

Lecture 8: Chromosome diseases.

Plan of the lecture

1. Chromosome disorders
2. Karyotyping as the method of diagnosis in pathological conditions
3. Medical significance of sex chromatin detection
4. DNA molecular diagnosis
5. Methods of prenatal diagnosis
6. Treatment and prophylaxis of heritable diseases

The goals of this lecture are to review the inherited diseases caused by damaged or improperly distributed chromosomes, to understand the mechanisms of chromosome non-disjunction and its role in origin of numerical chromosome disorders, to consider the causes and clinical manifestation of some chromosome diseases, and methods of their diagnosis, treatment and prophylaxis.

1. Chromosome disorders

Chromosome disorders are disorders due to abnormalities in structure or number of chromosomes.

STRUCTURAL CHROMOSOME ABNORMALITIES

Sometimes, chromosomes break, leading to 5 types of changes in chromosome structure

1. Deletion
2. Duplication
3. Inversion
4. Translocation
5. Insertion

1. Deletion: loss of portion of one chromosome. When this chromosome is passed on to offspring the result is usually lethal due to missing genes. Examples:

- 1) ***Cri du chat (cat~~B~~ cry syndrome)***
- 2) ***Prader - Willi syndrome*** and ***Angelman syndrome***

Cri du chat (cat~~B~~ cry syndrome)

The syndrome was first identified in 1963 by professor Lejeune, who also identified the genetic cause of Down's Syndrome. The syndrome is caused by the loss or misplacement of genetic material from the 5th chromosome. Most cases are the result of *de novo* deletions.

Karyotype: 46, XX or XY, del 5p.

Clinical features: wailing, cat-like cry in about 50% of those afflicted, round face; prominent nasal bridge; epicanthic folds; hypertelorism; micrognathia; microcephaly, hypotonia; heart and other organ deformities, severe psychomotor & mental retardation.

There are a few children who attend mainstream education, but the majority of the children need more specialized education.

Prader-Willi Syndrome & Angelman Syndrome Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are due to a microdeletion in the chromosome region 15q11-q13.

In the case of PWS, the absent contribution to this region is always paternal, leading to a loss of expression of paternally transcribed genes, whereas in AS, the maternal contribution of 15q11-q13 is missing, causing the syndrome via a lack of expression of maternally transcribed gene(s).

Prader-Willi syndrome is a complex genetic disorder that includes such ***clinical features:*** short stature and very small hands and feet in comparison to body; rapid weight gain and increasing obesity due to because the patient develops uncontrollable hunger; low muscle tone; almond-shaped eyes; mental retardation or learning disabilities, characteristic behavior problems; incomplete sexual development. ***Angelman Syndrome*** (also known as *Happy puppet syndrome*) is characterized by such ***clinical features:*** severe developmental delay or mental retardation, severe speech impairment, hand flapping, unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. In addition, microcephaly and seizures are common. Some patients may also develop epilepsy and have problems with balance.

In both syndromes, the loss of gene function may be due to three shared genetic defects:

1. microdeletion,
2. uniparental disomy (UPD),
3. an imprinting defect.

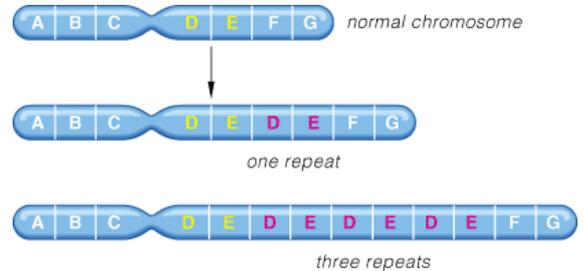
Genomic Imprinting. In human usually both copies of each gene (one from their mother and one from their father) are active, or turned on, in cells. In some cases, however, **only one of the two** copies is normally turned on. Which copy is active depends on the parent of origin. This phenomenon is known as **genomic imprinting** - the biological process whereby a gene or genomic domain exists in a state of epigenetic (reversible inheritable) differentiation that depends upon its parent of origin.

It is an inheritance process independent of the classical Mendelian inheritance

2. Duplication: if the fragment joins the homologous chromosome, then that region is repeated

Example: Fragile X syndrome (also **Martin-Bell syndrome**), the most common form of mental retardation.

The chromosome X of some people is unusually fragile at one tip. Fragile site is on long arm of X chromosome at band q27. The "fragile" sites are susceptible to breakage, at least *in vitro*, when subjected to insufficient concentrations of certain chemicals such as folic acid. Some of these regions are thus called "folate sensitive" sites. Certain humans have a folate sensitive region on the chromosome X.



It is associated with the expansion of a single trinucleotide gene sequence (CGG) on X chromosome, and results in a failure to express the *FMR-1 protein* (Fragile X mental retardation protein) which is required for normal neural development.

There are 4 generally accepted forms which relate to the length of the *repeated CGG sequence*:

- i. normal (29-31 CGG repeats)
- ii. premutation (55-200 CGG repeats),
- iii. full Mutation (more than 200 CGG repeats)
- iv. intermediate or Gray Zone Alleles (40-60 repeats)

Disease occurs in both males (1:1500) and females (1:2500), but males are typically affected more severely. This trait is dominant with variable penetrance. The trait has variable expressivity. About 80% of affected males express mental retardation.

Clinical features. Affected males have mental retardation; macro-orchidism; large size, characteristic facial features, including long face, prominent jaw, and large prominent ears; and stereotyped behavior and speech. Females affected with fragile X syndrome show varying degrees of mental retardation.

3. Inversion: a piece of a chromosome is lifted out, rotates 180 degrees and reinserted.

There are two types:

1. **pericentric inversion** that does not involve the centromeric region;
2. **paracentric inversion** that involves the centromeric region.

Example: inversion ***inv(9)(p12q13)***. This is the most common inversion on chromosome 9 is generally considered to have no harmful effects, but there is some evidence it leads to an increased risk for miscarriage for about 30% of affected couples.

4. Translocation: a fragment of a chromosome is *moved* ("trans-located") from one chromosome to another - joins a non-homologous chromosome. The balance of genes is still normal (nothing has been gained or lost) but can alter phenotype as it places genes in a new environment. Can also cause difficulties in egg or sperm development and normal development of a zygote.

There are two main types of translocations:

- 1) **Reciprocal** (also known as non-Robertsonian). Reciprocal translocations are usually an exchange of material between non-homologous chromosomes. They are found in about 1 in 600 human newborns.
- 2) **Robertsonian** that involves two acrocentric chromosomes, for example D/G translocation.

Examples of translocations:

1. **Chronic Myelogenous Leukemia** (chronic granulocytic leukemia (CGL)), characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood),
2. **Burkitt's lymphoma** is a solid tumor of B lymphocytes that the immune system uses to make antibodies. This cancer disease is usually (90%) caused by a translocation of chromosomes 8 and 14. This rare form of cancer predominantly affects young children in Central Africa, but the disease has also been reported in other areas. The form seen in Africa seems to be associated with infection by the **Epstein-Barr virus**, although the pathogenic mechanism is unclear.

3. **Translocation in Down syndrome.** The extra chromosome 21 or part of it may be attached to chromosome 14, sometimes - to 13, 15, or 22. In some cases, two chromosomes 21 can be attached to each other. Almost 50% of such translocation Down cases have parents as translocation carriers (*balanced translocation*).

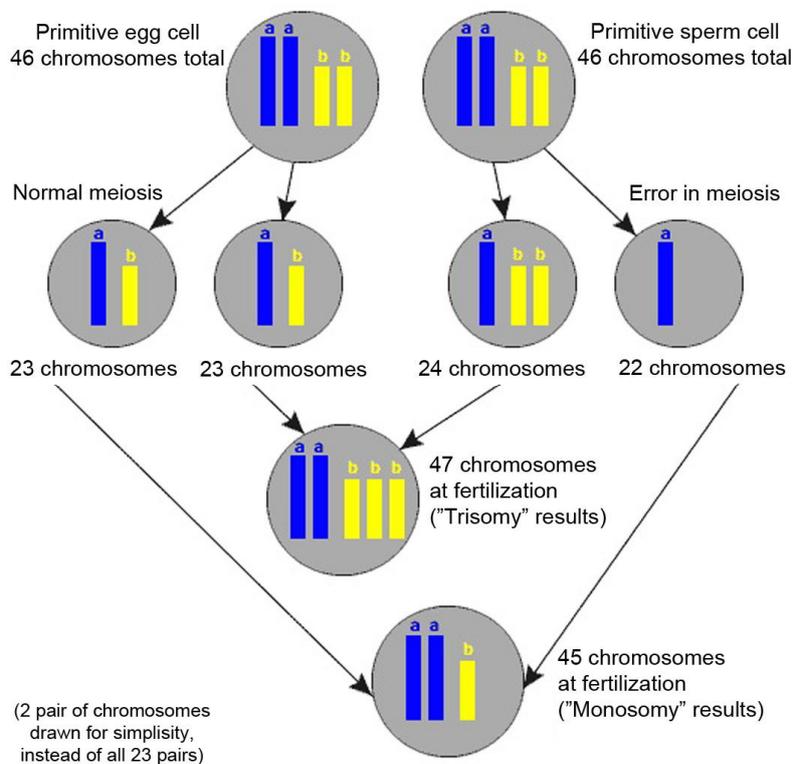
5. **Insertion** is a mutation where one portion of a chromosome is inserted into another. In this case, genetic material is not swapped; it is just moved to another chromosome.

NUMERICAL CHROMOSOME ABNORMALITIES

1/6th of all birth defects and mental retardation are due to chromosomal abnormalities which may be numerical or structural. Chromosomal mutations (*permanent changes that can be passed on to offspring if they occur in sex cells - gametes*) are changes in chromosome structure.

Genomic mutations include changes in quantity of chromosomes. 1/3 of all chromosome disorders are abnormal number of autosomes (aneuploidy . $2n \pm 1$, $2n \pm 2$)

1. $2n + 1$. **trisomy**, occurs when one extra copy of a chromosome is present.
2. $2n - 1$. **monosomy**, occurs when one chromosome lacks its homolog.
3. $2n - 2$. **nullisomy**, occurs when a chromosome is missing altogether. Generally, embryos that are nullisomic don't survive to be born.
4. $2n + 2$ - **tetrasomy**, occurs when four total copies of a chromosome are present. Tetrasomy is extremely rare.



Mutations increase the amount of variation among offspring.

Non-disjunction in meiosis or mitosis is a cause of most aneuploidies

It is the failure of chromosomes to separate. It occurs when either *homologues fail to separate* during anaphase I of meiosis, or *sister chromatids fail to separate* during anaphase II.

The result is that one gamete has 2 copies of one chromosome and the other has no copy of that chromosome (The other chromosomes are distributed normally).

The frequency of non-disjunction is quite high in humans, but the results are usually so devastating to the growing zygote that miscarriage occurs very early in the pregnancy. If the individual survives, he or she usually has a set of symptoms - a *syndrome* - caused by the abnormal dose of each gene product from that chromosome.

1.1. Chromosome disorders of autosomes

The majority of human chromosomal abnormalities occur in the **autosomes**

There are 3 trisomies that result in a baby which can survive for a time after birth; the others are too devastating and the baby usually dies in utero:

1. Down's syndrome (trisomy 21)
2. Patau's syndrome (trisomy 13)
3. Edward's syndrome (trisomy 18)

Down Syndrome – Trisomy 21

A cause of Down syndrome is an extra chromosome 21.

1. In 23% of cases, the sperm had the extra chromosome 21.
2. In 5% of cases, the syndrome is due to translocation.
3. About 2-4% is genetically mosaic.

Clinical features. Individuals with Down syndrome may have some or all of the following physical characteristics: oblique eye fissures with epicanthic skin folds on the inner corner of the eyes, muscle hypotonia (poor muscle tone), a flat nasal bridge, a protruding tongue (due to small oral cavity, and an enlarged tongue near the tonsils), a short neck, excessive joint laxity including atlanto-axial instability, congenital heart defects (30-50% of cases). Often sexually underdeveloped and sterile.

Most individuals with Down syndrome have mental retardation in the mild (IQ 50-70) to moderate (IQ 35-50) range, with individuals having Mosaic Down syndrome typically 10-30 points higher (**mosaicism** - the presence of two or more populations of cells with different genotypes in one individual).

The individuals with Down syndrome can also have serious abnormalities affecting any body system: intestinal malformations, hernias; epilepsy, hypothyroidism, crossed eyes, near-sightedness or far-sightedness, cataracts, hearing impairment.

Affected people have susceptibility to respiratory diseases and infections such as pneumonia, shorter lifespan, prone to developing early Alzheimer's and leukemia (childhood leukemia is as much as 20 times more common than average).

Dermatoglyph features: a single palmar crease (simian crease), excessive space between large toe and second toe, a single flexion furrow of the fifth finger, and a higher number of ulnar loop dermatoglyphs.

Patau's Syndrome (trisomy 13) is named for Dr. Klaus Patau, who reported the syndrome and its association with trisomy 13 in 1960. An extra copy of chromosome 13 is not the only cause of Patau syndrome. Other changes in chromosome 13, such as mispositioning (translocation), can also result in the characteristics classified as Patau syndrome. In these cases, an error occurs that causes a portion of chromosome 13 to be exchanged for a portion of another chromosome. There is no production of extra chromosomes, but a portion of each affected chromosome is "misplaced" (translocated) to another chromosome.

Frequency is 1:5000 live births.

Children rarely live more than a few months because of the life-threatening medical problems associated with this condition.. 85% of the patients do not survive beyond one year, and most children die before completing six months of age (In 2003, the case of Patau syndrome with a long survival (female patient, white, 28 months old) was reported)

Clinical features. The syndrome is associated with severe mental retardation and certain physical abnormalities. These abnormalities include a sloping forehead, a smaller than average head (microcephaly)small eyes that may exhibit a split in the iris (coloboma), a cleft palate and/or a cleft lip, weak muscle tone (hypotonia), skeletal abnormalities, an increased risk of heart defects, extra fingers and toes (polydactyly); abnormal genitalia; spinal defects; seizures; gastrointestinal hernias and other medical problems.

Edward's syndrome - trisomy 18, discovered by John Edward in 1960. It is caused by the presence of three . instead of two . copies of chromosome 18 in a fetus or infant's cells. A small percentage of cases occur when only some of the body's cells have an extra copy of chromosome 18, resulting in a mixed population of cells with a differing number of chromosomes. Such cases are sometimes called mosaic Edward's syndrome. Very rarely, a piece of chromosome 18 becomes attached to another chromosome (translocated) before or after conception. Affected people have two copies of chromosome 18, plus extra material from chromosome 18 attached to another chromosome. With a translocation, the person has a partial trisomy for chromosome 18 and the abnormalities are often less than for the typical Edwards syndrome.

Trisomy 18 affects about 1 in 5,000-8,000 live births, and it affects three times as often as boys. About 25% of Edward's syndrome victims die before they are one month old, and only 10% live for one year.

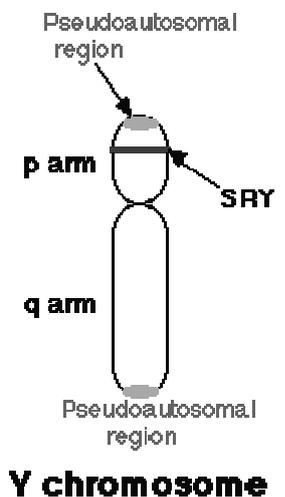
Clinical features may be extremely variable from case to case. However, in many affected infants, the following may be found: low birth weight, small head (microcephaly) with small jaws (micrognathia), cleft lip/palate, low-set, malformed ears, webbed hands, clenched fists, malformed finger nails, clubfeet.

Trisomy 6 (47, XX or XY, +6) has been reported as the sole cytogenetic aberration in 14 cases of acute myeloid leukaemia (AML) and 5 cases of myelodysplastic syndrome. **Acute myelogenous leukemia (AML)** is a cancer of blood forming cells in the bone marrow (the myeloid line of white blood cells), characterized by the rapid proliferation of abnormal cells which accumulate in the bone marrow. Abnormal immature white blood cells (blasts) fill the bone marrow and spill into the bloodstream. Production of normal blood cells is affected causing anaemia, bleeding problems, and infections. Treatment is mainly with chemotherapy. The outlook varies and depends on such things as the exact sub-type of the AML, and patient's age

1.2. Chromosome disorders of sex chromosomes

Sex chromosomes are the chromosomes that determine whether the offspring are male or female. Sex chromosomes called X and Y are not homologous and do not carry matching genes.

The Y is much smaller than the X. The presence of the Y chromosome is decisive for unleashing the developmental program that leads to a baby boy. Therefore it is the sperm that determines the sex of the offspring and not the egg. The human Y chromosome has relatively few gene loci compared to the X chromosome. The X and Y have homologous regions (i.e., with matching gene loci) which pair up during meiosis (synapsis) and undergo limited crossing over. These regions of homology are called pseudoautosomal regions. The pseudoautosomal regions have got their name because any genes located within them (so far only 9 have been found) are inherited just like any autosomal genes. Males have two copies of these genes: one in the pseudoautosomal region of their Y, the other in the corresponding portion of their X chromosome. So males can inherit an allele originally present on the X chromosome of their father and females can inherit an allele originally present on the Y chromosome of their father. Although 95% of the Y chromosome lies between the pseudoautosomal regions, fewer than 80 genes have been found here. Some of these genes encode proteins used by all cells (and both sexes). The others encode proteins that appear to function only in the testes, including **SRY**. **SRY** (for Sex-Determining Region Y) is a gene located on the short (p) arm just outside the pseudoautosomal region. It is the master switch that triggers the events that converts the embryo into a male.



On very rare occasions aneuploid humans are born with such karyotypes as XXY, XXXY, and even XXXXY. Despite their extra X chromosomes, all these cases are male.

Another rarity: XX humans with testicular tissue because a translocation has placed the **SRY** gene on one of the X chromosomes. Still another rarity that demonstrates the case: women with an XY karyotype who, despite their Y chromosome, are female because of a destructive mutation in **SRY**.

Sex Chromosome Aneuploidy Syndromes have an additional X or Y or lacking X or Y

1. Trisomy X . 47, XXX Turner's syndrome (Monosomy X) . 45, XO

3. Klinefelter syndrome - 47, XXY

4. Jacob syndrome - 47, XYY

47, XXX or 47, XYY do not have major birth defects . IQ might be slightly low at 90.

Turner Syndrome is a monosomy where an individual has single chromosome X (and one structurally defective X-chromosome) (**45, XO**), it is example of a non-lethal monosomy (only viable monosomy).

Clinical features. In most cases, females with this disorder are typically short in stature (average final adult height is 140 cm, i.e., 4 feet 7 inches) and may have a variety of associated physical features and medical problems including kidney and heart abnormalities, high blood pressure, obesity, diabetes mellitus, cataracts, thyroid problems, and arthritis.

They usually don't develop all of the secondary sexual characteristics expected during adolescence and are infertile as adults. Other health problems that may occur with Turner syndrome

Girls with Turner syndrome usually have normal intelligence, but sometimes developmental delays, learning disabilities, and behavioral problems are also possible, although these characteristics vary among affected females

Triple-X Syndrome (47, XXX) is caused by presence of extra chromosome X.

Clinical features There is no increased femininity; most lack any physical abnormalities. Affected females often are of tall stature. In addition, in some cases, certain physical abnormalities have been reported, such as a relatively small head, vertical skin folds that may cover the eyes' inner corners, and other findings.

Although sexual development and fertility are usually normal, some may have delayed puberty and/or fertility problems: menstrual irregularities, including early onset of menopause

Mental retardation rarely occurs, but infants and children with the syndrome may tend to have delayed of certain motor skills and delayed speech development.

Triple X syndrome is a relatively common cause of learning difficulties, particularly language-based disabilities in females.

There is an increased risk of having triple-X daughters or XXY sons.

Klinefelter's syndrome (47, XXY) is a condition caused by extra X chromosome(s) in a male.

Clinical features. Phenotype is male, but the phenotypic effects of the extra X chromosomes are mild because, just as in females, the extra X chromosomes are inactivated and converted into Barr bodies. The syndrome can affect different stages of physical, language and social development. The most common symptom is infertility. Such men have male sex organs; unusually small testes, breast enlargement and other feminine body characteristics. Usually they have also normal intelligence.

Syndrome may not be diagnosed until puberty because the symptoms may be very subtle until that age and secondary sex characteristics are not apparent before puberty.

YYY syndrome (47, XYY), also Jacob's syndrome, YY syndrome.

The majority of cases of XYY syndrome are due to a paternal non-disjunction. The prevalence of 47, XYY is currently estimated at ~ 1/1000 males. As it is typically not associated with marked phenotypic characteristics it is frequently undetected.

Clinical features. Phenotype is male, boys have increased growth velocity during childhood, and adult height is usually increased approximately 7 cm above what is expected. Puberty, testicular function and fertility are usually normal. There is increased risk of problems with distractibility, impulsivity and difficulties with temper management. Problems with social relatedness are also common.

2. Karyotyping as the method of diagnosis in pathological conditions

Basic cytogenetic methods applied in diagnosis of chromosome diseases are *karyotyping* and detection of sex chromatin.

Karyotyping is the process by which metaphase chromosomes are obtained for analysis.

Different tissue cultures use for determination of karyotype. The most commonly used sample is blood (white blood cells or lymphocytes) since it is the most accessible. However, other samples are used depending upon the indication: amniotic fluid cells, to analyze the karyotype of the fetus; products of conception, to analyze the cause of a miscarriage or stillbirth; bone marrow cells, to diagnose the presence or type of leukemia; and skin, to determine the presence of another cell line.

Application of karyotyping

1. **CLINICAL DIAGNOSIS.** Karyotyping helps in reaching a clinical diagnosis. It is especially indicated in patients with congenital malformations.
2. **ROLE IN CANCER.** The detection of Philadelphia chromosome in patients of chronic myelogenous leukaemia (CML) alters prognosis. The formation of Philadelphia chromosome involves translocation between long arms of chromosomes 22 and 9. The Philadelphia positive CML cases have a longer survival than those without Philadelphia chromosome.
3. **REPEATED FETAL LOSS.** On chromosome analysis, the couple may reveal a chromosomal defect in any one of the partner. Chromosomal aberrations account for a sizable number of spontaneous abortions in the first trimester of pregnancy.
4. **PRENATAL DIAGNOSIS.** Chromosome analysis of chorion villous samples and amniotic cells may reveal a chromosome abnormality in a fetus warranting medical termination of pregnancy.

3. Medical significance of sex chromatin detection

In 1949, a Canadian physician and medical researcher M. Barr with graduate student E.G. Bertram, while studying cat neurons found that some of these cells show a chromatin mass in their nuclei. This was observed only in females but not in males. Subsequently it was labelled as *sex chromatin* or *Barr body*. Barr body represents one of the two X chromosomes of a female cell. This remains condensed and is in inactive state throughout interphase. Its replication is also late as compared to its homologue.

Barr's method of sex detection on the basis of quantitative determination of the sex chromatin content in the cell nuclei (1949) is widely used in clinical medicine.

Barr body can be found in many cell types but can be conveniently examined in buccal mucosa. Procedure is relatively simple. Scraping from the inner side of the cheek is taken on a slide and smeared evenly. Subsequently it is fixed in alcohol and stained with thionin. It is then mounted in neutral medium and observed under a microscope.

Once upon a time buccal smear (sex chromatin study) was used as a diagnostic tool for disorders of sexual development. Number of Barr bodies in a cell will depend upon the number of X chromosomes in the cell. For example, in an individual with 47, XXX complement, there are 3 X chromosomes and 2 Barr bodies. A Turner's syndrome patient having 45 XO complement has only one X chromosome. Therefore the number of Barr bodies is 0, i.e. no Barr body.

4. DNA molecular diagnosis

DNA analysis is now becoming a standard procedure for locating particular gene defects and for identifying carriers. The pattern of bases in a DNA molecule can be achieved using the technique known as **DNA profiling**.

The DNA is extracted from the fetal material. In order to extract the DNA from the nucleus, restriction enzymes known as **restriction endonucleases** are heated and break apart at certain points in the sequence. DNA can be replicated artificially by the **polymerase chain reaction (PCR)** which makes it possible to synthesize large numbers of copies of very small samples of DNA. Once the DNA is copied researchers then determine the size of the short tandem repeats. These are the portions that contain the same nucleotide sequence or same order of bases on a DNA strand. DNA fragments can be separated by *gel electrophoresis*. A voltage is applied to the gel and the negatively charged DNA fragments move towards the positive electrode. Smaller fragments move faster than large ones. The last step is to discover if there is a positive DNA match. Using the sizing procedure, scientist can compare DNA to find matches. If the profiles are the same between two samples then it is nearly impossible that the sample came from a different person. Scientists obtain strong evidence that matches the person's identity with comparing strands of DNA.

This method is now used successfully to detect conditions such as *Huntington's disease*, *phenylketonuria*, *cystic fibrosis*, *Duchenne muscular dystrophy*, *hemophilia*, and *familial Alzheimers*, *sickle cell anemia*, *thalassemia*, and many others.

5. Methods of prenatal diagnosis

Prenatal diagnosis of genetic disorders and fetal anomalies has expanded significantly for hundreds of conditions. The purpose of prenatal diagnosis is to rule out the presence in the fetus of a particular medical condition for which the pregnancy is at an increased risk. This information is provided to the couple to assist in their decision-making process regarding the available options, such as carrying the pregnancy to term, preparing for a difficult delivery and for special newborn care, or terminating the pregnancy. Genetic counselling is particularly important prior to prenatal diagnosis and, after a result indicating an affected fetus, to secure fully informed choices.

Prenatal tests allow detection of abnormalities in the fetus. Procedures include:

- ultrasound scanning
- amniocentesis
- chorionic villus sampling
- fetoscopy
- fetal blood sampling
- maternal blood screening

Ultrasound scanning uses high frequency sound waves to build up picture on TV screen of features within the body, confirms viable pregnancy, monitors fetal growth, and detects major deformities.

Amniocentesis is a procedure in which amniotic fluid is removed from the uterus for testing or treatment. Amniotic fluid is the fluid that surrounds and protects a baby during pregnancy. A sample of amniotic fluid contains fetal cells withdrawn through the abdominal wall. The amniotic cells can be used

for further tests (biochemical analysis on fluid or cultured cells for diagnosis of errors of metabolism). The cells can yield karyotype to see chromosome pattern or undergo the analysis of DNA to locate specific gene defects. The results from fluid are in about 1 week, from cultured cells in about 3 to 4 weeks. Amniocentesis is performed at about 15 to 16 weeks' gestation, risk of increasing miscarriage is 1-1,5 %.

Chorionic villus sampling

Chorionic villi are microscopic projections that line the chorion, the outermost layer of the embryonic sac. These projections contain the same genetic material as a fetus.

For the procedure, material is taken from chorionic villus (fetal membranes) removed through the cervix or through abdominal wall (under ultrasonic guidance). Biochemical and chromosomal tests are carried out on material but culturing of cells is not needed (so results obtained more quickly than amniocentesis). The procedure is performed at between 9 and 12 weeks' gestation, risk of miscarriage slightly higher than normal at this time.

Fetoscopy involves visualization of fetus using a fiberoptic self-illuminated instrument called *fetoscope* which is inserted in the amniotic cavity. The procedure is performed at between 18 and 22 weeks' gestation and detects limb malformations, facial defects (cleft lip, cleft palate, ear defects) or defects involving the genitals. It is useful in obtaining fetoscopic skin biopsy and fetal blood sampling. Risk of miscarriage is 3-5 %.

Fetal blood sampling (FBS) is the collecting of fetal blood directly from the umbilical cord or fetus. FBS is also known as *cordocentesis* or *percutaneous umbilical cord blood sampling*. It can be done in two ways:

1. Placental aspiration (indirect tap). In this technique both maternal and fetal blood cells are mixed and need to be separated before sample processing.
2. Sampling under direct vision. In this case sample is obtained under direct vision using a fetoscope. Both techniques carry about 10% risk of abortion. It can detect *sickle cell anaemia*, *thalassaemias*, *haemophilia A*, *Duchenne muscular dystrophy*.

Maternal blood screening This test has a number of names, including ***maternal serum (blood) screening test, multiple marker screening test, triple screen*** and ***quad screen***.

The test looks for 3 specific substances: AFP, hCG, and Estriol.

1. **AFP:** *alpha-fetoprotein* is a protein that is normally produced by the fetus. Maternal serum shows AFP increment during 16-18 weeks of gestation.
2. **hCG:** *human chorionic gonadotropin* is a hormone produced within the placenta
3. **Estriol:** *estriol* is an estrogen produced by both the fetus and the placenta

The procedure is used for the detection of neural tube defects (anencephaly).

6. Treatment and prophylaxis of heritable diseases

The vast majority of genetic disorders are serious, none is curable and relatively few are treatable. The principal approach to the control of genetic disease is, therefore, prevention through genetic counselling, with prenatal diagnosis and selective abortion, where possible. Table 1 gives possible modes of management of some of the genetic disorders.

Examples of various methods for managing genetic disease

Therapy	Disorder
<i>Replacement of deficient protein</i> antihaemophilic globulin	haemophilia
<i>Replacement of deficient vitamin</i> vitamin D	vit. D resistant rickets
<i>Replacement of deficient product</i> cortisone thyroxine	adrenogenital syndrome congenital cretinism

Substrate restriction in diet Phenylalanine Carbohydrate	phenylketonuria galactosemia
Gene therapy (replacement of deficient gene)	severe combined immunodeficiency (SCID) cystic fibrosis
Drug therapy insulin	diabetes mellitus
Preventive therapy avoidance of certain drugs and Injection of Rh gamma globulin	G6PD deficiency, porphyria Rh incompatibility
Removal of diseased tissues <i>Splenectomy</i>	hereditary spherocytosis

1. When an enzyme block is responsible for the disorder, **the defective enzyme or protein may be replaced, its substrate restricted, or the deficient product replaced.** For example, a child born with PKU is normal at birth, but subsequently as it receives phenylalanine in the diet the toxic metabolites of phenylalanine metabolism accumulate causing damage. This leads to mental retardation.
2. The ideal way to treat these children would be to offer them defective enzyme. Somehow it is not possible and hence we resort to other alternatives, i.e. to eliminate phenylalanine from the diet. Since it forms one of the essential amino acids, it cannot be totally removed from the diet. So, what one can do is to give a controlled amount phenylalanine in the diet, simultaneously monitoring the blood level of this amino acid. An early detection of the defect is essential, otherwise mental retardation results. An amount of damage once caused is irreversible. However, most of the enzymes which are involved in hereditary disorders, are not identifiable. The majority of the enzymes work within cells and so even if enzymes were to get identified, injection of the enzymes would not be effective. Transplantation of tissue possessing normal enzyme activity is a dream of the future. In mucopolysaccharidoses, infusion of normal plasma or leukocytes helps to a certain extent.
3. **Drugs help** in certain diseases. For example, chelating agents such as penicillamine increase the urinary excretion of copper, and so are proving beneficial in the treatment of patients with Wilson's disease (Hepatolenticular degeneration).
4. **Some severe genetic disorders can be treated by gene therapy.** Healthy genes are cloned and then transferred to target cells in the body to take over the function of defective genes that cause the disorder.
5. Two forms of gene therapy are being developed to treat cystic fibrosis. (Cystic fibrosis is a genetic disorder caused by a mutant allele that produces a defective form of the channel protein, called CFTR. This protein normally transports chloride ions out of cells). In the first form of gene therapy, healthy CFTR genes are inserted into liposomes, which fuse with cell membranes and take the genes into the cells. In the other, harmless viruses are used to insert the CFTR genes into the cells.
6. **Preventive therapy.** Avoidance of harmful drugs by individuals with hereditary disorders such as porphyria or G6PD deficiency, or prophylaxis for preventing sensitization by Rh-antigen are important examples.
7. **Surgical removal of diseased tissue.** Colectomy in polyposis coli, and splenectomy in hereditary spherocytosis are important examples of this mode of treatment.
8. **Transplantation of normal tissues.** This remains a future possibility.