UNIT 3 PREVENTION OF GENETIC DISEASES

Contents

Learning Objectives

It is expected that after reading this unit, you would be able to:

- explain what is genetic disease and types of genetic diseases;
- discuss the processes of genetic screening and genetic counselling;
- describe on prenatal diagnosis; and
- explain gene therapy and its importance.

3.1 INTRODUCTION

Genetic diseases are those pathological conditions that are caused or influenced by abnormalities in the genetic material (genome) of a person and these are caused by genemutations and chromosomal abnormalities. Genetic diseases place a substantial health, emotional, and economic load on affected people, their families and on the society. There are a number of diverse types of genetic disorders. Geneticists group genetic disorders into four categories: single gene/monogenic genetic diseases, multifactorial/polygenic genetic diseases, chromosomal diseases and mitochondrial DNA disorders.

Single Gene Genetic diseases: These are also called as monogenic genetic diseases or Mendelian genetic disorders. These type of disorders are caused by changes or mutations that occur in the DNA sequence of a single gene. Single gene disorders are passed on between generations from parents to offspring. Four patterns of inheritance occur: autosomal dominant, autosomal recessive, X-linked dominant and X-linked recessive. Some of the diseases of single gene disorders are sickle cell anaemia, cystic fibrosis, Aicardi Syndrome, Huntington's disease etc.

Polygenic genetic diseases: These diseases are also called multifactorial genetic disorders. These diseases are influenced by the interaction of multiple genes and interaction between genes and environmental factors. Heart disease, diabetes, hypertension, Alzheimer's disease are some of the examples of polygenic diseases.

Chromosomal diseases: These diseases are caused by the loss or gain of one or more chromosomes or by alterations in chromosome structure. Down syndrome, Turner syndrome and Klinefelter syndrome are some of the examples for chromosomal diseases.

Mitochondrial DNA disorders: involve the defects in mitochondrial DNA not nuclear DNA. Ex: Some rare neurological and skeletal disorders.

So far we have studied what are genetic disease and their types. Now let us discuss how to prevent them. The desire of all parents is to have normal and healthy children. Hence many parents think ways to prevent or lower the risk of passing the genetic diseases to their offspring by preventing the genetic diseases. To prevent genetic diseases, parents have to undergo certain preventive measures such as Genetic screening, Genetic counselling, Prenatal diagnosis and Gene therapy. A brief description of the above mentioned preventive measures is described below.

3.2 GENETIC SCREENING

Genetic screening is a routine diagnostic procedure devised to detect those who are carriers of, or who are themselves affected by, a hereditary disease. Genetic screening applies to populations rather than to individuals.

The most-widespread application of genetic screening in the United State is for phenylketonuria (PKU). All hospitals in the United States screen newborn babies for PKU by a blood test called Guthrie test.

After genetic screening if both the parents are heterozygous for a genetic disease and the genotypes of both the prospective parents become known and they can decide to produce a child or not. It is simple matter to work out the probability of their child inheriting the disease. This can be done through appropriate tests around 2-3 months after conception. This is achieved through amniocentesis or through chorionic villus biopsy; the cultured fetal cells may be used for determining their karyotype, levels of the critical enzymes and restriction patterns of DNA. Such an antenatal diagnosis is now available for several genetic diseases and for a variety of chromosomal defects. The purpose of such a diagnosis is premature termination of abnormal fetuses.

Genetic counselling and antenatal diagnosis provide definite relief to the prospective parents and reduce the frequency of genetically defective individuals in the population. However, it is unlikely that these measures would eliminate the deleterious alleles from a population. This is so because most genetic defects are recessive and heterozygotes for such alleles. Thus even after a total ban on reproduction by the homozygotes for such recessive alleles they would remain in the population through the heterozygots, therefore even such an extreme selection would lead to only a slow decline in their frequency. Further, it is not likely that all the couples in any society will willingly submit themselves, at least in the foreseeable near future, to these procedures. But genetic counselling has become a routine aspect of medical practice in most developed countries.

It has been advocated that defective genes may be corrected through sophisticated genetic techniques either during the early stages of embryo development (embryo

therapy) or in specific tissues of the adult patient (patient therapy); such an approach is referred to as genetic surgery. Embryo therapy would involve:

1) In vitro fertilization of egg.
2) Production of several copies of the normal allele of the defective gene.
3) Introduction of this DNA into the zygote or in the cells of the developing embryo.
4) Integration of DNA, preferably in place of the defective allele, so that it may function normally.

The aim of patient therapy is to introduce the normal gene into the critical tissue of the patient that is affected by a genetic disease, i.e., the tissue where the concerned gene is required to express itself the most e.g., pancreas in the case of diabetes. The steps involved in patient therapy would be similar to those of embryo therapy. But in this case, cells from the concerned tissues may have to be exercised and treated in vitro to correct their genetic defects and then reintroduced into the tissue where they may function normally. Techniques for isolation, identification and multiplication of many human genes are now available, and for many others they are likely to be developed soon. The techniques for gene transfer in eukaryotes are being refined and it may not remain a great problem in the near future.

A suggestion has also been made to use highly specific chemical mutagens that will correct the defect in the concerned gene. Such a directed mutagenesis however is a dream that may be more difficult to fulfil the patient and embryo therapies through DNA mediated genetic modifications. Genetic screening and counselling may also lead to certain problems. The cases of mistaken paternity, the problem of confidentiality, delayed counselling are important among them.

3.3 GENETIC COUNSELLING

Genetic counselling is essentially a communication process that informs prospective parents about the nature of genetic disorders, about the risk of their having a genetically defective child, and about the options available to them in dealing with that risk. Or it can help them cope with the care of an existing genetically handicapped child. The advanced knowledge of the applied aspect of human genetics has gained importance. Therefore genetic counseling is an important area of applied human genetics. The counselor should have adequate knowledge in the counseling process. The counselor is preferably a medical doctor or a profession who is having knowledge in human genetics. The duty of a counselor is to offer the necessary genetic information and also the information about social, economic and psychological aspects related through the case. The persons receiving genetic counseling are called the consultands.

Genetic Counselling, as defined by Harper (1984), is “the process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing and transmitting it, and the ways in which this may be prevented or ameliorated”. However the American Society of Human genetics (1975) formulated the definition as “Genetic counselling is a communication process which deals with the human problems associated with the risk of occurrence of a genetic disorder in a family”. This process involves an attempt by one or more appropriately trained persons to help

the individual or family to: (1) comprehend the medical facts including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the way hereditary contributes to the disorder and the risk of recurrence in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action which seems to them appropriate in their view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

Genetic counselling involves the following steps:

The prospective parents either suffering from or suspected to be heterozygous for some genetic disease on the risk of their children suffering from the same disease should be educated. By creating a suitable social environment such parents may be encouraged to voluntarily abstain from producing children. To identify people suffering from a genetic disease is relatively easy for a trained clinician. It is difficult to identify a carrier for genetic disease and in most cases not possible. Information on the likelihood of an individual being a carrier for a genetic disease can be obtained by the analysis of family pedigree in some conditions or possible in case of certain conditions by biochemical and molecular tests.

The process of Genetic counselling

1) After genetic screening of a disorder, patients or their parents should be informed about the genetic or medical implications of the disease;
2) The likelihood of occurrence of such genetic disorder in the family should be calculated; and
3) To suggest ways in which the occurrence of the genetic disorder can be controlled.

Pedigree Analysis

Pedigree is a family history of hereditary condition or diagram of a family history indicating the family members, their relationships to proband (the affected individual that brings family to medical attention), and their status with respect to a particular hereditary condition.

Pedigree analysis assists the counsellor to decide if a trait is Mendelian. It also helps to establish the mode of inheritance. The first step in pedigree analysis is to observe the number and relationships of all individuals who express the same or similar clinical features. From this, it should be possible to determine if the disorder is dominant or recessive, autosomal or X-linked or Y-linked by looking for the typical patterns of inheritance. For example, a Y-linked disease can usually be distinguished by seeing male-to-male transmission of mutation, but since males pass only the Y chromosome to their sons, should never be father to son transmission of an X-linked gene. Males will be most commonly affected in an X-linked disease, whereas males and females should be equally affected in autosomal disorders. In general, a dominant disease will be seen in approximately half of the individuals in each generation, but recessives occur very rarely. If the mutation is in the mitochondrial genome, affected mothers will pass the trait to all of their children, but none of the offspring of an affected male should have the disease.

Once the inheritance pattern of the disorder is determined, the status of family members in the pedigree can be evaluated. By carefully observing the position of affected individuals, mutation carriers may be identified. From this data, the risk of carrier status for other family members or the chance that a couple may have an affected child can be estimated.

3.4 PRENATAL DIAGNOSIS

Prenatal diagnosis is the detection or exclusion of abnormality in the foetus prior to birth. In the process of having healthy progeny, prenatal diagnosis useful in detecting health of a baby to be born. It is useful to detect genetic disorders where the couple or populations are at high risk of inheriting genetic disorders. If an abnormality is detected in the pregnancy, the parents can take decision as to whether to continue with the abnormal foetus or to go for abortion. Prenatal diagnosis enables: (1) Timely medical or surgical treatment of a condition before or after birth, (2) parents to abort a foetus with the diagnosed condition, and (3) parents he to be prepared psychologically, socially, financially and medically for a baby with a health problem or disability or for likelihood of a still birth.

Prenatal diagnosis for genetic diseases is now commonly available for pregnancies at risk. Prior to prenatal diagnosis genetic counselling could only give likelihood of recurrence, based on Mendelian laws or empirical data. If an abnormality is detected in the pregnancy the medical people have to convey the information to parents and allow the parents to take a decision as to whether to continue with the abnormal foetus or to go for abortion. The couples at high risk of having a child with a genetic disorder has to choose between taking the risk or considering other reproductive options such as long term conception, sterilization and termination of pregnancies. Most parents would terminate an affected pregnancy but some choose to use the information to prepare for the birth of an affected child. When the foetus is found to be normal it allows the parents to continue the pregnancy with mental relief.

Many factors are to be considered before undertaking prenatal diagnosis, like risk of inheriting a genetic disorder, severity of genetic disease etc. Some genetic diseases lead to death in utero, or infancy or childhood. Some diseases are compatible with survival for many years with severe handicaps. Many genetic diseases cannot be cured even if the basis for the diseases is known. In some cases gene therapy may help. Currently prenatal diagnosis tests are available for more than 200 genetic disorders. Before going to a test one should be careful in finding the reliability of the test.

Indications for Prenatal Diagnosis

There are many indications for offering prenatal diagnosis. While undertaking prenatal diagnosis the risk of an abnormal foetus is at least as great as risk of the procedure itself. The following are some of the indications:

Advanced maternal age: Women who are pregnant at 35 or more have higher risk of giving birth to a baby with the defect in chromosomes. Down syndrome (trisomy 21) is the common chromosomal defect. A child with Down syndrome can be born to parents of any age; however, the risk rises steeply once the mother's age is over 35 years.

Previous child with a chromosome abnormality: Parents who have had a child with trisomy 21 (Down syndrome) or any other trisomy are at increased risk of having a trisomy in subsequent pregnancies.

Family history of a chromosome defect: A pregnant woman with a family history of chromosome defect are often advised for prenatal diagnosis. The most common abnormality is Down syndrome (Trisomy 21).

Family history of a neural tube defect: If a first-degree relative of the foetus (parent or sib) has a neural tube defect, the risk to the foetus is in the 2 to 5 percent range. If more remote relatives are affected, the risk of the foetus is less but may still be above the population risk.

Other indications for prenatal diagnosis include structural aberrations in a family or previous pregnancy, single gene genetic disorders, parental consanguinity, mental retardation etc.

Techniques of prenatal diagnosis: There are several techniques available for prenatal diagnosis. The following are some of the methods.

Amniocentesis: In this technique amniotic fluid would be aspirated by inserting a needle through the abdomen into the mother's amniotic cavity (Fig. 3.1). This procedure is to be performed under ultrasound guidance. Amniocentesis is usually carried out between 14-16 weeks of gestation and 10-20ml of amniotic fluid is aspirated. The cells have to be cultured for an average of 8-14 days to obtain a foetal karyotype. The risk of the method appears very small; however there is a small risk of inducing miscarriage. With this method Karyotyping and some biochemical disorders can be detected.

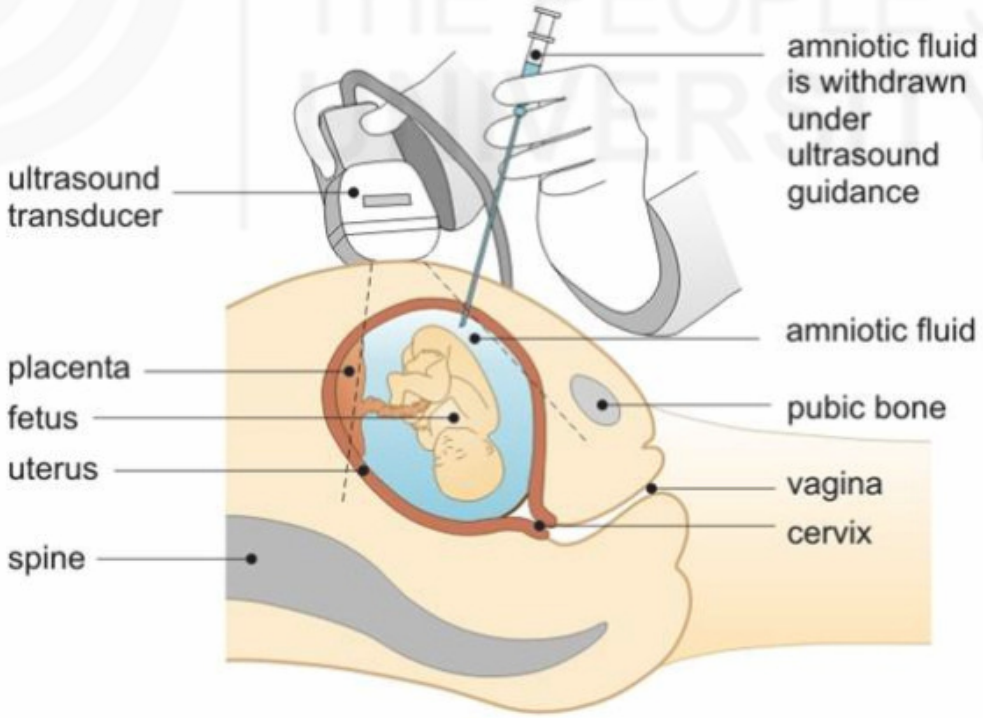

Fig. 3.1: Aspiration of amniotic fluid (source:gi.net.au)

Chorionic villus sampling: This technique is carried out between 9 and 12 weeks of gestation and involves the removal of small amount of placenta. This

technique is suitable for chromosome analysis following the determination of a high risk of chromosome abnormality. The advantage of this technique is early and definitive chromosomal analysis. This test bears a risk of pregnancy loss varying from 1 to 3 percent. In this technique karyotyping, DNA and biochemical disorders can be detected.

Foetal blood sampling: This technique is also called cordocentesis. It involves the removal of small amount of foetal blood by inserting a small needle into the site where the cord joins the placenta. In this technique rapid karyotyping can be done.

3.5 GENE THERAPY

Gene therapy can be defined as the insertion of genetic material into cells for the treatment of disease. Although gene therapy was envisaged initially as a means of treating inherited genetic diseases, disciplines as diverse as oncology, cardiology, endocrinology, and infectious diseases are currently developing novel therapeutic strategies that have in common gene transfer into cells.

Gene therapy naturally intends to supplement a defective mutant allele with a functional one. In most gene therapy studies, a normal gene is inserted into the genome to supplement an abnormal disease causing gene. To deliver the therapeutic gene to the patient's target cells, a carrier called a vector have to be used. Currently, the most common vector is a virus that has been genetically altered to carry normal human DNA. The vector unloads its genetic material containing the therapeutic human gene into the target cell. The generation of a functional protein product from the therapeutic gene restores the target cell to a normal state.

Types of Gene Therapy

Gene Therapy can be classified into two types: Somatic gene therapy and Germ line gene therapy.

Somatic gene therapy

In this gene therapy, the therapeutic genes are moved into the somatic cells or body of a patient. Due to somatic gene therapy the modifications that occur will be restricted to the individual patient only. But these modifications will not be inherited by the patient's offspring or later generations.

Germ line gene therapy

In this type, germ cells such as sperm or eggs are modified by the introduction of genes which are in function and these functional genes are included into their genomes. In this type the modifications would be heritable to and passed on to later generations. But this type is highly controversial for a variety of technical and ethical reasons.

The gene therapy can be categorised into two types: *in vivo* therapy and *ex vivo* therapy. In the case of *in vivo* therapy the therapeutic genes are directly introduced in to the patient's body (fig. 3.2) and in *ex vivo* category the cells are removed from the patient and after manipulation they are returned to the patient (fig. 3.3).

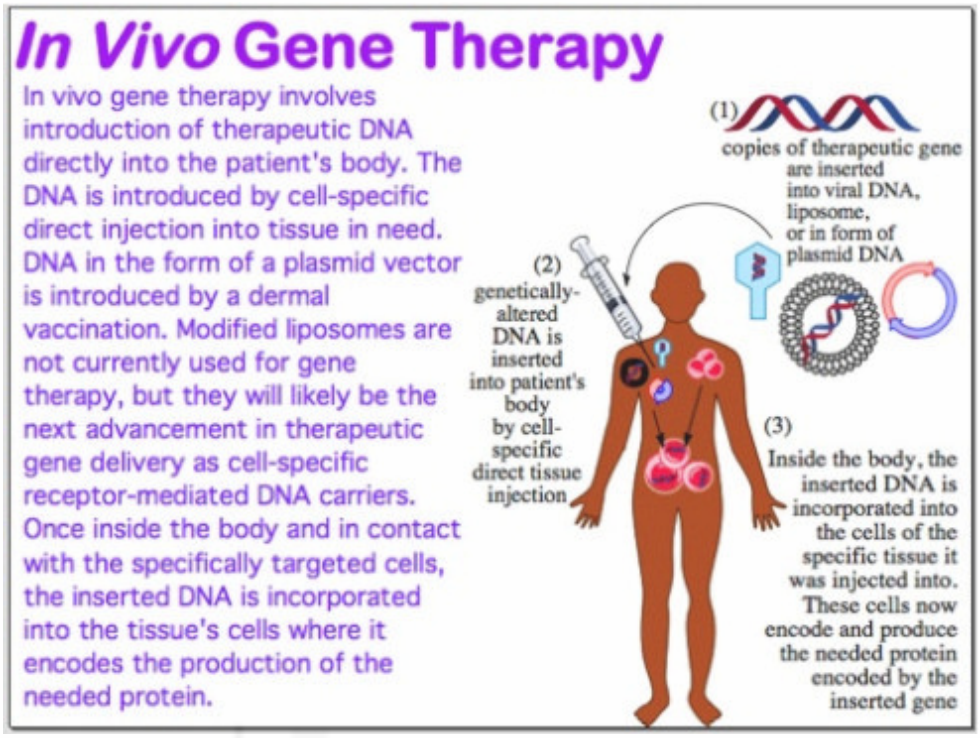

Fig. 3.2: Schematic representation of *in vivo* Gene therapy (source: gene-therapy.yolasite.com)

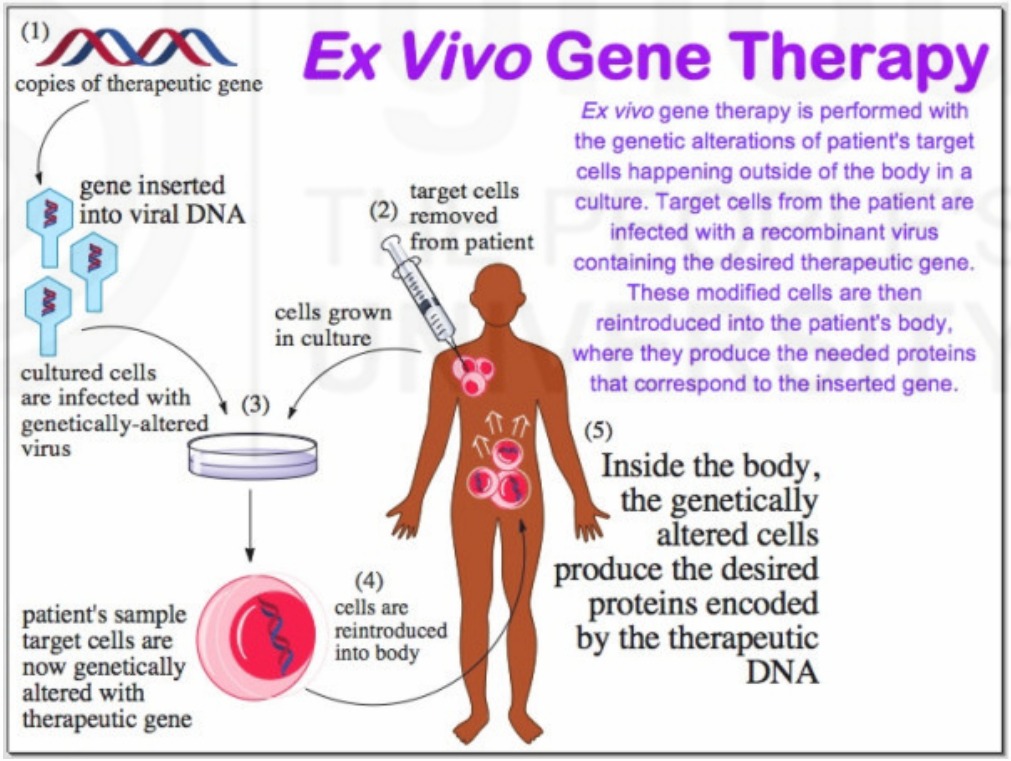

Fig. 3.3: Schematic representation of ex *vivo* Gene therapy (source: en.wikibooks.org)

3.6 SUMMARY

Genetic disease is caused by variation or alteration called mutation in gene, or alteration in chromosome. Genetic diseases can be classified into simple and complex diseases. Simple genetic diseases are also called as monogenetic or Mendelian diseases caused by a mutation. Complex diseases have multi-factorial causation. They are caused by the interaction of many genes and gene -

environmental interaction. Screening the genetic diseases in the population and genetic counselling to the couples is a prerequisite in avoiding the defective progeny. To prevent the genetic diseases, prenatal diagnosis and termination of defective zygote is one of the best ways. Gene therapy is the treating method for genetic diseases, it involves in correcting the default genetic sequence. Currently available method for preventing genetic diseases is to identify the faulty genetic code at an early stage and change the life style. By changing the life style we can prevent some late onset genetic diseases. In curing the genetic diseases future research may bring success in gene therapy.

Further Reading

Gardner, A, Howell, R.T and Davies, T. 2008. Human Genetics. New Delhi: Viva Books private Ltd.

Hartl, D.L. 1991. Basic Genetics. Boston: Jones and Bartlett Publishers.

Mueller, RF and Young, ID. 1995. Emery's Elements of medical genetics. New York and London: Churchill Livingstone.

Thompson, JS and Thompson, MW. 2005. Genetics in Medicine. Philadelphia and London: WB Saunders Company.

Uhlmann, WR, Schuette, JL and Yashar, BM. 2009. A guide to Genetic counseling. New Jersey: Wiley-Blackwell.

Verma, PS and Agarwal, VK. 1999. Cell Biology, Genetics, Molecular Biology, Evolution and Ecology. New Delhi: S. Chand & company Ltd.

Sample Questions

1) What is a genetic disease? Briefly explain on various genetic diseases.
2) Discuss briefly about Prenatal diagnosis.
3) What is genetic screening? Explain its processes.
4) Write short notes on the following:
    a) Gene therapy
    b) Genetic counselling