Lesson 9

Methods of Human Genetics

Human Genetics is the division of Biological Sciences for the study of basic principles of genetics as applied to human disease. Human genetics encompasses a variety of overlapping fields including: classical genetics, cytogenetics, molecular genetics, biochemical genetics, genomics, statistical and population genetics, developmental genetics, clinical genetics, and genetic counseling.

PEDIGREE ANALYSIS

Pedigree analysis (a pictorial description of a family tree) is the method of human genetics that provides information about the medical history of analyzing family.

Pedigrees can be used in the clinical setting, such as genetic counseling sessions or genetic evaluations, or in genetic research. By analyzing how many family members have a genetic disorder, how these individuals are related, and the sex of the affected individuals, it is often possible to determine the inheritance pattern of the genetic disorder in the family. Together, the inheritance pattern and an accurate diagnosis help the genetic professional provide accurate risk information to the family. This includes risk information for future pregnancies or relatives who are currently unaffected, but who are at risk for developing the disorder.

Pedigree analysis includes three steps:

1. Collecting of the family history.
2. Drawing and Recording Pedigree.
3. Analyzing of pedigree.

Collecting of the family history. The individual who brought the family to the attention of the medical professional or researcher is called a "***proband***". The informant is the individual who was interviewed to obtain the pedigree. The informant may or may not be the same person as the proband. The process of collecting the family history includes

interviewing the informant and asking questions to get the detailed information in three general categories. First, the interviewer asks standard questions about the family members, such as their names, names of their parents, siblings, and children, dates of birth, dates of death, cause of death, and pregnancies. Detailed information is also included about general health problems, their specific symptoms, onset, and age at diagnosis. The interviewer may also ask about the ethnic background of family members and any possible consanguineous relationships (relationships between individuals who are related to each other by blood, such as first cousins). Second, the interviewer may ask general questions to identify common genetic syndromes in the family, such as birth defects, mental retardation, vision and hearing loss, and common genetic disorders found more prevalently in certain ethnic backgrounds. Lastly, the interviewer may collect targeted information about the specific genetic disease for which the family was referred. Information is gathered on the symptoms of the disease, age of onset, and age at diagnosis. These targeted questions help genetic counselors identify the typical course of disease in the family, disease severity, possible variable expression, reduced penetrance, or genetic anticipation.

Note! Pedigrees contain very personal and identifying information about families. It is therefore essential that pedigrees be kept confidential. This is important not only in the genetic counseling clinic or research group, but also within the family.

Drawing and Recording Pedigrees. Pedigrees are hand — drawn or created using special computer software. The standard pedigree typically includes at least three generations.

Figure 1 illustrates some of the symbols that are used in drawing pedigrees. Circles represent females and squares designate males. If the sex of an individual is unknown, a diamond (rhomb) is used. An arrow indicates the proband. This term applies to either a male or a female. A single horizontal line generally connects parents to each other, and vertical lines lead to their offspring. If the parents are related — that is, consanguineous — such as first cousins, a double line connects them. Offspring are called ***sibs*** (short for ***siblings***) and are connected by a horizontal ***sibship line***. Sibs are placed in birth order from left to right and are labeled with Arabic numerals. Parents also receive an Arabic number

designation. A Roman numeral indicates each generation. When a pedigree traces only a single trait, the circles, squares, and diamonds are shaded if the phenotype being considered is expressed and unshaded if not. In some pedigrees, those individuals that fail to express a recessive trait but are known with certainty to be heterozygous carriers have a shaded dot within their unshaded circle or square. If an individual is deceased and the phenotype is unknown, a diagonal line is placed over the circle or square. Diagonal lines stemming from a vertical line connected to the sibship line indicate twins. For identical, or ***monozygotic***, twins, a horizontal line links the diagonal lines. Fraternal, or ***dizygotic***, twins lack this connecting line. A number within one of the symbols represents that number of sibs of the same sex and of the same or unknown phenotypes.

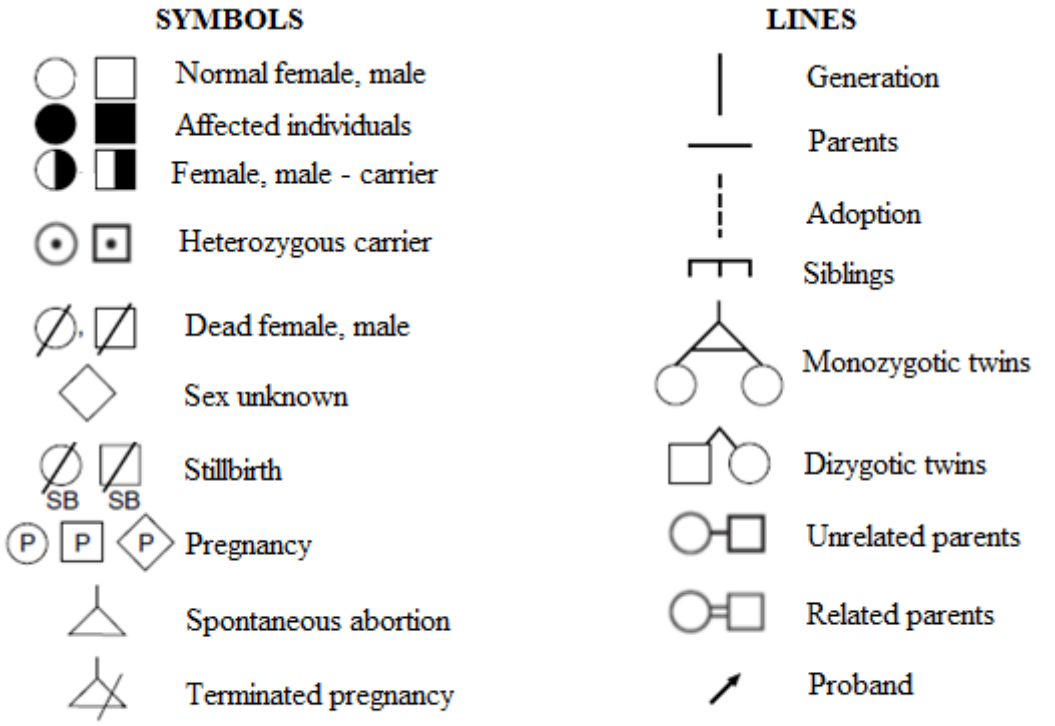


Fig. 1. Pedigree components

Analyzing of pedigree. One of the purposes of analyzing of pedigree is to determine the pattern of inheritance.

There are six patterns of inheritance: *Autosomal Dominant, Autosomal Recessive, X-Linked Dominant, X-Linked Recessive, Y- Linked,* and *Maternal (mithochondrial) inheritance.*

Autosomal Dominant inheritance

The common features:

1. Dominant traits show a *vertical pattern* of inheritance: the trait shows up in every generation.
2. The trait occurs with the same frequency in both sexes.

Figure 2 illustrates a typical pedigree of the trait inherited in an autosomal dominant manner.

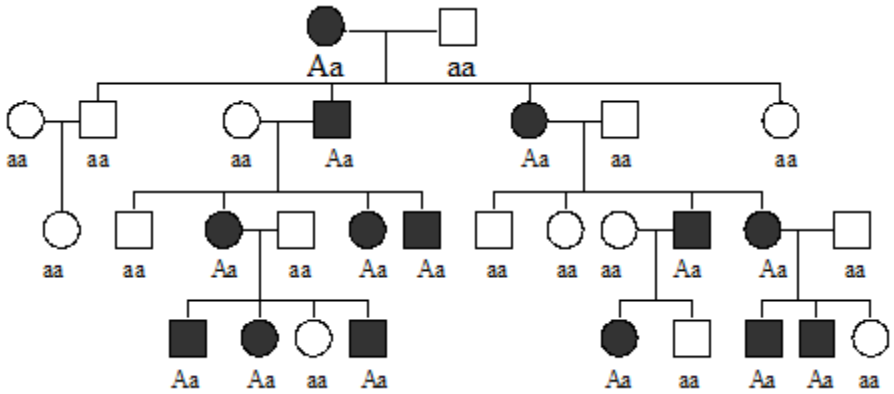


Fig. 2. A family pedigree of Autosomal Dominant inheritance

Examples of Human Disorders Inherited in an Autosomal Dominant Manner

Achondroplasia

Achondroplasia is a common form of dwarfism associated with a defect in the growth of long bones (fig.3). The condition occurs in 1 in 15,000 to 40,000 newborns.

Fig.3. The appearance of girl with Achondroplasia

Autosomal Recessive inheritance

The common features:

1. *Rare* recessive traits show a *horizontal pattern* of inheritance: the trait first appears among several members of one generation and is not seen in earlier generations.
2. The trait occurs with the same frequency in both sexes.

Figure 4 illustrates a typical pedigree of the trait inherited in an Autosomal Recessive manner.

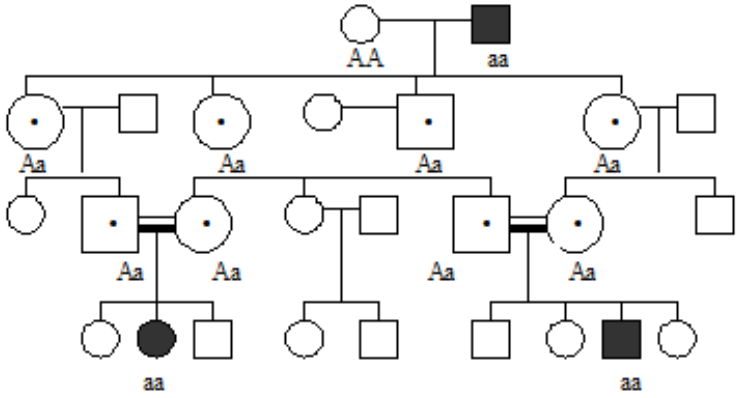


Fig. 4. A family pedigree of Autosomal Recessive inheritance

Examples of human disorders inherited in an Autosomal Recessive manner

Albinism (Oculocutaneous albinism type I)

Oculocutaneous albinism is a condition that affectы coloring (pigmentation) of the skin, hair, and eyes. Affected individuals typically have very fair skin and white or light-colored hair. Long-term sun exposure greatly increases the risk of skin damage and skin cancers, including an aggressive form of skin cancer called melanoma (fig. 5). This condition affects about 1 in 20,000 people worldwide.

Fig.5. The appearance of a child with Oculocutaneous albinism

Phenylketonuria (PKU)

Phenylketonuria is a metabolic disease that is caused by a buildup of Phenylalanine in the body due to an enzyme deficiency, particularly the hepatic enzyme Phenylalanine

Hydroxylase (PAH). People with PKU can not convert the amino acid Phenylalanine to Tyrosine due to a mutation in the gene that codes for PAH. PKU can lead to severe brain damage and mental retardation if not treated (fig. 6). PKU occurs in 1 in 10,000 to 15,000 newborns. Most cases of PKU are detected shortly after birth by newborn screening, and treatment is started promptly. As a result, the severe signs and symptoms of classic PKU are rarely seen.

Fig. 6. The child on the left has PKU

X-Linked Dominant inheritance

The common features:

1. Females are much more likely to exhibit the trait when it is lethal to males.

Figure 7 illustrates a typical pedigree of the trait inherited in an X-linked Dominant manner.

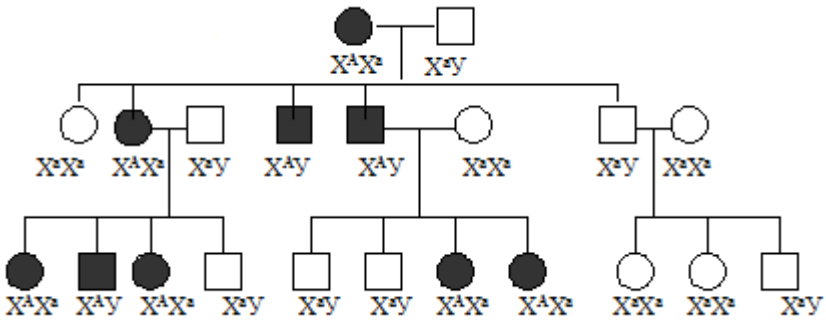


Fig. 7. A family pedigree of Vitamin D-resistant rickets (X-linked Dominant inheritance)

Examples of human disorders inherited in an X-linked Dominant Manner

Vitamin D-resistant rickets

Vitamin D- resistant rickets is a disorder that results in defects of bone mineralization at the sites of bone growth or remodeling, leading to bone deformity and stunted growth in children (fig. 8). Rickets affects an estimated 1 in 200,000 children.

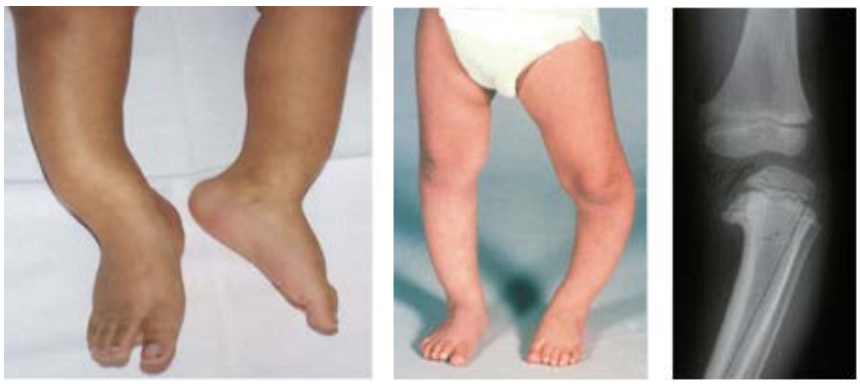


Fig. 8. The bone deformity in children affected by Vitamin D- resistant rickets

X-Linked Recessive inheritance

The common features:

1. Males are much more likely to exhibit the trait.

Figure 9 illustrates a typical pedigree of the trait inherited in an X-linked Recessive manner.

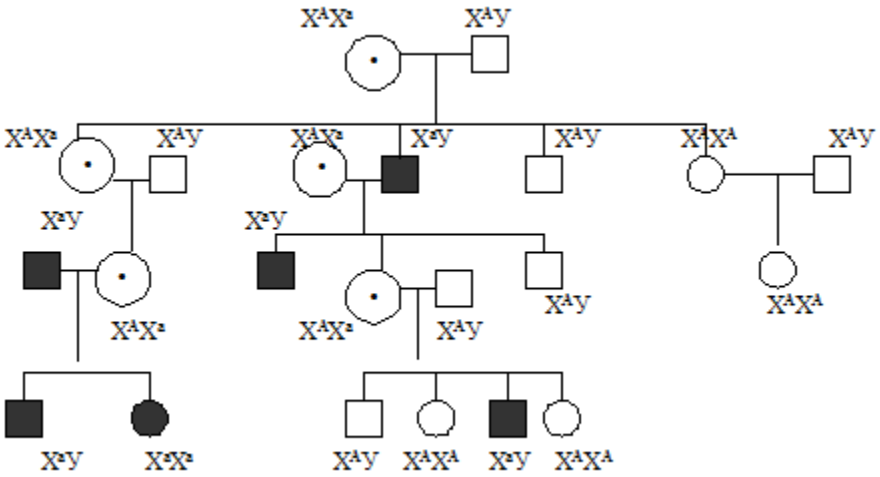


Fig. 9. A family pedigree of hemophilia A (X-linked Recessive inheritance)

Examples of Human Disorders Inherited in an X-linked Recessive Manner

Hemophilia (A, B)

Hemophilia is a bleeding disorder that slows the blood clotting process. People with this condition experience prolonged bleeding or oozing following an injury, surgery, or

having a tooth pulled or even in the absence of injury (spontaneous bleeding). Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs (fig. 10). The two major forms of hemophilia occur much more commonly in males than in females. Hemophilia A is the most common type of the condition; 1 in 4,000 to 1 in 5,000 males worldwide are born with this disorder. Hemophilia B occurs in approximately 1 in 20,000 newborn males worldwide.

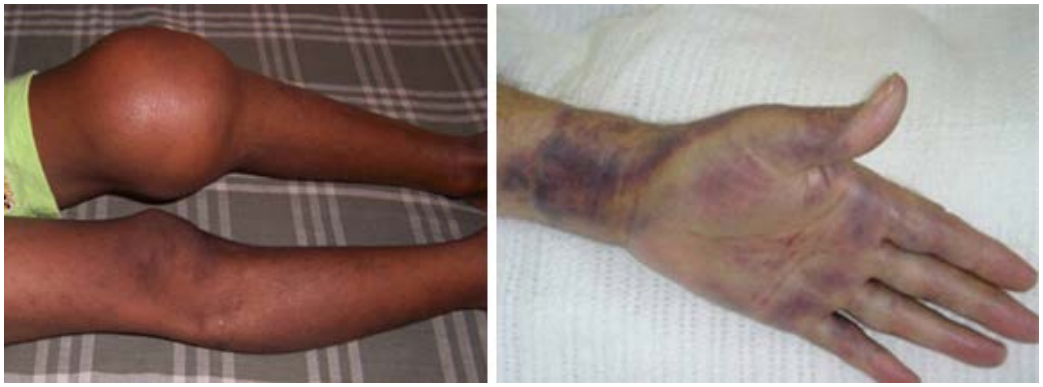


Fig. 10. Muscle and joint hemorrhages

Red-green color blindness

Red-green color vision defects are the most common form of color vision deficiency. Affected individuals have trouble distinguishing between some shades of red, yellow, and green (fig. 11). This defect disrupts color perception but does not affect the sharpness of vision (visual acuity). About 8 percent of males, and 0.5 percent of females, are color blind in some way or another.

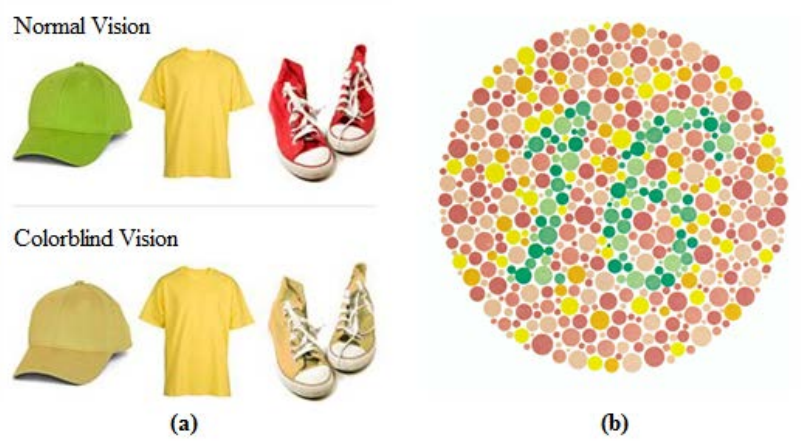


Fig. 11. Color perception of colorblind individuals: (a) Comparing normal and colorblind perception, (b) Persons with red-green color blindness cannot see the number 16 within this pattern of circles, as a person with normal color vision can

Y-Linked inheritance

The common features:

The concepts of dominant and recessive do not apply to **Y**-linked traits, as only one allele (on the **Y**) is present in any one (male) individual. Males with a single **Y**- or **X**-linked allele are described as ***hemizygotes***, because only one allele is present. **Y**-linked traits *never* occur in females, and occur in *all* male descendants of an affected male.

Figure 12 illustrates a typical pedigree of the trait inherited in an Y-linked manner.

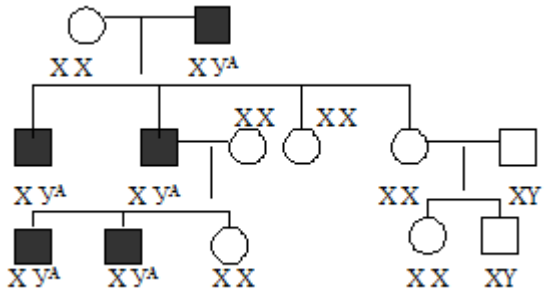


Fig. 12. A family pedigree of Hypertrichosis pinnae (Y-linked inheritance)

Examples of Human Disorders Inherited in a Y-linked Manner

Hypertrichosis pinnae

Excessive hair on the ear pinna (fig. 13).

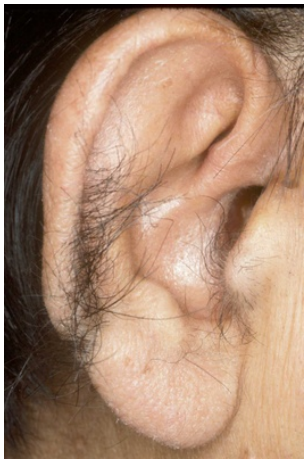


Fig. 13. Hypertrichosis pinnae

Maternal (mithochondrial) inheritance

The common features:

1. The traits are passed only from mother.

Figure 14 illustrates a typical pedigree of the neutral trait inherited through mitochondrial inheritance.

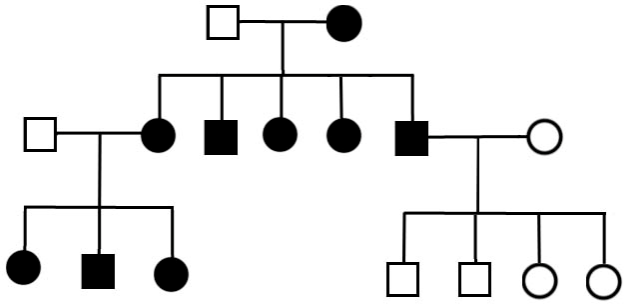


Fig. 14. A family pedigree of the transmission of neutral trait through mitochondrial inheritance

TWINS STUDIES

Twin studies is an informative approach for understanding the genetic (**H**) and environmental influences (**E**) affecting behavioral, physical, and medical traits. The simple yet elegant logic of the twin method derives from the differences in genetic relatedness between the two types of twins.

There are two types of twins:

- ✓ Monozygotic (MZ, Identical Twins)
- ✓ Dizygotic (DZ, Fraternal Twins)

MZ twins result when a fertilized egg (ovum) divides during the first two weeks following conception, while DZ twins result when a woman simultaneously releases two eggs that are fertilized by two separate sperm (fig. 15).

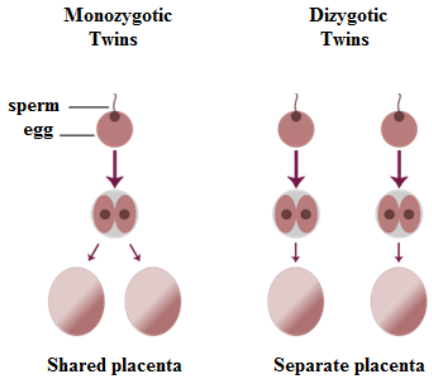


Fig. 15. Comparison of zygote development in MZ and DZ twins

There are two theoretical approaches to the study of twins:

- ✓ The comparison of monozygotic (MZ) twins reared together and dizygotic (DZ) twins reared together.
- ✓ The study of MZ twins reared apart.

The prevailing method of estimating heritability from MZ and DZ twins has been by means of the H index devised by Holzinger.

H – genetic effect, E - environmental effects, Holzinger's H index:

$$H = \frac{C\,MZ - C\,DZ}{100 - C\,DZ} \times 100\%$$

$$E = 1 - H$$

H = 1 – greater genetic effects,

H = 0 – greater environmental effects,

H = 0,5 – equal genetic and environmental effects.

CYTOGENETIC TECHNIQUES

Cytogenetics is the field of Human genetics that involves the microscopic examination of normal and abnormal chromosomes. This includes examination of chromosome structure, learning and describing the relationships between chromosome structure and phenotype, and seeking out the causes of chromosomal abnormalities.

Application of cytogenetic techniques

Abnormalities in chromosome number

Down syndrome (Trisomy 21, 47, XX (XY) +21)

Down syndrome is due to trisomy of chromosome 21. The extra chromosome results in abnormalities of the body and brain development. The physical development is slower and may have delayed mental development. The symptoms of Down syndrome vary from one person to another ranging from mild to severe (fig. 16).

Fig. 16. The appearance of people with Down's syndrome

Patau syndrome (Trisomy 13, 47XX (XY), 13+)

Patau syndrome is a genetic disorder in which a person has three copies of chromosome 13, instead of the usual two copies. The infants who are born often have congenital heart disease (atrial septal defect, patent ductus arteriosus, ventricular septal defect). Most of the children with trisomy 13 die in the first month of their life (fig. 17).

Fig. 17. The appearance of babies with Patau's syndrome: (a) cyclopia and proboscis, (b) Facial features; (c) polydactily

Edwards syndrome (Trisomy 18, 47XX (XY), 18+)

Edwards syndrome is a rare genetic chromosomal syndrome where the child has an extra third copy of chromosome 18. This syndrome results in mental retardation and various physical defects which causes mortality of the infants at an early stage (fig. 18).

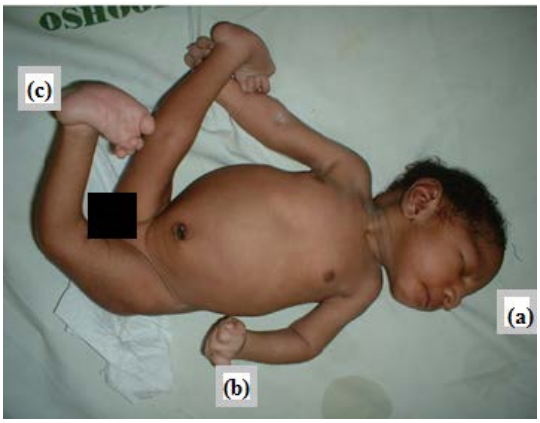


Fig. 18. A child with Edwards's syndrome: (a) – microcephaly; (b) overlapping toes; (c) rocker bottom foot)

Turner syndrome (Monosomy 45, XO)

Turner syndrome is due to the lack of the second sex chromosome or parts of it. The Turner syndrome patients can have a normal life. Symptoms: infertility, short stature, widely spaced nipples, swollen hands and feet, wide and webbed neck, absence of secondary sexual characters (fig. 19).

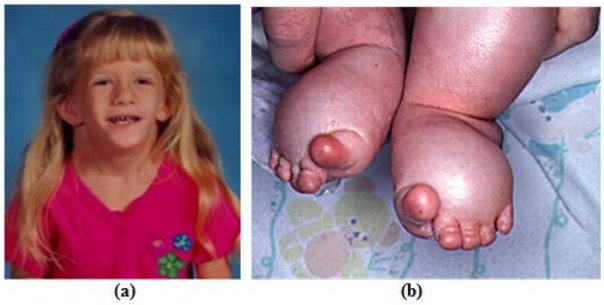


Fig. 19. Turner syndrome signs: (a) Short and webbed neck, (b) Swollen feet

Klinefelter's syndrome (47, XXY or XXY)

Klinefelter syndrome is the presence of an extra X chromosome in a male. The XXY karyotype is the most frequent of this syndrome. Symptoms: infertility, thinness, tall stature, gynecomastia, cryptorchidism (fig. 20).

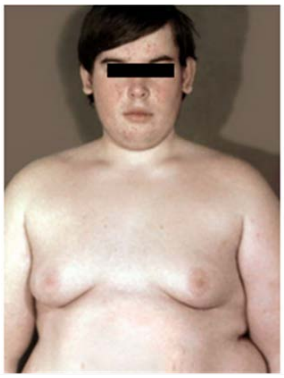


Fig. 20. The appearance of male with Klinefelter syndrome

Abnormalities in chromosome structure

Cri du chat syndrome

Cri du chat syndrome (*Cat-cry syndrome*, 5p−) is a rare genetic disorder due to a deletion of short arm of chromosome 5. Signs: severe cognitive, speech, and motor delays; behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements; unusual facial features which may change over time (fig. 21).

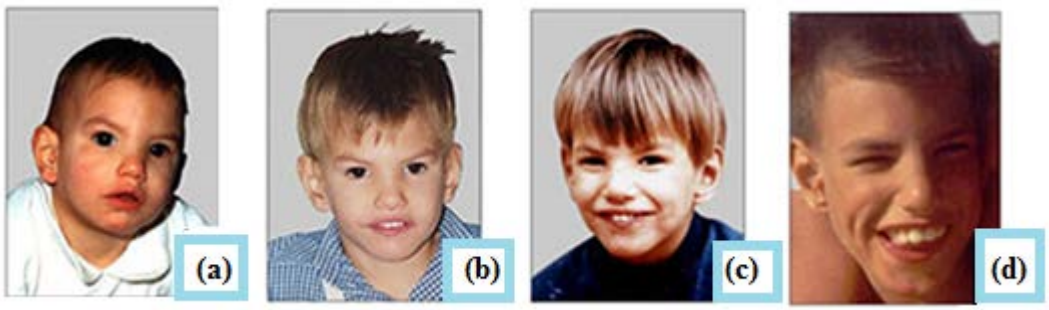


Fig. 21. Facial features of a patient with Cri du Chat syndrome
at age of 8 months (a), 2 years (b), 4 years (c) and 9 years (d)

BIOCHEMICAL TESTING

Biochemical testing is used for detecting of the enzymatic activity of a protein *in vitro.* The objects of biochemical testing may be urine, blood plasma and blood cells. The subject of a biochemical testing may serve various classes of organic and inorganic substances (amino acids, carbohydrates, lipids, mucopolysaccharides etc.). Biochemical methods are divided into *qualitative* and *quantitative*.

POPULATION STUDY (STATISTICAL METHOD)

Population genetics is the study of allele frequencies and genotype frequencies in the population, and the determination of how these frequencies change from one generation to the next.

A ***population*** is any group of members of the same species in a given geographical area. The genes in a population comprise its gene pool. The ***allele frequency*** is a proportion of alleles for that gene in the gene pool. The ***genotype frequencies*** are the proportions of heterozygotes and the two types of homozygotes in the population. The relationship between the relative proportions of alleles in the gene pool and the frequencies of different genotypes in a population is described by ***Hardy – Weinberg Law***, The expression of population genetics in algebraic terms begins with the simple equation

$$p + q = 1$$

Where ***p*** represents all dominant alleles for a gene, and ***q*** represents all recessive alleles. "$p + q = 1$" simply means that all the dominant alleles and all the recessive alleles comprise all the alleles for that gene in a population.

Next, Hardy and Weinberg described the genotypes for a gene with two alleles using the binomial expansion

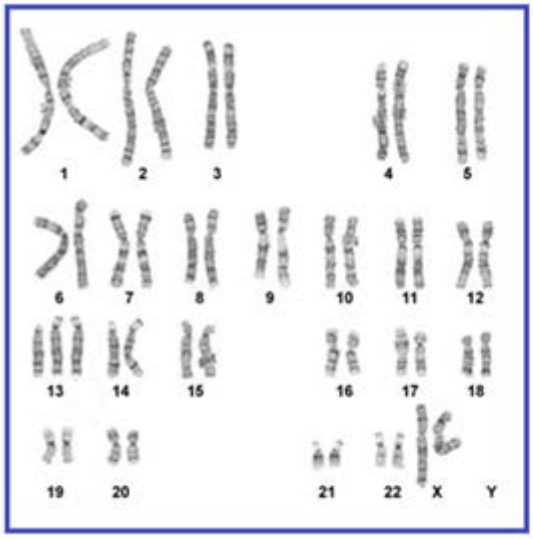
$$P^2 + 2pq + q^2 = 1$$

In this equation, $p2$ represents homozygous dominant individuals (AA), $q2$ represents homozygous recessive individuals (aa), and $2pq$ represents heterozygotes (Aa).

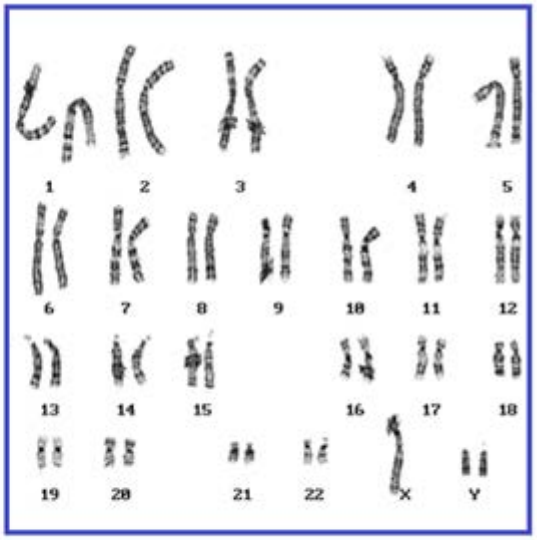
Analyze the karyograms and try to determine the syndrome

(Where is: Down syndrome, Patau syndrome, Edwards syndrome, Triploidy, Terner syndrome, Cat-cry syndrome, Klinefelter syndrome)

(a) – ?; (b) – ?; (c) – ?; (d) – ?; (e) – ?; (f) – ?; (g) – ?; (h) – ?



(a)



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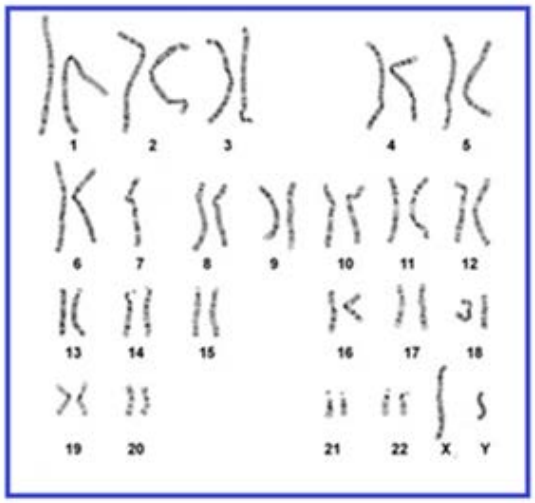

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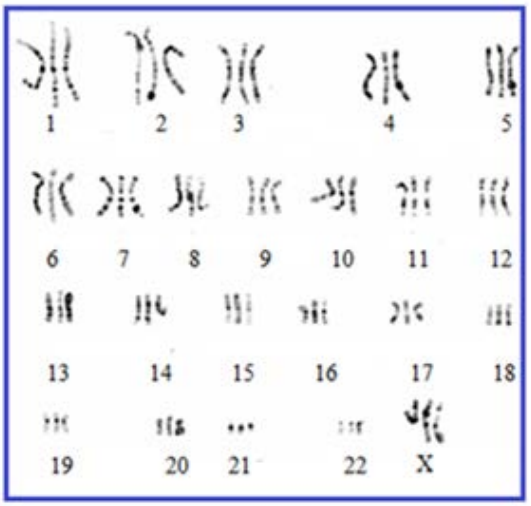

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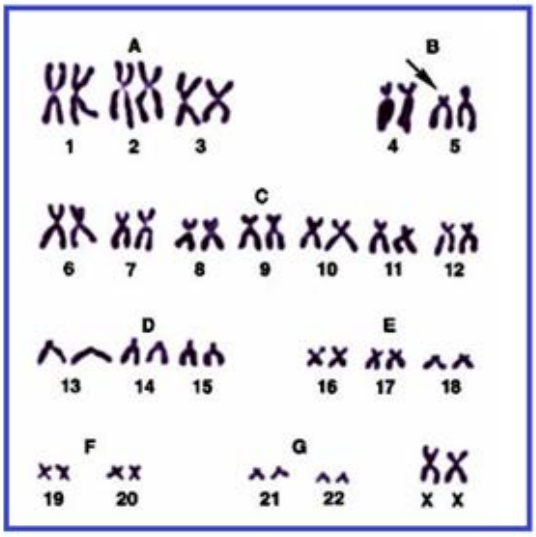
A
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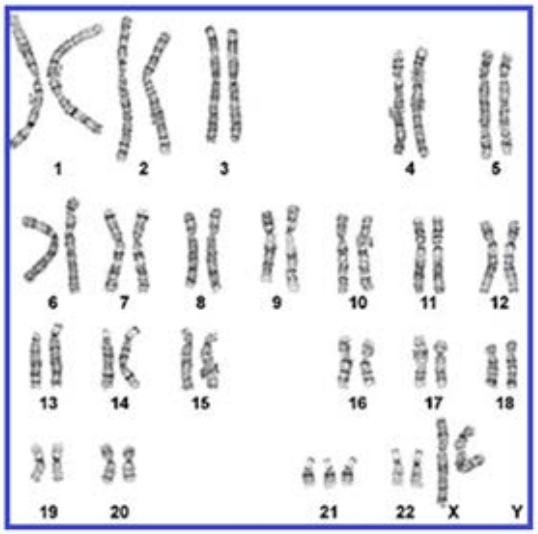
19 20 21 22 X X

(e)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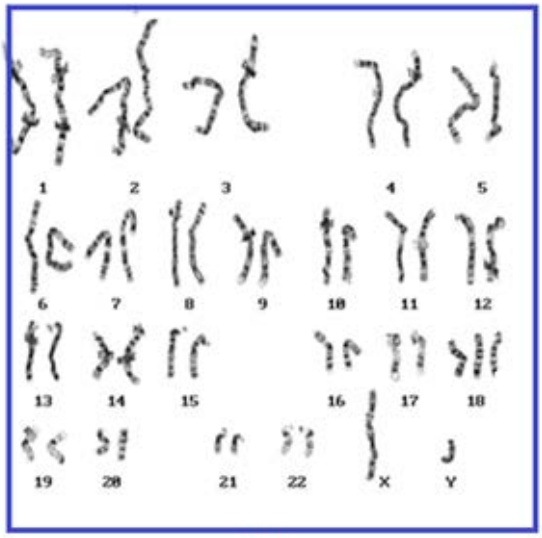
(f)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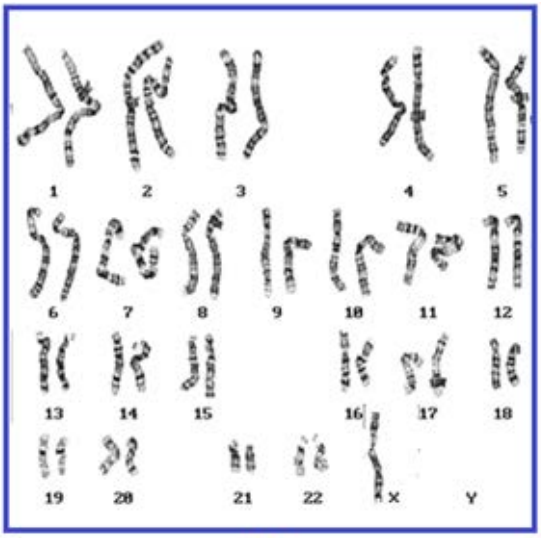
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y

(g)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6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y

(h)