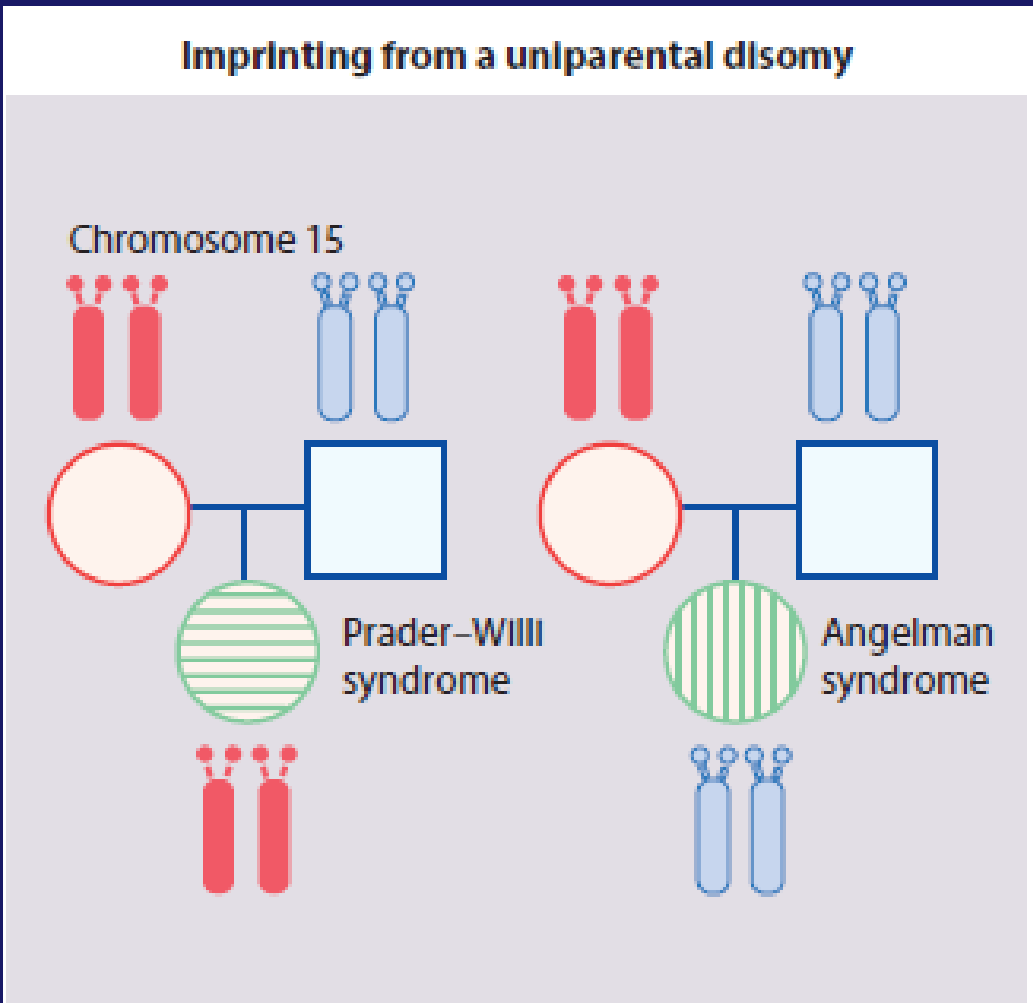


Figure 9.15 Genetic disorder resulting from uniparental disomy affecting imprinted chromosome region. A child who inherits two maternal chromosome 15s will have Prader–Willi syndrome. A child who inherits two paternal chromosome 15s will have Angelman syndrome.

Polygenic, multifactorial or complex inheritance

There is a spectrum in the aetiology of disease, from environmental factors (e.g. trauma) at one end to purely genetic causes (e.g. Mendelian disorders) at the other. Between these two extremes are many disorders that result from the interacting effects of several genes (hence the term polygenic) with or without the influence of environmental or other unknown factors, including chance (multifactorial or complex). These terms are used interchangeably (Box 9.10).

Variation in quantitative traits, such as height and intelligence, results from complex interactions between environmental factors and multiple genetic influences. The environmental factors include early-life (including intrauterine) experiences. These parameters are thought to show a Gaussian (normal) distribution in the population. Similarly, the liability of an individual to develop a disease of multifactorial or polygenic aetiology has a Gaussian distribution. The condition occurs when a certain threshold level of liability is exceeded. Relatives of an affected person show an increased liability due to inheritance of genes conferring susceptibility, and so a greater proportion of them than in the general population will fall beyond the threshold and will manifest the disorder (Fig. 9.16). The risk of recurrence of a polygenic disorder in a family is usually low and is most significant for first-degree relatives. Empirical recurrence risk data are used for genetic counselling. They are derived from family studies that have reported the frequencies at which various family members are affected. Factors that increase the risk to relatives are:

- having a more severe form of the disorder, e.g. the risk of recurrence to siblings is greater in bilateral cleft lip and palate than in unilateral cleft lip alone
- close relationship to the affected person, e.g. overall risk to siblings or children is greater than to more distant relatives
- multiple affected family members, e.g. the more siblings already affected, the greater the risk of recurrence
- sex difference in prevalence, with the recurrence risk greater in the more commonly affected sex and if the affected individual is of the less commonly affected sex.

The phenotype (clinical picture) of a disorder may have a heterogeneous (mixed) basis in different families, e.g. hyperlipidaemia leading to atherosclerosis and coronary heart disease can be due to a single gene disorder such as autosomal dominant familial hypercholesterolaemia, but some forms of hyperlipidaemia are polygenic and result from an interaction of the effect of several genes and dietary factors on various lipoproteins.

In some complex disorders, such as Hirschsprung disease, the molecular genetic basis and the important contribution of new mutations are becoming clear. In many multifactorial disorders, however, the 'environmental factors' remain obscure. Clear exceptions include dietary fat intake and smoking in atherosclerosis, and viral infection in insulin-dependent diabetes mellitus. For neural tube defects, the risk of recurrence to siblings is lowered from about 4% to 1% or less in future pregnancies if the mother takes folic acid before conception and in the early weeks of pregnancy.

Multifactorial, polygenic or complex inheritance

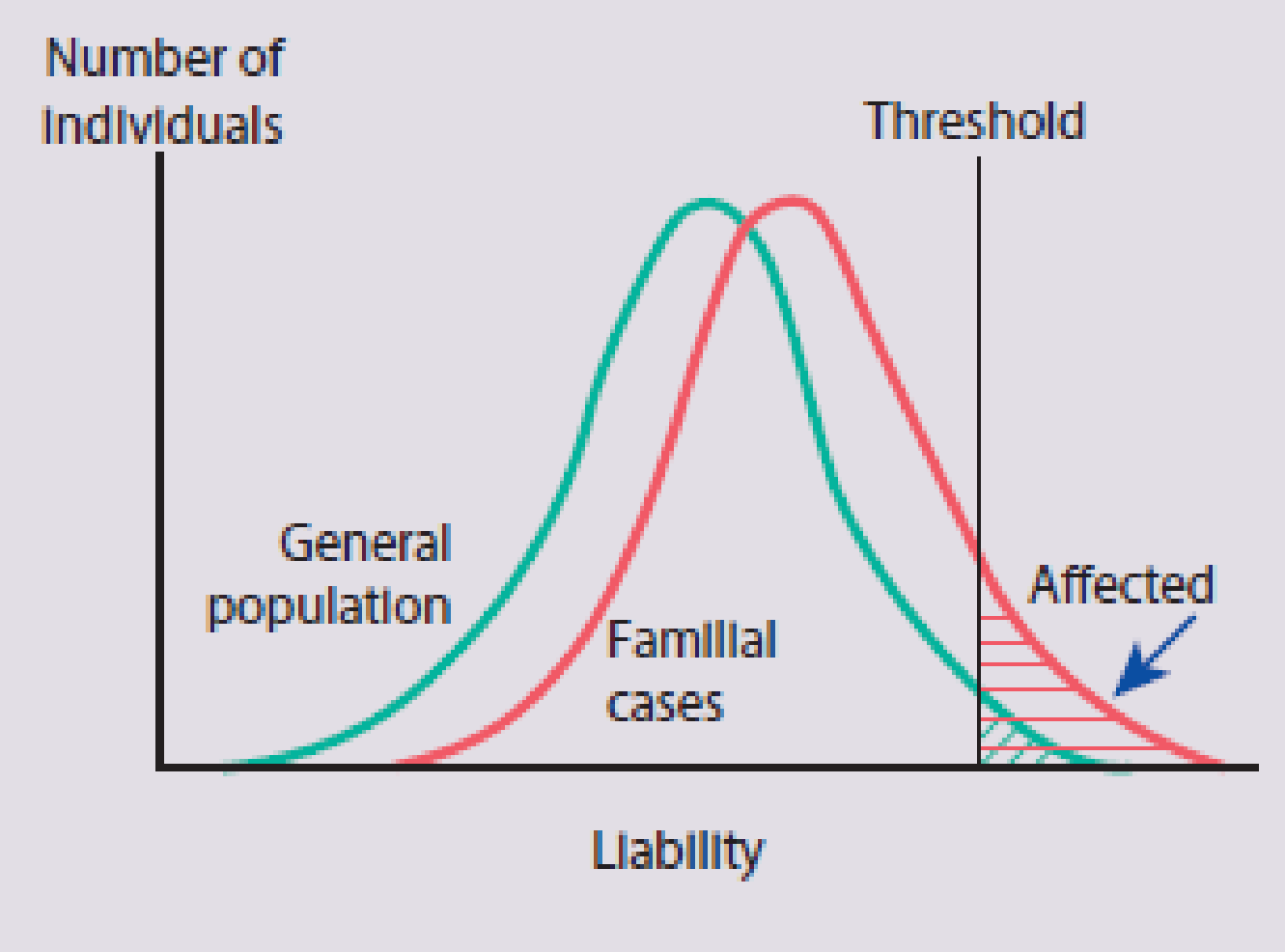


Figure 9.16 Diagram showing the increased liability to a multifactorial disorder in relatives of an affected person.

Box 9.10 Conditions often associated with multifactorial (polygenic, complex) inheritance

Congenital malformations:

- neural tube defects (anencephaly and spina bifida)
- congenital heart disease
- cleft lip and palate
- pyloric stenosis
- developmental dysplasia of the hip (DDH)
- talipes equinovarus
- hypospadias.

Childhood:

- atopy (especially asthma and eczema)
- epilepsy
- diabetes mellitus type 1 (insulin-dependent diabetes).

Adult life:

- atherosclerosis and coronary artery disease
- diabetes mellitus type 2
- Alzheimer disease
- malignancy (especially the common cancers, e.g. breast and colorectal cancer)
- hypertension
- cerebrovascular disease (especially stroke).

علم الشوهات (الشوهيات)

Dysmorphology

The term 'dysmorphology' literally means 'the study of abnormal form' and refers to the assessment of birth defects and unusual physical features that have their origin during embryogenesis.

Pathogenic mechanisms

Malformation

التشوه

A primary structural defect occurring during the development of a tissue or organ, e.g. spina bifida, cleft lip, and palate.

Deformation

التشويه

Implies an abnormal intrauterine mechanical force that distorts a normally formed structure, e.g. joint contractures or pulmonary hypoplasia due to fetal compression caused by severe oligohydramnios.

Disruption

التخرب (التمزق)

Involves destruction of a fetal part that initially formed normally, e.g. amniotic membrane rupture may lead to amniotic bands that may cause limb reduction defects. Drugs such as phenytoin, warfarin, or thalidomide can cause teratogenic effects. Viruses such as rubella or cytomegalovirus may damage the normally formed embryo or fetus.

خلل التنسج

Dysplasia

Refers to abnormal cellular organization or function of specific tissue types, e.g. skeletal dysplasias, dysplastic kidney disease.

Clinical classification of birth defects

Single-system defects

عيوب الجهاز المفردة

These include single congenital malformations, such as spina bifida, which are often multifactorial in nature with fairly low recurrence risks.

المتوالية

Sequence

Refers to a pattern of multiple abnormalities occurring after one initiating defect. 'Potter syndrome' (fetal compression and pulmonary hypoplasia) is an example of a sequence in which all abnormalities may be traced to one original malformation causing failure of fetal urine excretion from renal agenesis or posterior urethral valves.

التراابط

Association

A group of malformations that occur together more often than expected by chance, but in different combinations from case to case, e.g. *v*ertebral anomalies, *a*nal atresia, *c*ardiac defects, *t*racheo-*o*esophageal fistula, *r*enal anomalies, *l*imb defects (VACTERL) association.

Syndrome

المتلازمة

When a particular set of multiple anomalies occurs repeatedly in a consistent pattern and there is known or thought to be a common underlying causal mechanism, this is called a 'syndrome'. Multiple malformation syndromes are often associated with moderate or severe cognitive impairment and may be due to:

- chromosomal defects
- a single gene defect (dominant, recessive, or sex linked)
- exposure to teratogens such as alcohol, drugs (especially anticonvulsants such as valproate, carbamazepine, and phenytoin), or viral infections during pregnancy
- unknown cause.

Syndrome diagnosis

Although most syndromes are individually rare, recognition of a dysmorphic syndrome is worthwhile as it may give information regarding:

- risk of recurrence
- prognosis
- likely complications, which can be sought and perhaps treated successfully if detected early
- the avoidance of unnecessary investigations
- experience and information, which parents can share with other affected families through family support groups.

Examples of syndromes recognizable by facial appearance are shown in Figs 9.17–9.19 (see also Boxes 9.11–9.13). The importance and impact of syndrome diagnosis is demonstrated in Case History 9.1. Databases are available to assist with the recognition of thousands of multiple congenital anomaly syndromes (e.g. London Dysmorphology Database and Pocket Similarity Search using Multiple-Sketches).

Syndromes recognized by 'Gestalt' (clinical recognition)

متلازمة نونان

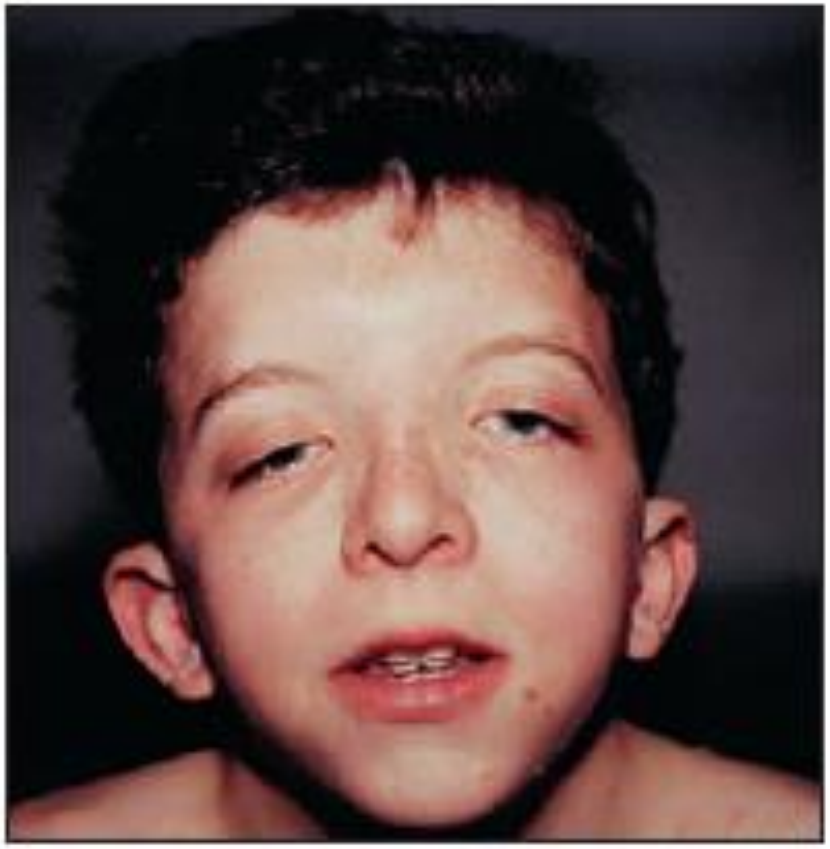


Figure 9.17 Noonan syndrome affects both males and females. There are some similarities to the phenotype in Turner syndrome, but it is caused by mutation in an autosomal dominant gene and the karyotype is normal.

Box 9.11 Clinical features of Noonan syndrome

- Characteristic facies
- Occasional mild learning difficulties
- Short webbed neck with trident hair line
- Pectus excavatum
- Short stature
- Congenital heart disease (especially pulmonary stenosis, atrial septal defect)

متلازمة ويليام

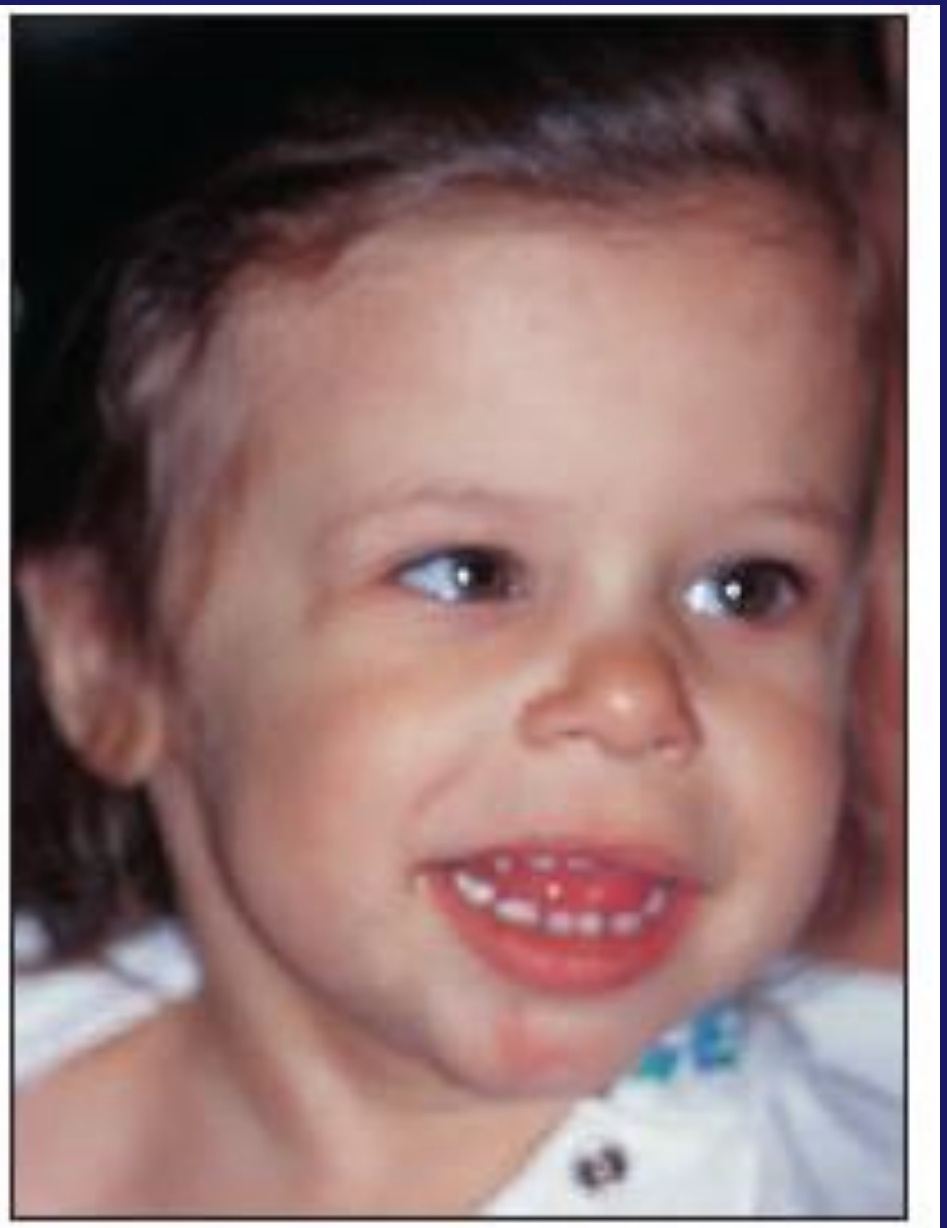
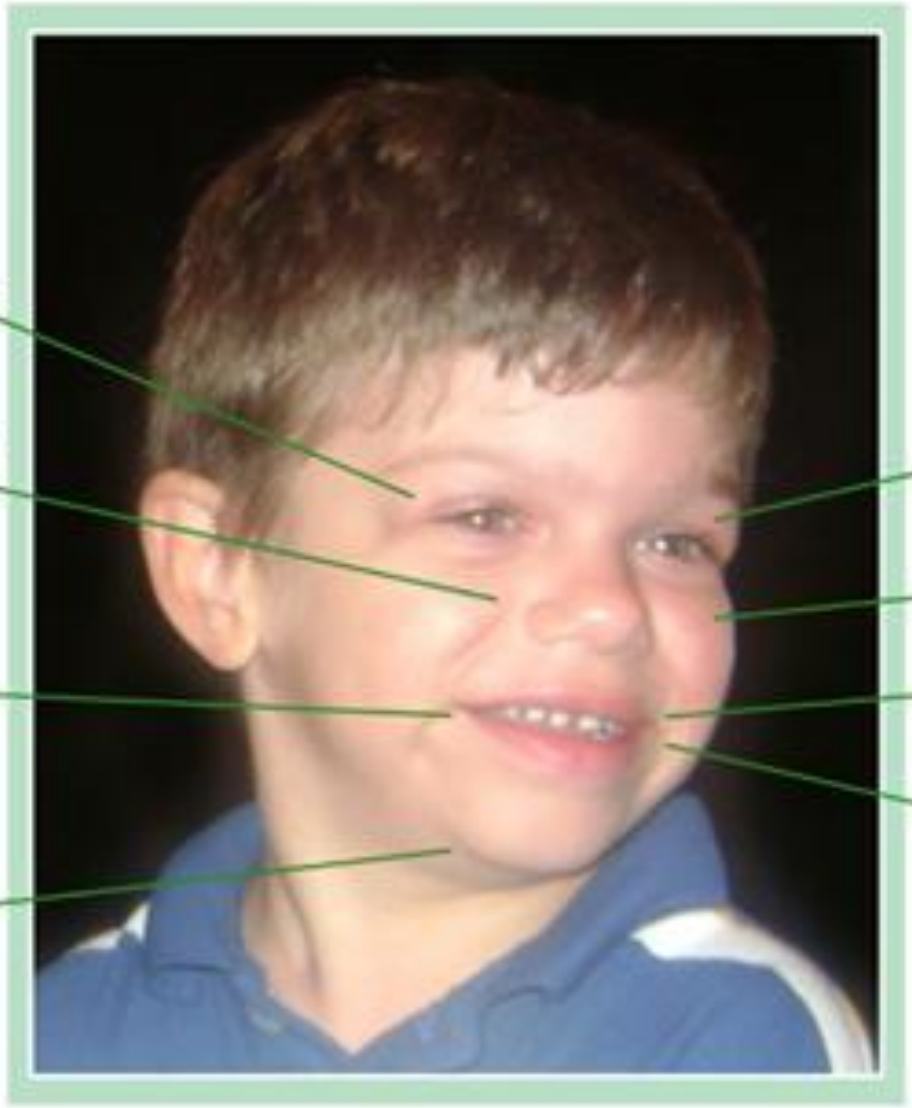


Figure 9.18 Williams syndrome is usually sporadic.

Facial Features of Williams Syndrome



Box 9.12 Clinical features of Williams syndrome

- Short stature
- Characteristic facies
- Transient neonatal hypercalcaemia (occasionally)
- Congenital heart disease (supravalvular aortic stenosis)
- Mild-to-moderate learning difficulties

متلازمة برادر- ويلي

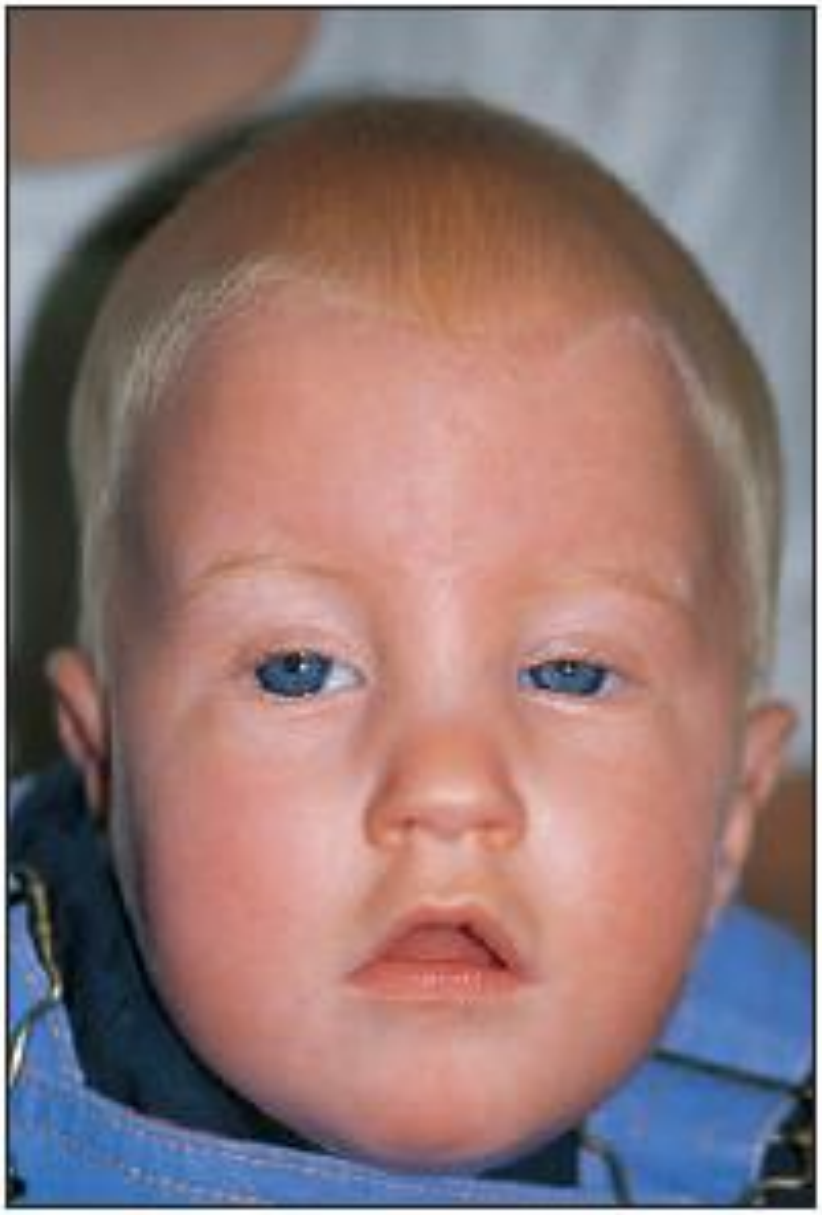


Figure 9.19 Prader–Willi syndrome.

Box 9.13 Clinical features of Prader–Willi syndrome

- Characteristic facies
- Hypotonia
- Neonatal feeding difficulties
- Faltering growth in infancy
- Obesity in later childhood
- Hypogonadism
- Developmental delay
- Learning difficulties

Gene-based therapies

The treatment of most genetic disorders is based on conventional therapeutic approaches.

Gene therapy involves the repair, suppression, or artificial introduction of genes into genetically abnormal cells with the aim of curing the disease and is at an experimental stage for most genetic conditions being studied. There are still many technical and safety issues to be resolved. Gene therapy has been initiated in adenosine deaminase deficiency (a rare recessive immune disorder), malignant melanoma, and cystic

Summary

Dysmorphology

- Comprises birth defects and abnormal clinical features originating during embryogenesis.
- May be a malformation, deformation, disruption, or dysplasia.
- May be classified as a single-system defect, sequence, association, or syndrome.
- Syndromes are recognized by 'Gestalt', which may be aided by dysmorphology databases.

Case history 9.1

Syndrome diagnosis and genetic counselling

Sean, the second child of healthy parents, was born at term by emergency caesarean section for fetal distress. The pregnancy had been uneventful and no abnormalities were detected on antenatal ultrasound scan. He developed respiratory distress and investigation triggered by a cardiac murmur revealed an interrupted aortic arch and ventricular septal defect that required surgical correction in the neonatal period.

The parents asked about recurrence risk for congenital heart disease and were referred to the genetic clinic. At that time, Sean was thriving and early developmental progress appeared normal. On examination, there were minor dysmorphic features, including a short philtrum, thin upper lip, and prominent ears (Fig. 9.20). There was no family history of congenital heart disease or other significant problems and no abnormalities were detected on examination of the parents.

Because of an association between outflow tract abnormalities of the heart and deletions of chromosome 22, cytogenetic analysis was performed using FISH. A submicroscopic deletion of the long arm of one chromosome 22 (band 22q11) was detected. Other features of DiGeorge syndrome (hypocalcaemia and T-cell deficiency), which occurs with the same chromosome deletion, were excluded but could have been important in Sean's medical management.

Parental chromosome analysis showed no deletion at chromosome 22q11 in either parent, indicating a low recurrence risk for future pregnancies because gonadal mosaicism for this deletion is very rare. The older sibling was also normal on testing. Because the parents had normal karyotypes, their own brothers and sisters were not required to be tested.

Identification of a 22q11 deletion indicated that other associated problems were likely. Subsequently, Sean required assessment by a multidisciplinary child development team (for developmental delay), which led to the formal assessment of his educational needs and the recommendation for placement in an appropriate school for children with learning difficulties, input from a clinical psychologist when behavioural problems appeared (ritualistic behaviour and obsessional tendencies), input from speech therapist and plastic surgeon (indistinct speech due to velopharyngeal incompetence), and audiology review (conductive hearing loss due to recurrent otitis media).

The impact of the diagnosis and its implications was considerable for the family and the parents needed support from a variety of professionals while coming to terms with the various problems as they became apparent. Written information and details of the 22q11 support group were given to the parents. Medical care was coordinated by the paediatrician.

There was the additional worry for the family about a subsequent pregnancy. Fetal echocardiography showed no evidence of congenital heart disease, and the offer of invasive tests for cytogenetic analysis was declined because of the low chance of recurrence and the risk of miscarriage from the test. The baby was born unaffected, with chromosome studies performed on a cord blood sample revealing no abnormality.

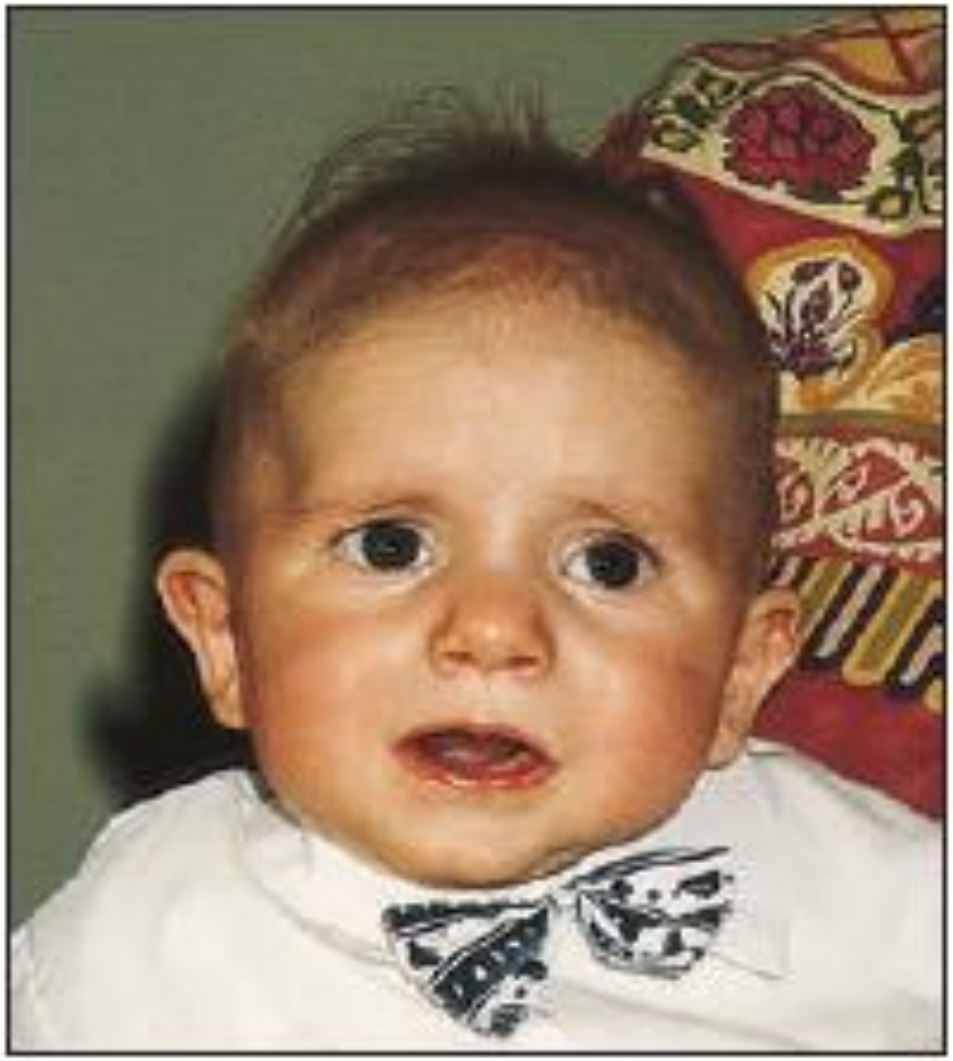


Figure 9.20 Sean's facial appearance showing the short philtrum (vertical groove in the upper lip), thin upper lip, and prominent ears.

fibrosis, and some clinical benefit has been reported in a few patients. At present, it is generally accepted that gene therapy should be limited to somatic (not germ-line) cells, so that the risk of adversely affecting future generations is minimized.

However, other treatments based on a genetic understanding of disease are being introduced into practice. Current areas of research include Duchenne muscular dystrophy, cystic fibrosis and retinitis pigmentosa.

An increasing understanding of the molecular mechanisms underlying the pathophysiology of many genetic conditions has also led to new targeted drug treatments in several condtions, including enzyme replacement therapy for certain inborn errors of metabolism and mTOR inhibitor therapy in tuberous sclerosis.

Genetic services

In the UK, all health regions have a clinical genetics centre where specialist genetic services are provided by consultants and other medical staff, genetic counsellors, and laboratory scientists. Specialist clinical genetic assessment and genetic counselling are provided at the centre and in a network of clinics throughout the region. Genetic investigations can be accessed through these clinical services as well as directly through primary and secondary care. Increased recognition of disorders antenatally has necessitated expansion of perinatal genetic services in addition to paediatric and adult services.

Genetic investigations

For many years, genetic investigation relied on determining the karyotype by visualization of the chromosomes with light microscopy. This has been transformed by the tremendous advances in molecular testing (Table 9.3).

DNA analysis using polymerase chain reaction (PCR) allows rapid analysis on small samples. Its main impact for genetic counselling is:

- confirmation of a clinical diagnosis of an increasing number of single gene disorders
- detection of female carriers in X-linked disorders, e.g. Duchenne and Becker muscular dystrophies, haemophilia A and B
- carrier detection in autosomal recessive disorders, e.g. cystic fibrosis
- presymptomatic diagnosis in autosomal dominant disorders, e.g. Huntington disease, myotonic dystrophy, familial cancer syndromes
- antenatal diagnosis of an increasing number of Mendelian conditions.

These are accomplished by the following methods.

Mutation analysis

For an increasing number of Mendelian disorders, it is possible to directly detect the actual mutation causing the disease. This provides very accurate results for confirmation of diagnosis, and presymptomatic or predictive testing. Identifying the mutation in an affected individual may be very time consuming, but once this has been done, testing other relatives is usually fairly simple. Examples are:

- deletions – large deletion mutations, of at least one exon, are common in a variety of disorders including Duchenne and Becker muscular dystrophies, alpha-thalassaemia, and 21-hydroxylase deficiency (congenital adrenal hyperplasia)
- point mutations and small deletions – these can be readily identified if the same mutation causes all cases of the disorder, as in sickle cell disease. For most disorders, however, there is a spectrum of mutations. About 78% of cystic fibrosis carriers in the UK possess the ΔF508 mutation, but over 900 other mutations have been identified. Most laboratories test for a certain number of the most common mutations in the population they serve. This means that patients must be informed of the small risk that a mutation will not be detected

- trinucleotide repeat expansion mutations – these can be readily identified because the mutation in a given disease is virtually always at the same site and can be amplified from the same oligo-DNA primers used in the amplification by PCR: the only difference is the size of the repeat sequence, which can be determined from the size of the DNA fragment containing the repeat.

Next-generation sequencing

It is now possible to generate large volumes of DNA sequence data in a rapid and cost-effective fashion. These techniques of high-throughput sequencing are used to enable:

- gene panel testing – where a specific set of genes is sequenced, for example all the genes known to be relevant to a specific disease presentation (e.g. retinal degeneration, cardiomyopathy, infantile-onset epilepsy)
- whole exome sequencing – the coding regions of the genome are sequenced to determine variants, which are then analyzed to interpret the findings

- whole genome sequencing – the whole genome is sequenced, including noncoding regions. This is predominantly used as a research tool but development in this field is rapid and whole genome sequencing (WGS) has technical advantages over whole exome sequencing, so that the current use of whole exome sequencing is likely to be replaced by WGS over the next few years.

Recent studies have focused on implementation of next-generation sequencing into clinical practice. The Deciphering Developmental Disorders study utilized exome sequencing in a large cohort of undiagnosed patients with developmental delay. The results are being used to compile a database (DECIPHER) of genotypes and related phenotypes.

In the UK, the 100 000 Genomes Project is utilizing WGS to study a wide range of clinical conditions in adults and children (see Further Reading).

Table 9.3 Genetic investigations

Investigation	Application
Cytogenetic analysis – karyotype	Chromosomes stained and visualized under a microscope Detects alterations in chromosome number and structural rearrangements; this method is being replaced by molecular methods such as comparative genomic hybridization
Molecular cytogenetic analysis – fluorescence in situ hybridization (FISH)	Fluorescent-labelled DNA probes to detect the presence, number, and chromosomal location of specific chromosomal sequences Useful for microdeletion syndromes
Microarray comparative genomic hybridization	Detects chromosomal imbalances using thousands of DNA probes to investigate a whole genome with much greater sensitivity than cytogenetic methods
PCR	Amplification of a specific target site within the genome, which then permits the conventional Sanger sequencing of the amplified DNA
Next generation sequencing	Rapid sequencing of whole genomes or of selected loci within the genome
Linkage disequilibrium and genome-wide association studies	Comparing the frequency of combinations of alleles at nearby loci in a given population to identify genetic variants associated with specific diseases through a common ancestral origin

Genetic counselling

The main aims of genetic counselling are supportive and educational. Genetic counselling aims to support and provide information for individuals, couples, and families:

- to understand their situation
- to make their own decisions about managing the disease or risk of disease, including decisions about genetic testing and reproduction
- to adjust to their situation of being affected by or at risk of the genetic condition.

A primary goal of genetic counselling is to provide information to allow for greater autonomy and choice in reproductive decisions and other areas of personal life. Avoiding additional cases of genetic disease in a family may be a consequence of genetic counselling but is not the primary aim. The elements of genetic counselling include:

- listening to the questions and concerns of the patient, or family
- establishing the correct diagnosis – this involves detailed history, examination, and appropriate investigations that may include chromosome or DNA or other molecular genetic analysis, biochemical tests, X-rays, and clinical photographs. Despite extensive investigation, including searching databases, the diagnosis may remain unknown, e.g. in children with learning disability and normal appearance or only mild and nonspecific dysmorphic features

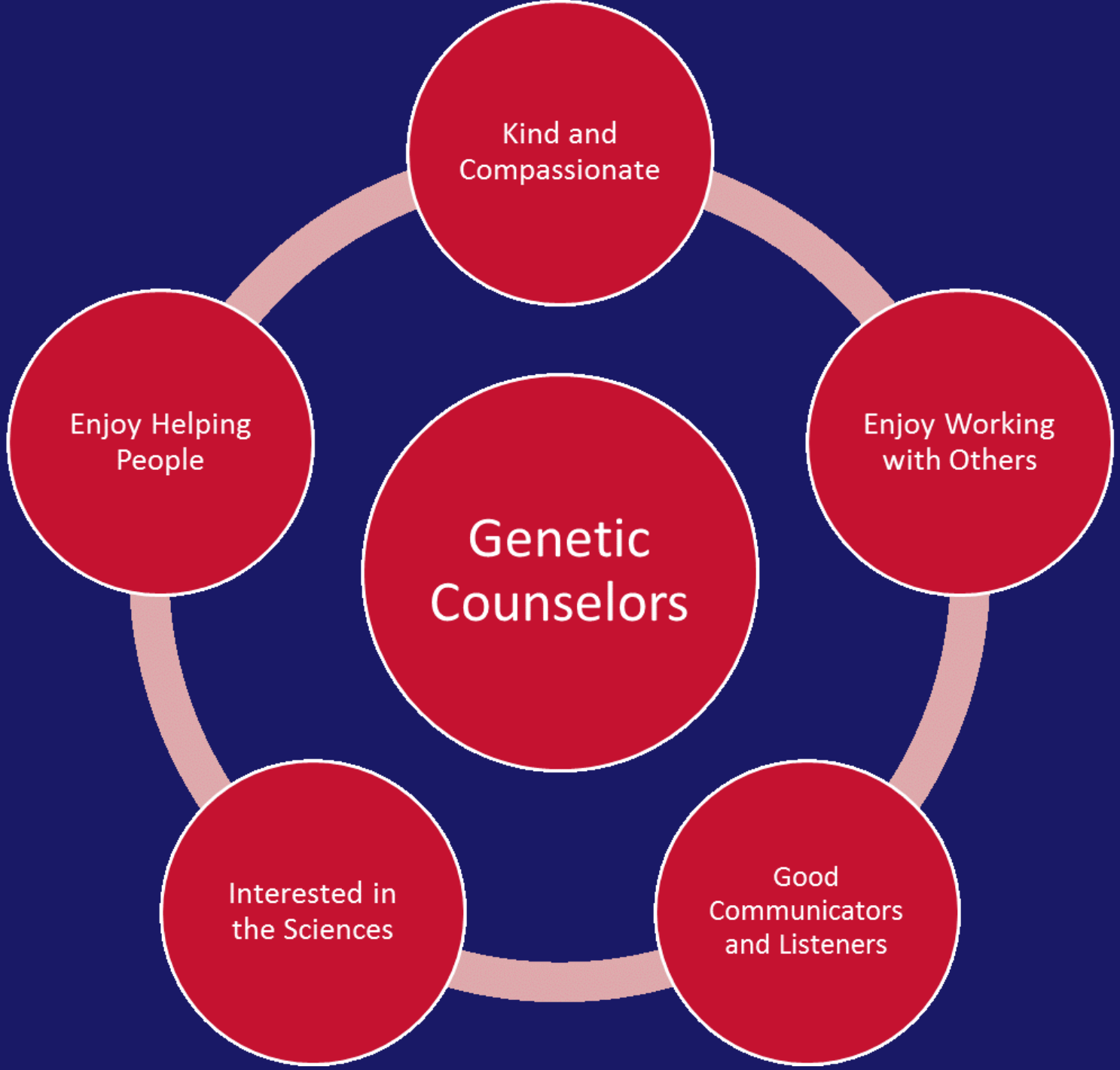
- risk estimation – this requires both diagnostic and pedigree information. Drawing a pedigree of three generations is an essential part of a clinical genetic assessment. The mode of inheritance may be apparent from the pedigree even when the precise diagnosis is not known. In some cases it may not be possible to define a precise recurrence risk and uncertainty may remain, e.g. conditions that only affect one member of a family and are known to follow autosomal dominant inheritance in some families and autosomal recessive inheritance in others (genetic heterogeneity)

- communication – information must be presented in an understandable and unbiased way. Families often find written information helpful to refer back to, and diagrams are often used to explain patterns of inheritance. The impact of saying 'the recurrence risk is 5% or 1 in 20' may be different from saying 'the chance of an unaffected child is 95% or 19 out of 20', and so both should be presented

- discussing options for management and prevention – if there appears to be a risk to offspring, all reproductive options should be discussed. These include not having (any more) children, reducing intended family size, taking the risk and proceeding with pregnancy or having antenatal diagnosis, and selective termination of an affected fetus. For some couples, donor insemination or ovum donation may be appropriate and for others, achieving a pregnancy through in vitro fertilization and preimplantation genetic diagnosis may be possible

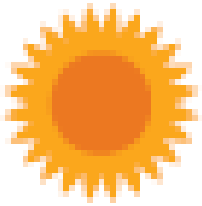
- putting parents in touch with appropriate sources of support, such as the charity Unique, which provides support for families affected by rare chromosomal imbalances.

Counselling should be nondirective, but should also assist in the decision-making process (Box 9.14). Information from lay support groups may also be helpful.


Kind and Compassionate
Enjoy Working with Others
Good Communicators and Listeners
Interested in the Sciences
Enjoy Helping People
Genetic Counselors

Box 9.14 Influences on decisions regarding options for genetic counselling

- Magnitude of risk
- Perceived severity of disorder
- Availability of treatment
- Person's experience of the disorder
- Family size
- Availability of a safe and reliable prenatal diagnostic test
- Parental cultural, religious, or ethical values



Genetic counselling aims to allow parents greater autonomy and choice in reproductive decisions

Presymptomatic (predictive) testing

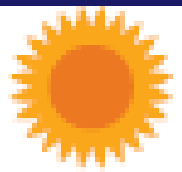
Children may be referred because they are at increased risk of developing a genetic disorder in childhood or adult life.

If the condition is likely to manifest in childhood (e.g. Duchenne muscular dystrophy) or if there are useful medical interventions available in childhood (e.g. screening by colonoscopy for colorectal tumours in children at risk of familial adenomatosis polyposis coli), then genetic testing is appropriate in childhood.

If the child is at risk of a late-onset and untreatable disorder (e.g. Huntington disease), then there is a very strong case for deferring genetic testing until the child becomes an adult, or at least sufficiently mature to be actively involved in seeking the test and can make the decision for himself/herself.

If the child is not at risk of developing the condition but may be a carrier at risk of transmitting the disorder to their future children, then there is also a good case for deferring testing until the young person can participate actively in the decision. There may be less at stake with these reproductive carrier tests than with predictive tests for untreatable disorders but there are still good grounds for caution and for careful discussion before proceeding with such tests.

These difficult issues are often best handled through a process of genetic counselling supporting open and sustained communication within the family and especially between parents and children.



Presymptomatic testing of disorders which manifest in adult life should not be performed until the individual can consent on their own behalf unless there is clear clinical benefit from testing earlier


اسمها سورية


رحمة


Thank you!