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A REVIEW ON GENETIC LEVEL THERAPY FOR NEONATAL PROBLEMS

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Abstract

In spite of developments of neonatal intensive care medicine. It is still difficult or impossible to treat several inherited genetic disorders using conventional pharmacological methods. Gene therapy is a promising alternate approach for treating a variety of genetic disorders. By the time the patient reaches adulthood, however, it is often too late for effective treatment. But several of these cases, neonatal gene therapy appears potentially useful against inherited disorders that are not obviously treatable through any other methods.

Key Words: Genetic therapy, Neonatal Problems, DNA, RNA.

1. INTRODUCTION

Although there have been significant advances in neonatal intensive care medicines several neonatal disorders remain major causes of mortality and morbidity. Consequently there is an urgent need for development for new safe and effective therapies to improve the outcomes of these interactable devastating neonatal disorders. Gene therapy is an exciting and promising approach to treat many diseases for which there are still no effective therapies to date, more than 2400 clinical trails of gene therapy protocols have been attempted in afford to treat various genetic diseases as well as many types of cancers and infectious diseases The results of preclinical studies suggest that neonatal gene therapies represent potentially although neonatal gene therapies have several advantages over similar therapies used in adult patients, there is as yet no clinical protocol for use of gene therapy in newborninfants. This chapter describes a strategy per the use of neonatal gene therapy in the treatment of inherited disorder.

Figure-1

GENE

- The gene is considered the basic unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify physical and biological traits. Most genes code for specific proteins, or segments of proteins, which have differing functions within the body.
- Gene structure is the organization of specialized sequence elements within a gene. Gene contains most of the information necessary for living cells to survive and reproduce. In most organisms, genes are made of DNA, where the particular DNA sequence determines thefunction of the gene.

DNA

- Deoxyribonucleic acid [abbreviated DNA] is the molecule that carries genetic information forthe development and functioning of an organism. DNA is mad of two linked strands that wind around each other to resemble a twisted ladder – a shape known as a double helix.
- Most DNA is located in the cell nucleus [where it is called nuclear DNA], but a small amountof DNA can also be found in the mitochondria [where it is called mitochondrial DNA or mtDNA]

RNA

- Ribonucleic acid [RNA] is a molecule that present in the majority of living organisms and viruses. It is made up of nucleotides, which are ribose sugars attached to nitrogenous bases and phosphate groups. The nitrogenous bases include adenine, guanine, uracil, and cytosine.
- The primary functions of RNA:Facilitate the translation of DNA into proteins. Functions as an adapter molecule in protein synthesis. Serves as a messenger between DNA and the ribosomes. They are the carrier of genetic information in all living cells.

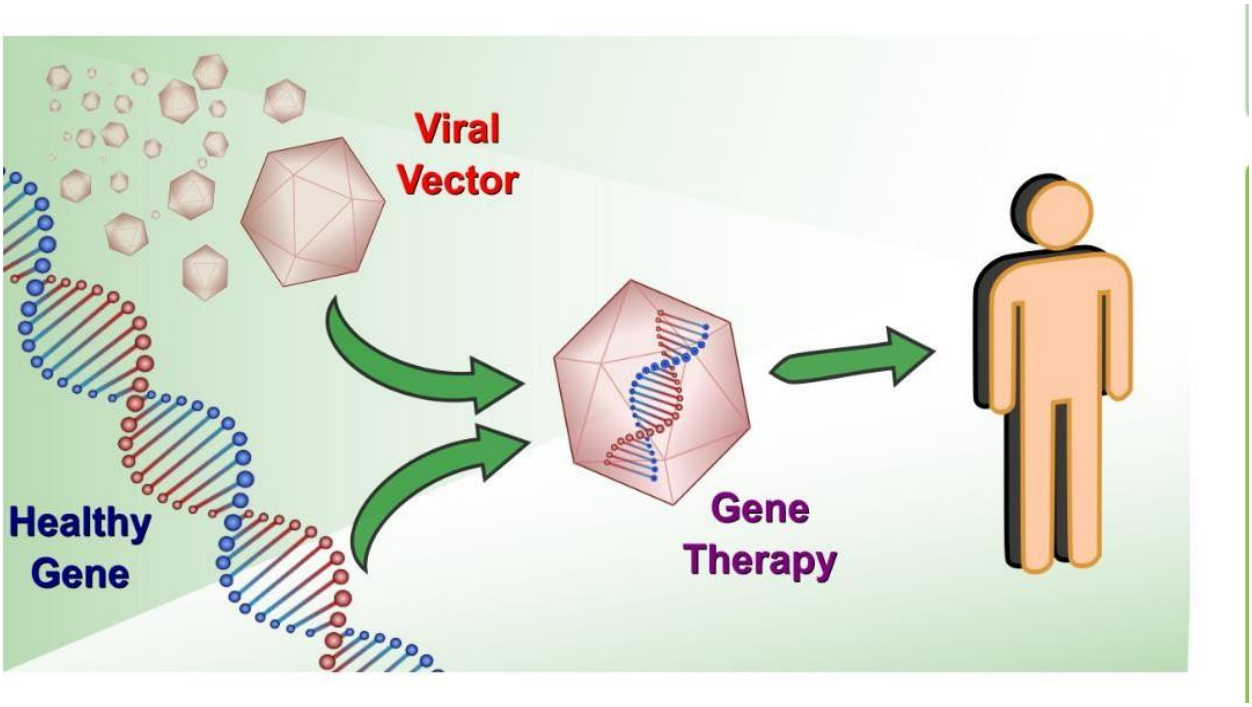
CHROMOSOMES

- Chromosomes are thread like structures located inside the nucleus of animal and plant cells. Each chromosome is made of protein and a single molecule of deoxy ribonucleic acid(DNA).Passed from parents to offspring, DNA contains the specific instructions that make each type of living creature unique.

GENE THERAPY

- Gene therapy is the introduction of genes into existing cells to prevent or cure a wide range of diseases.
- It is a technique for correcting defective genes responsible for disease development.
- The first approved gene therapy experiment occurred on September 14,1990 in USA, when Ashanti De Silva was treated for ADA-SCID.

Figure-2



TYPES OF GENE THERAPY

The gene therapy is of two types

1. Somatic cell gene therapy
2. Germ line gene therapy

Somatic cell gene therapy:

- Therapeutic genes transferred into the somatic cells.
- Eg: Introduction of genes into bone marrow cells, blood cells, skin cells etc.
- Will not be inherited later generations.
- At present all researchers directed to correct genetic defects somatic cells.

Germ line gene therapy:

- Therapeutics genes transfer into the germ cells.

- Eg: Genes introduced into eggs and sperms.
- It is heritable and passed on to later generations.
- For safety, ethical and technical reasons it is note being attempted at present.

APPROACHES IN GENE THERAPY

There are two types of approaches:

1. In vivo gene therapy
2. Ex vivo gene therapy

In vivo gene therapy

- Direct delivery of therapeutic gene into target cell intopatient`s body.
- Carried out by viral or non viral vector systems.
- It can be the only possible option in patients where individual cells cannot be cultured in vitroin sufficient numbers (e.g. brain cells).
- In vivo gene transfer is necessary when cultured cells cannot be re-implanted in patients effectively.

Ex vivo gene therapy

Isolate cells with genetic defect from a patient

↓

Grow the cells in culture

↓

Introduce the therapeutic genes

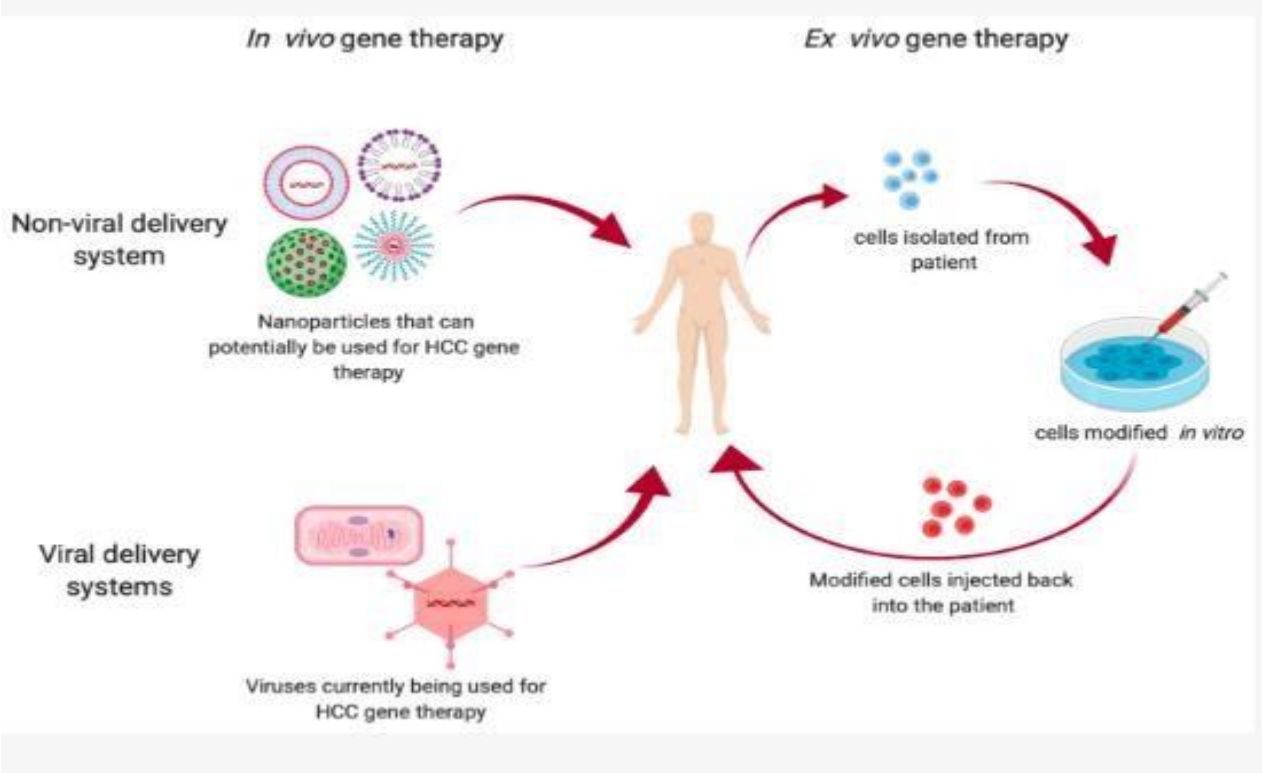
↓

Select genetically corrected cells and grow

↓

Transplant the modified cells to the patient

Figure-3



OTHER TYPES OF GENE THERAPY

There are two types of gene therapy

1. Gene augmentation therapy
2. Gene inhibition therapy

GENE AUGMENTATION THERAPY

- Most common form of gene therapy
- Foreign gene replaces missing or defective gene
- E.g. Replacement of defective p53 gene by a normal one in liver cancer

GENE INHIBITION THERAPY

- Done to block the over production of some proteins
- 2 types-Antigene and Antisense therapy

1. Anti gene-Blocks transcription using anti gene oligonucleotide
2. Antisense -blocks translation using antisense oligonucleotide

Vectors in Gene Therapy

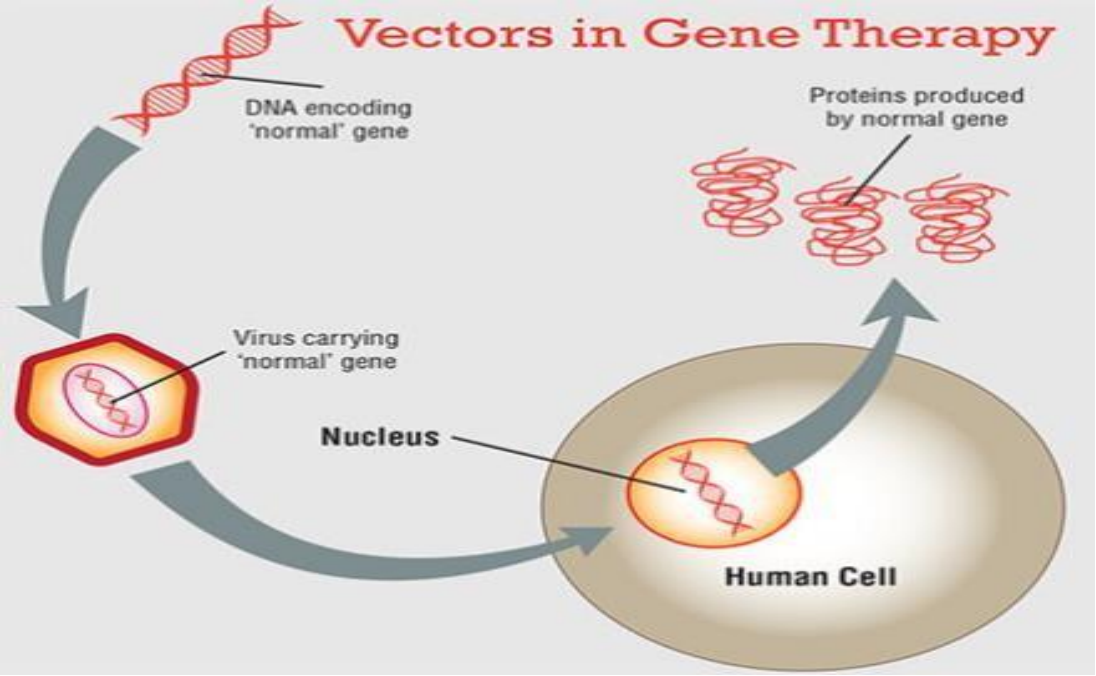
1. To transfer the desired gene into a target cell a carrier is required. such vehicles gene delivery are known as vectors.

2. Two main classes

- Viral vector

➢ Non viral vector

Figure-4



VIRAL VECTORS:

EX: Retro virus vector systemAdeno virus vector system

NON VIRAL VECTORS:

EX: Pure DNA constructs Human artificial chromosomes

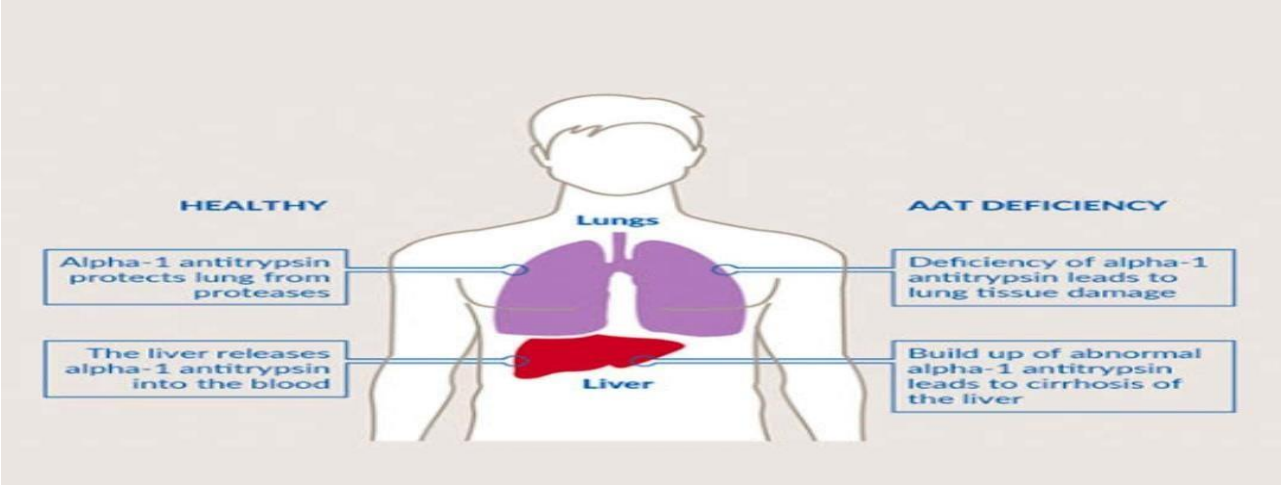
3. Diseases treated by gene therapy:

There are several types of diseases treated by the gene therapy.

- Alpha-1 antitrypsin deficiency
- Cystic fibrosis
- Hemophilia
- Beta thalassemia
- Sickle cell disease
- Fragile x syndrome
- Cancer
- Heart disease
- Aids

ALPHA 1 Antitrypsin [AAT] deficiency3.1DEFINITION:

It is a condition that raises your risk lung and other disease AAT is a protein made in your liver to



help protect the lungs If your body does not make enough AAT Your lungs are more easily damagedfrom smoking pollution or dust from the environment.Alpha -1 antitrypsin is a protease inhibitor produced primarily in the liver.

Figure-5

ETIOLOGY:

- Exposure to tobacco smoke
- Chemicals
- Dust
- Deficiency is caused by mutations in the SERPINA 1 gene located on chromosome 14

SYMPTOMS:

- ❖ Shortness of breath
- ❖ Wheezing
- ❖ Chronic cough with spectrum
- ❖ Fatigue or tiredness

Diagnosis:

➢ A blood test: check the level of AAT protein in your blood. If the level is lower than normal ,it is likely that you have AAT deficiency.

➢ A genetic test: The most certain way to check foe AAT deficiency and should be done to deficiency and should be done to confirm the results of the blood test and find the mutation inthe AAT gene .

Treatment:

The general strategy of AAT gene therapy to argument lung levels of AAT focuses on delivering the normal human M-type AAT complementary DNA under control of a constituent promoter using a gene transfer

vector so the transduced cells secrete the protein to the blood after a single administration

CYSTIC FIBROSIS

DEFINITION:

An inherited life threatening disorder that damages the lungs and digestive system. Cysticfibrosis effects the cells the produce mucus sweat and digestive juices it causes these fluids to become thick and sticky they then plug up tube`s ducts and passageways.

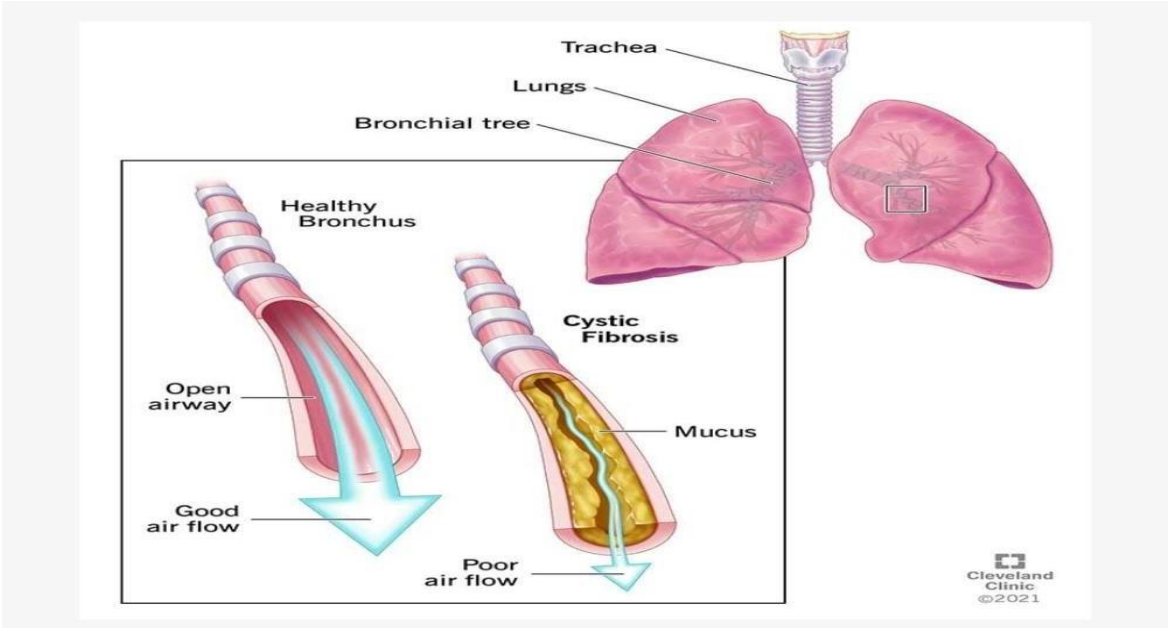


Figure-6

Etiology:

- Cystic fibrosis is due to a mutation in the CF gene on chromosome 7.
- The CF gene encodes a protein in patients known as the cystic fibrosis trans membraneregulator (CFTR).

SYMPTOMS:

- Pneumonia
- Wheezing
- Shortness of breath
- Bronchitis

DIAGNOSIS:

❖ A genetic test: May be used to look for carriers of mutated CFRT genes and to screen relatives of people who have cystic fibrosis.

Treatment:

I. IN cystic fibrosis gene therapy is a process in which a new correct version of the CFTR gene would be placed into the cells in a person`s body.

II. Although the mutant copies of the CFTR gene would still be there , the presence of the correct copies would give cells the ability to make normal CFTR.

HAEMOPHILLIA

DEFINITION:

Hemophilia is a usually an inherited bleeding disorder in which the blood does not clot properly.

ETIOLOGY:

- ❖ Father without hemophilia [XY] C4 Carrier mother [XX]
- ❖ Father with hemophilia [XY] and mother whomis not carrier

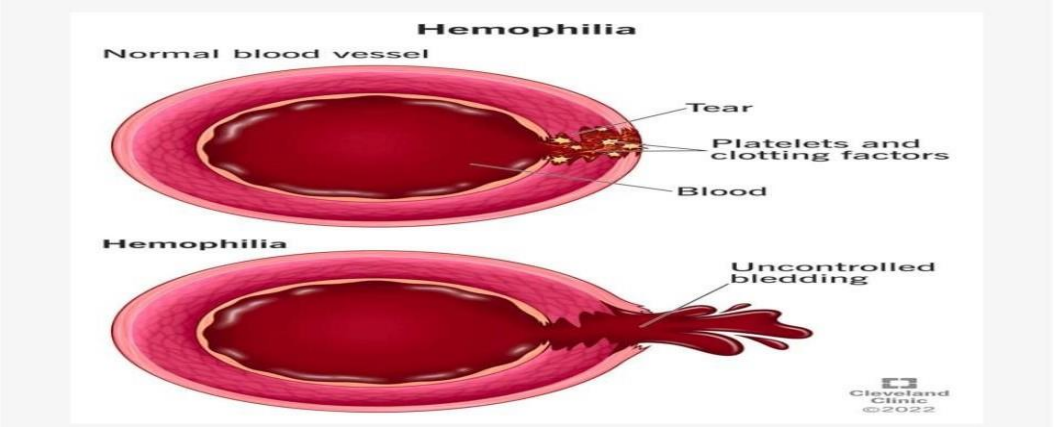


Figure-7

HEMOPHILLIA TYPES

1 .Hemophilia A [classic hemophilia]

This type is caused by a lack or decreasing of clotting factor 8

2. Hemophillia B [Christmas disease]

This type is caused by a lack or by decreasing of clotting factors 4.

SYMPTOMS:

- ❖ Bleeding into the joints causing swelling C4 pain
- ❖ Easy bruising C4 bleeding
- ❖ Bleeding of the mouth C4 gums that is hard to stop
- ❖ Blood in the urine or stop
- ❖ Frequent and hard to stop nose bleeds
- ❖ Heavy bleeding from minor injuries

DIAGNOSIS:

- Screening tests
- Clotting factor test

TREATMENT:

- Gene therapy for hemophilia is based on the transfer of a non -pathogenic and non - replicating recombinant adeno-associated virus [AAV] the viral of DNA which as been replaced by a bio-engineering gene cassette with a tissue -specific promoter and other regulatory
- The history of hemophilia dates back to the 2nd century AD with the first modern description of the appearing during the 1800 s
- Treatment of hemophilia patient in east Germany prior to and after reunification in 1990

CANCER

DEFINITION:

cancer is a disease in which some of the body`s cells grow uncontrollably and spread to other partsof the body

- Cancer another name is malignant tumor.

Cancer is the uncontrolled growth of abnormal cells anywhere in a body -cancer cell it is also called malignant.

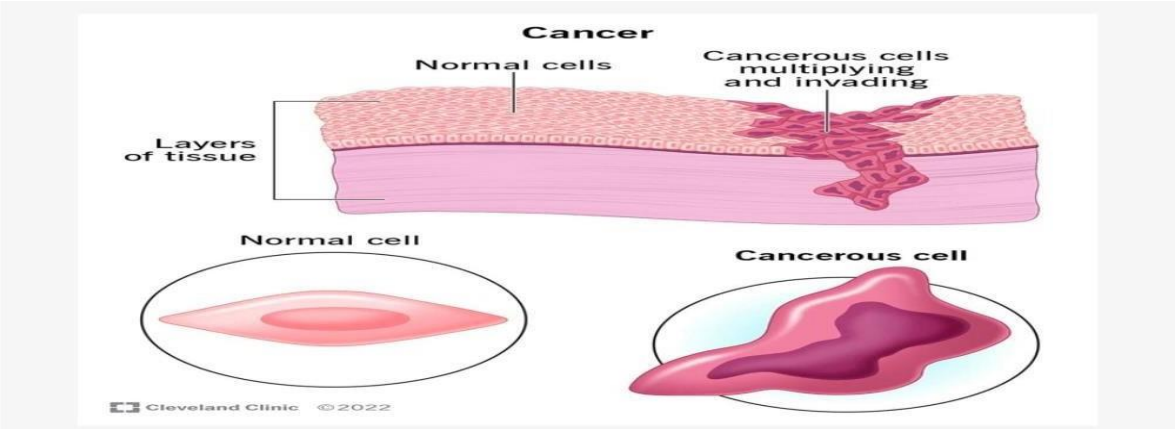


Figure-8

CANCER TYPES

Natural cancer institute gives the common types1 Bladder cancer

2 Breast cancers 3Endometrial cancer4 Leukemia cancers

5 Thyroid cancers

6 lungs cancer

7 melanoma cancer

8 kidney cancer

9 lymphoma cancer

10 prostate cancers

ETIOLOGY:

- Smoking
- Radiation
- Viruses
- Carcinogens
- Obesity
- Hormones
- Chronic inflammation

SYMPTOMS:

- ❖ Fatigue
- ❖ Lump or area of thickening that can be felt under the skin
- ❖ Weigh changes including dead loss [or] gain
- ❖ Skin changes such as changes such as yellowing darkening [or] redness of the skin
- ❖ Changes in bowel [or] bladder habits
- ❖ Persistent cough [or] trouble breath
- ❖ Difficulty swallowing
- ❖ Persistent indigestion [or] discomfort after eating
- ❖ Persistent explained fever [or] night sweats
- ❖ Bruising

DIAGNOSIS:

- Computerized tomography (CT)
- Magnetic resonance imaging (MRI)

- Positron emission tomography (PET)
- Bone scan
- X-ray
- Biopsy

TREATMENT:

➢ A patient participating in a dose escalation gene therapy trail`s in 1999

➢ Gene transfer is a new treatment modality that introduces new genes into a cancer our cells [or] the surrounding tissues to cause cell death [or] slow the growth of the cancer this treatment techniques is very flexible ,and a wide range of gene and vectors are being used in clinical trail`s with success full outcomes

➢ Gene therapy treatment side effects fever and cold If the agent is injected there is after localized swelling and inflammation of the site of the injection

BETA THALASSEMIA

DEFINITION:

Beta thalassemia is an inherited blood disorder in which the body does not make as muchbeta globin as it should Beta globin and alpha globin are building blocks of hemoglobin is a part of red blood cells that carries oxygen throughout the body.

ETIOLOGY:

Beta thalassemia is caused by changes (variants or mutations) in the hemoglobin beta (HBB) gene.

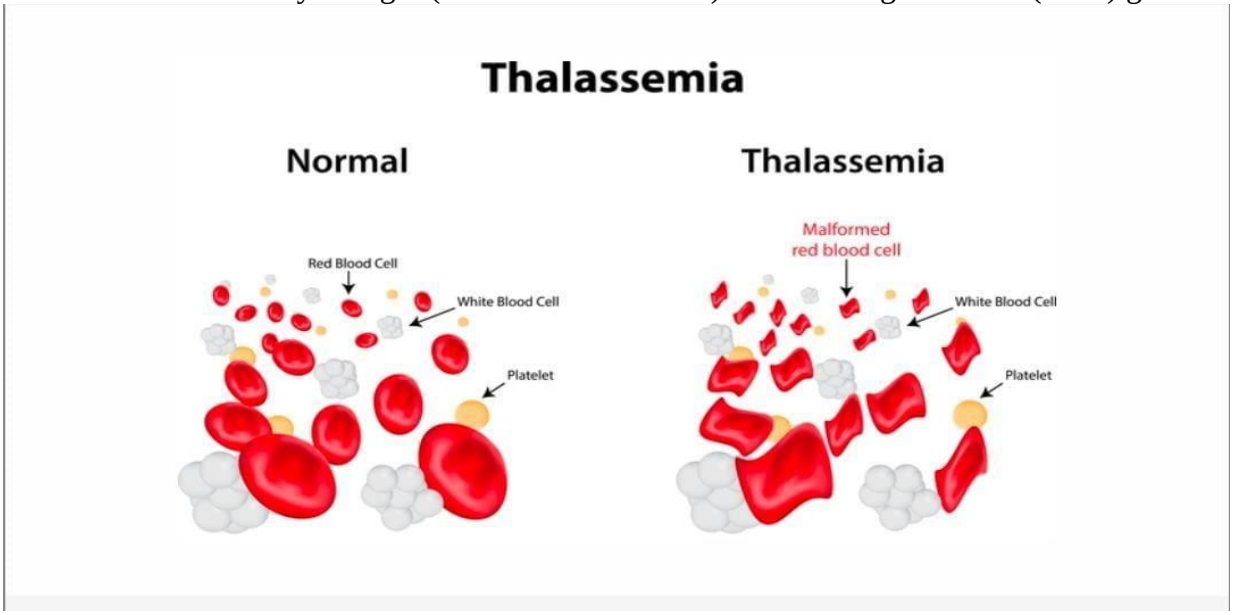


Figure-9

SYMPTOMS:

❖ Extreme tiredness

❖ Pale skin

- ❖ Shortness of breath
- ❖ A fast heartbeat
- ❖ Moodiness or irritability
- ❖ Slow growth
- ❖ Change in the shape of bones in the face and head.

DIAGNOSIS:

Hemoglobin analysis, for which various techniques likeHigh performance liquid chromatography (HPLC)

Electrophoresis

Chromatography

TREATMENT:

➢ The only FDA -approved gene therapy for beta thalassemia brings back normal red blood cells it works by putting functional copies of the abnormal gene into a patients own blood stem cells. The red blood cells are then able to make normal or near normal levels of hemoglobin.

SICKLE CELL ANEMIA

DEFINITION: Sickle cell disease is a genetic disorder in which red blood cells control into a sickle shape thecells die early leaving a shortage of healthy red blood cells [sickle cell anemia] and can block blood flow causing pain [sickle cell crises].

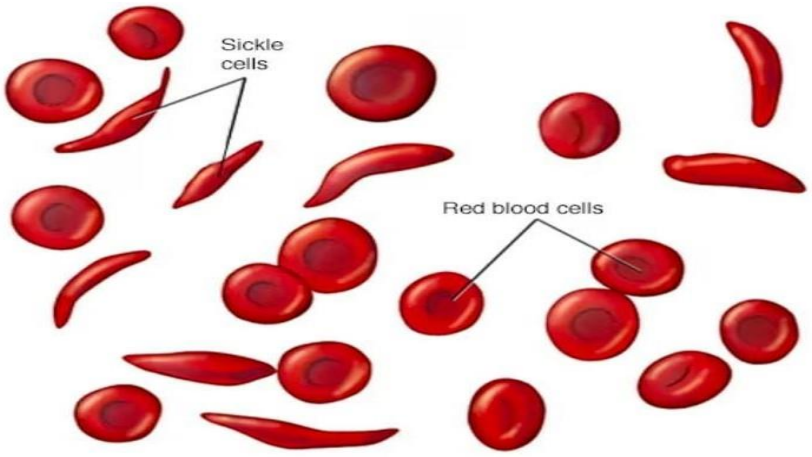


Figure-10

ETIOLOGY:

Caused by defect in a gene.

SYMPTOMS:

- ❖ Anemia sickle cells break apart easily and die
- ❖ Episodes of pain periodic episodes of extremely pain called pain crises are a major symptomsof

sickle cell anemia

- ❖ Swelling of hands and feet
- ❖ Frequent infections
- ❖ Delayed growth or puberty
- ❖ Vision problems

DIAGNOSIS:

- o Blood test
- o Genetic test

TREATMENT:

- ➢ In case of LYFGENIA the gene therapy is specifically designed to treat the underlying cause of sickle cell disease by adding a functional gene that does not form into the crescent shape associated with the disease.

FRAGILE X SYNDROME

DEFINITION:

Fragile x syndrome is a genetic disorder FXS is caused by changes in a gene called fragile x syndrome messenger ribonucleoprotein 1 FMR1 usually makes a protein called FMRP that is needed for brain development.

ETIOLOGY:

It is caused by a change to a gene on the X chromosome called FMR1 gene this gene produces a protein that helps the brain functioning normally if the gene is changed or altered in any way it cannot produce its normal protein which can result in fragile x syndrome

SYMPTOMS:

- ❖ Intellectual disability
- ❖ Autism spectrum disorders
- ❖ Abnormal facial features
- ❖ Prominent forehead
- ❖ Large ears

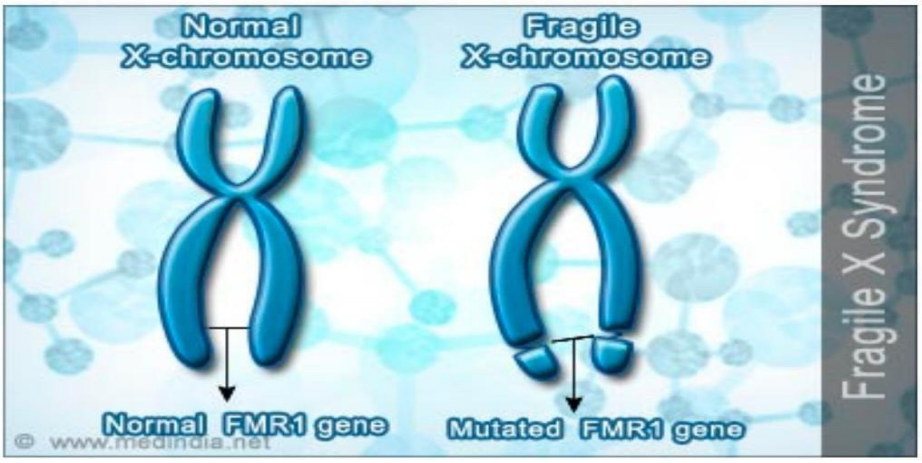


Figure-11

DIAGNOSIS:

- ❖ Testing a person`s DNA from a blood test.

TREATMENT:

- ➢ Gene therapy is a therapeutic approach to treat fragile x a functioning FMR1 gene is delivered to cells using a harmless modified adeno -associated viral vector to induce the expression of FMRP protein
- ➢ Reactivation of FMR1 gene expression is promising strategy for fragile x syndrome therapy the FMR1 gene is subjected to complicated alternative splicing that effects the presence of exons 12 and 14 as well as the choice of acceptor sites in exons 15 and 17.

HEART FAILURE

DEFINITION:

A chronic condition in which the heart doesn`t pump blood as well as it should.

Heart failure can occur if the heart cannot pump blood (systolic) or fill (diastolic) adequately.

ETIOLOGY:

Heart failure is caused by coronary artery disease.

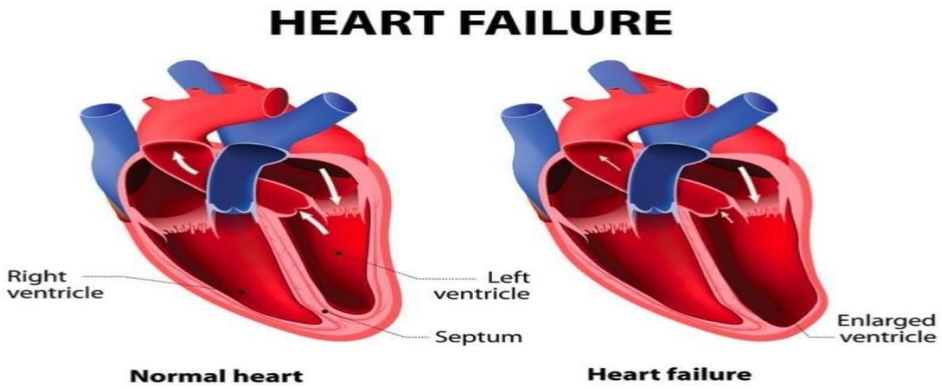


Figure-12

DIAGNOSIS:

Echocardiogram is a test to diagnosis the heart failure.

SYMPTOMS:

- Short of breath
- Tired
- Swollen ankles
- Loss of appetite
- Coughing
- Dizziness
- Sleep disturbance

TREATMENT:

Loss of function variants result in a diminished level of function proteins, which can potentially be addressed through gene replacement therapy. This approach involves introducing a functional transgene into the affected cells, allowing for the restoration of the proper expression of functional protein.

AIDS (Auto immune disorder)

DEFINITION:

HIV causes AIDS and interferes with the body`s ability to fight infections.

The virus can be transmitted through contact with infected blood, semen or vaginal fluids.

ETIOLOGY:

Caused by the human immunodeficiency virus, also called HIV.

SYMPTOMS:

- Rapid weight loss
- Tiredness

- Diarrhea
- Pneumonia
- Sores of the mouth, anus, or genitals.

DIAGNOSIS:

- ELISA (Enzyme linked immunosorbent (assay).
- Antigen antibody test performed by a lab on blood from a vein can usually detect HIV 18 to 45 days after exposure.

TREATMENT:

➢ In this therapy can be achieve in two ways: by preventing de novo infection of susceptible cells by inserting a therapeutic gene before the cell is exposed to the virus and by suppressing ongoing replication in chronically infected cells.

METHODS OF GENE THERAPY

4. METHODS OF GENE THERAPY

GENE THERPY

- Employes a high -pressure delivery system to shoot tissue with gold or tungsten particles thatare coated with DNA

MICROINJECTIONS

- Process of using a glass micropipette to insert microscopic substances into a single living cell
- Normally performed under a specialized optical microscopic setup called micromanipulator

CHEMICAL METHODS USING DETERGENT MIXTURES

❖ Certain charged chemical compounds like calcium phosphates are mixed with functional DNA of desired functions

❖ The mixture is introduced near the vicinity of recipient cells

❖ The chemicals disturb the cell membrane widens the pore size and allows DNA to pass through the cell

LIPOFECTION

- It is a technique used to inject genetic inject genetic materials into a cell by means oliposomes
- Liposomes are artificial phospholipid vesicles used to delivery used to deliver a variety ofmolecules including DNA into the cells

DISADVANTAGES

➢ Long lasting therapy is not achieved by gene therapy due to rapid dividing of cells benefitsof gene therapy is short lived

➢ Immune responses to transferred gene stimulates a potential risk to gene therapy

➢ Viruses used as vectors for gene transfer many cause toxicity immune responses and inflammatory reactions in the host

➢ Disorders caused by defects in multiple genes cannot be treated effectively using genetherapy

5.2.-ADVANTAGES

- Gene therapy has the potential to eliminate to eliminate and prevent hereditary disease suchas cystic fibrosis ADA-SCID etc.
- It is a possible cure for heart disease AIDS and cancer
- It gives someone born with a genetic disease a chance to life
- It can be used to eradicate diseases from the future generations.

6. GENE THERAPY SUCCESSES

Researches have been working for decades to bring gene therapy to the clinic yet very few patients have received any effective gene therapy treatments but the doesn't mean gene therapy is an impossible dream even though gene therapy has been reach patients its future is very encouraging decades of research have taught us a lot about designing safe and effective vectors targeting different types of cells and managing and minimizing immune responses in patients .we have also learned a lot about the disease genes themselves today many clinical traits are under ways where researchers are carefully testing treatments to ensure that any gene therapy brought into the clinical is both safe and effective .

Below are some gene therapy success stories success represent a variety of approaches different vectors different target cells populations and both in vivo and ex vivo approaches to treating a variety of disorders

IMMUNE DEFICINENCES

Several inherited immune deficiencies have been treated successfully with gene therapy most commonly blood cells are used to deliver working copies of the defective genes after the genes have been delivered the stem cells are returned to the patient because the cells are treated outside the patients body the virus will infect and transfer the gene to only the desired target cells

RECENT DEVELOPMENTS

- In a new gene therapy method developed by university of Florida in January 2012 researchers found treatment for a common form of blindness [x -linked retinitis pigmentosa] that strikes both youngsters and adults.
- A gene therapy called NLX-P101 dramatically reduces movement impairment in Parkinson`s patient according to results of a phase 2 study published on march ,2011 in the journal Lancet Neurology.

7. EVOLUTION OF GENE THERAPY:

Gene therapy 1.0: First introduction of corrected genes.Gene therapy 2.0: Improved viral vectors.

Gene therapy 3.0: Gene editing and base editing.

8. CONCLUSION:

- Theoretically gene therapy is the permanent solution for genetic diseases
- But it has several complexities at its current stage it is not accessible to most people due toits huge cost
- A breakthrough may come anytime and a day may come when almost every disease will have a gene therapy
- Gene therapy has the potential to revolutionize the practice of medicine.

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2. INTRODUCTION

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Figure-1

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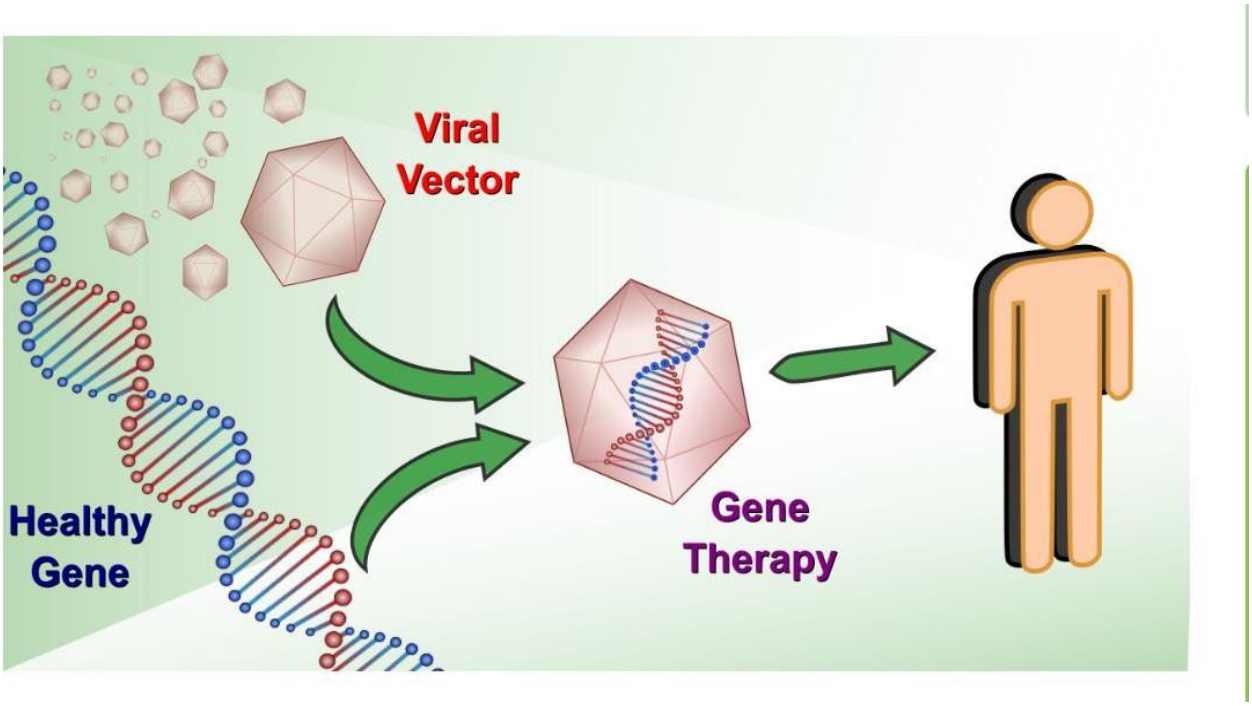

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4. Germ line gene therapy

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- Will not be inherited later generations.
- At present all researchers directed to correct genetic defects somatic cells.

Germ line gene therapy:

- Therapeutics genes transfer into the germ cells.
- Eg: Genes introduced into eggs and sperms.

- It is heritable and passed on to later generations.
- For safety, ethical and technical reasons it is note being attempted at present.

APPROACHES IN GENE THERAPY

There are two types of approaches:

3. In vivo gene therapy
4. Ex vivo gene therapy

In vivo gene therapy

- Direct delivery of therapeutic gene into target cell in to patient`s body.
- Carried out by viral or non viral vector systems.
- It can be the only possible option in patients where individual cells cannot be cultured in vitroin sufficient numbers (e.g. brain cells).
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Ex vivo gene therapy

Isolate cells with genetic defect from a patient

↓

Grow the cells in culture

↓

Introduce the therapeutic genes

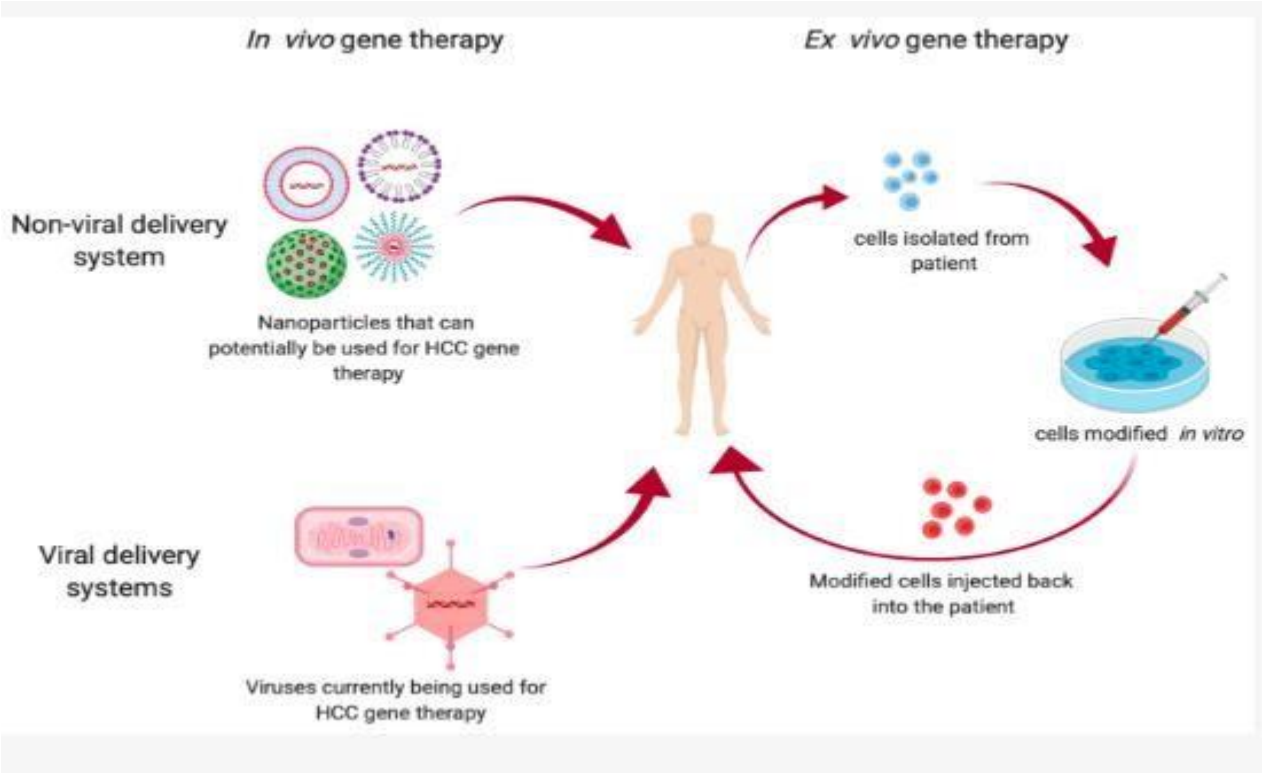
↓

Select genetically corrected cells and grow

↓

Transplant the modified cells to the patient

Figure-3



OTHER TYPES OF GENE THERAPY

There are two types of gene therapy

3. Gene augmentation therapy
4. Gene inhibition therapy

GENE AUGMENTATION THERAPY

- Most common form of gene therapy
- Foreign gene replaces missing or defective gene
- E.g. Replacement of defective p53 gene by a normal one in liver cancer

GENE INHIBITION THERAPY

- Done to block the over production of some proteins
- 2 types-Anti gene and Antisense therapy

3. Anti gene-Blocks transcription using anti gene oligonucleotide
4. Antisense -blocks translation using antisense oligonucleotide

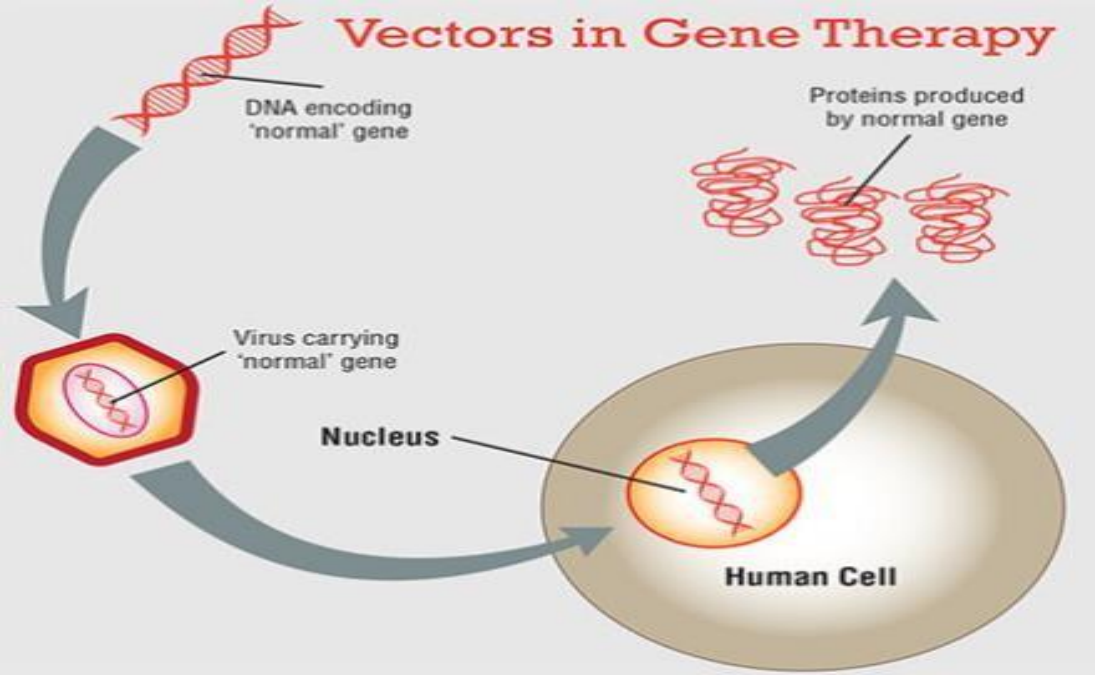
Vectors in Gene Therapy

4. To transfer the desired gene into a target cell a carrier is required. such vehicles gene delivery are known as vectors.

5. Two main classes

- Viral vector
- Non viral vector

Figure-4



VIRAL VECTORS:

EX: Retro virus vector systemAdeno virus vector system

NON VIRAL VECTORS:

EX: Pure DNA constructs Human artificial chromosomes

6. Diseases treated by gene therapy:

There are several types of diseases treated by the gene therapy.

- Alpha-1 antitrypsin deficiency
- Cystic fibrosis
- Hemophilia
- Beta thalassemia
- Sickle cell disease
- Fragile x syndrome
- Cancer
- Heart disease
- Aids

ALPHA 1 Antitrypsin [AAT] deficiency3.1DEFINITION:

It is a condition that raises your risk lung and other disease AAT is a protein made in your liver to help protect the lungs If your body does not make enough AAT Your lungs are more easily damagedfrom smoking pollution or dust from the environment.

Alpha -1 antitrypsin is a protease inhibitor produced primarily in the liver.

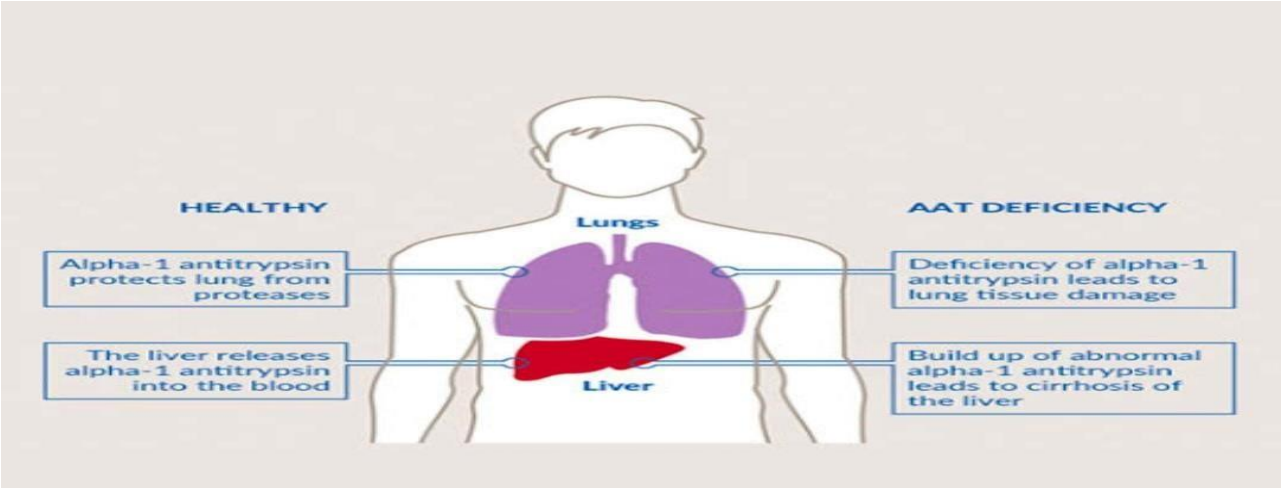


Figure-5

ETIOLOGY:

- Exposure to tobacco smoke
- Chemicals
- Dust
- Deficiency is caused by mutations in the SERPINA 1 gene located on chromosome 14

SYMPTOMS:

- ❖ Shortness of breath
- ❖ Wheezing
- ❖ Chronic cough with spectrum
- ❖ Fatigue or tiredness

Diagnosis:

➢ A blood test: check the level of AAT protein in your blood. If the level is lower than normal ,it is likely that you have AAT deficiency.

➢ A genetic test: The most certain way to check foe AAT deficiency and should be done to deficiency and should be done to confirm the results of the blood test and find the mutation inthe AAT gene .

Treatment:

The general strategy of AAT gene therapy to argument lung levels of AAT focuses on delivering the normal human M-type AAT complementary DNA under control of a constituent promoter using a gene transfer vector so the transduced cells secrete the protein to the blood after a single administration

CYSTIC FIBROSIS

DEFINITION:

An inherited life threatening disorder that damages the lungs and digestive system. Cysticfibrosis effects the cells the produce mucus sweat and digestive juices it causes these fluids to become thick and sticky they then plug up tube`s ducts and passageways.

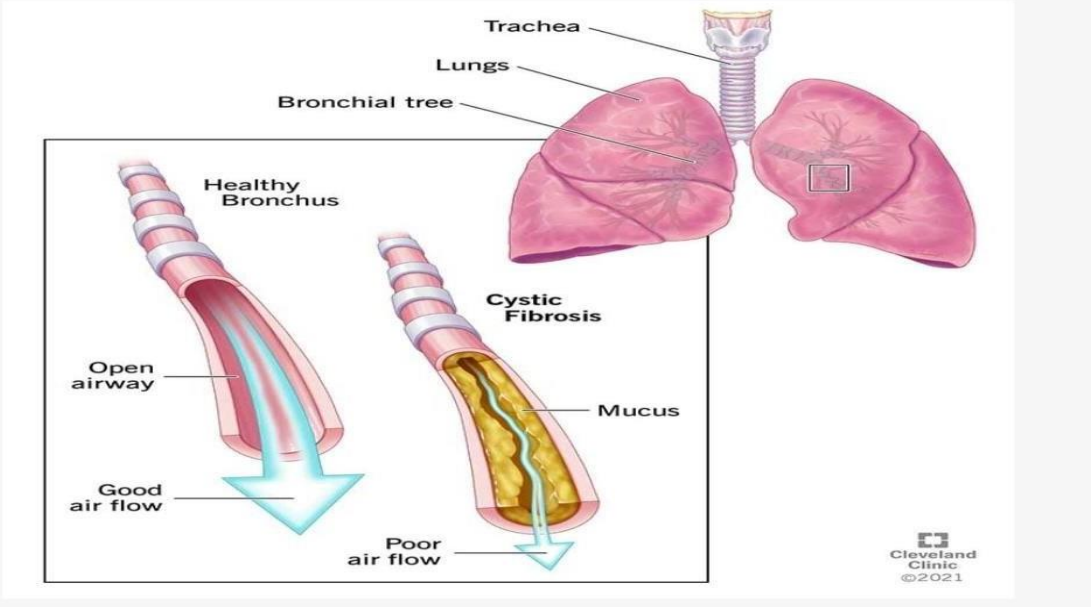


Figure-6

Etiology:

- Cystic fibrosis is due to a mutation in the CF gene on chromosome 7.
- The CF gene encodes a protein in patients known as the cystic fibrosis trans membraneregulator (CFTR).

SYMPTOMS:

- Pneumonia
- Wheezing
- Shortness of breath
- Bronchitis

DIAGNOSIS:

❖ A genetic test: May be used to look for carriers of mutated CFRT genes and to screen relatives of people who have cystic fibrosis.

Treatment:

III. IN cystic fibrosis gene therapy is a process in which a new correct version of the CFTR gene would be placed into the cells in a person`s body.

IV. Although the mutant copies of the CFTR gene would still be there , the presence of the correct copies would give cells the ability to make normal CFTR.

HAEMOPHILLIA

DEFINITION:

Hemophilia is a usually an inherited bleeding disorder in which the blood does not clot properly.

ETIOLOGY:

- ❖ Father without hemophilia [XY] C4 Carrier mother [XX]
- ❖ Father with hemophilia [XY] and mother whomis not carrier

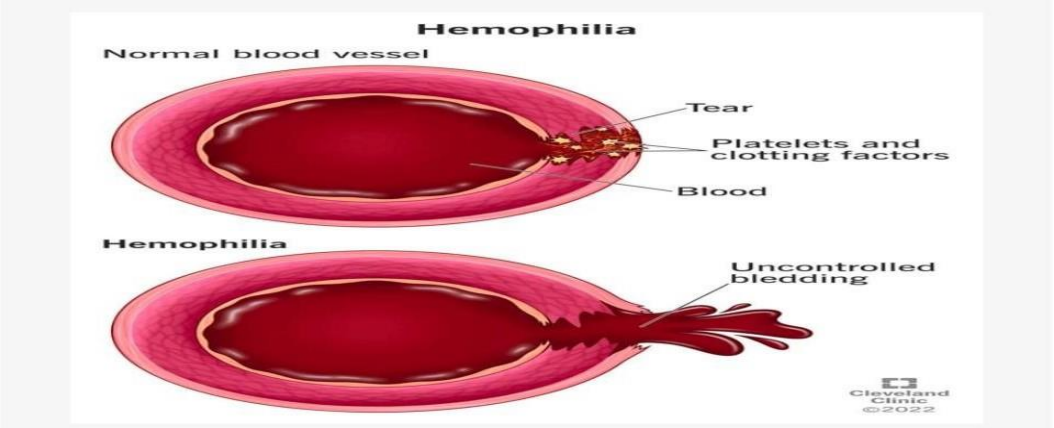


Figure-7

HEMOPHILLIA TYPES

3 .Hemophilia A [classic hemophilia]

This type is caused by a lack or decreasing of clotting factor 8

2. Hemophillia B [Christmas disease]

This type is caused by a lack or by decreasing of clotting factors 4.

SYMPTOMS:

- ❖ Bleeding into the joints causing swelling C4 pain
- ❖ Easy bruising C4 bleeding
- ❖ Bleeding of the mouth C4 gums that is hard to stop
- ❖ Blood in the urine or stop
- ❖ Frequent and hard to stop nose bleeds
- ❖ Heavy bleeding from minor injuries

DIAGNOSIS:

- Screening tests
- Clotting factor test

TREATMENT:

- ➢ Gene therapy for hemophilia is based on the transfer of a non -pathogenic and non - replicating recombinant adeno-associated virus [AAV] the viral of DNA which as been replaced by a bio-engineering gene cassette with a tissue -specific promoter and other regulatory
- ➢ The history of hemophilia dates back to the 2nd century AD with the first modern description of the appearing during the 1800 s
- ➢ Treatment of hemophilia patient in east Germany prior to and after reunification in 1990

CANCER

DEFINITION:

cancer is a disease in which some of the body`s cells grow uncontrollably and spread to other partsof the body

- Cancer another name is malignant tumor.

Cancer is the uncontrolled growth of abnormal cells anywhere in a body -cancer cell it is also called malignant.

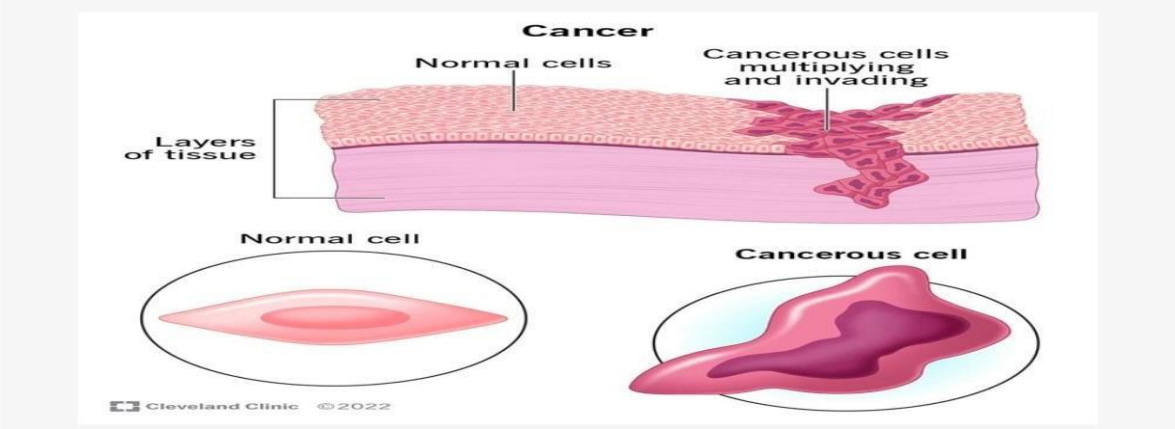


Figure-8

CANCER TYPES

Natural cancer institute gives the common types1 Bladder cancer

4 Breast cancers 3Endometrial cancer4 Leukemia cancers

11 Thyroid cancers

12 lungs cancer

13 melanoma cancer

14 kidney cancer

15 lymphoma cancer

16 prostate cancers

ETIOLOGY:

- Smoking
- Radiation
- Viruses
- Carcinogens
- Obesity
- Hormones

- Chronic inflammation

SYMPTOMS:

- ❖ Fatigue
- ❖ Lump or area of thickening that can be felt under the skin
- ❖ Weigh changes including dead loss [or] gain
- ❖ Skin changes such as changes such as yellowing darkening [or] redness of the skin
- ❖ Changes in bowel [or] bladder habits
- ❖ Persistent cough [or] trouble breath
- ❖ Difficulty swallowing
- ❖ Persistent indigestion [or] discomfort after eating
- ❖ Persistent explained fever [or] night sweats
- ❖ Bruising

DIAGNOSIS:

- Computerized tomography (CT)
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Bone scan
- X-ray
- Biopsy

TREATMENT:

- ➢ A patient participating in a dose escalation gene therapy trail`s in 1999
- ➢ Gene transfer is a new treatment modality that introduces new genes into a cancer our cells [or] the surrounding tissues to cause cell death [or] slow the growth of the cancer this treatment techniques is very flexible ,and a wide range of gene and vectors are being used in clinical trail`s with success full outcomes
- ➢ Gene therapy treatment side effects fever and cold If the agent is injected there is after localized swelling and inflammation of the site of the injection

BETA THALASSEMIA

DEFINITION:

Beta thalassemia is an inherited blood disorder in which the body does not make as muchbeta globin as it should Beta globin and alpha globin are building blocks of hemoglobin is a part of red blood cells that carries oxygen throughout the body.

ETIOLOGY:

Beta thalassemia is caused by changes (variants or mutations) in the hemoglobin beta (HBB) gene.

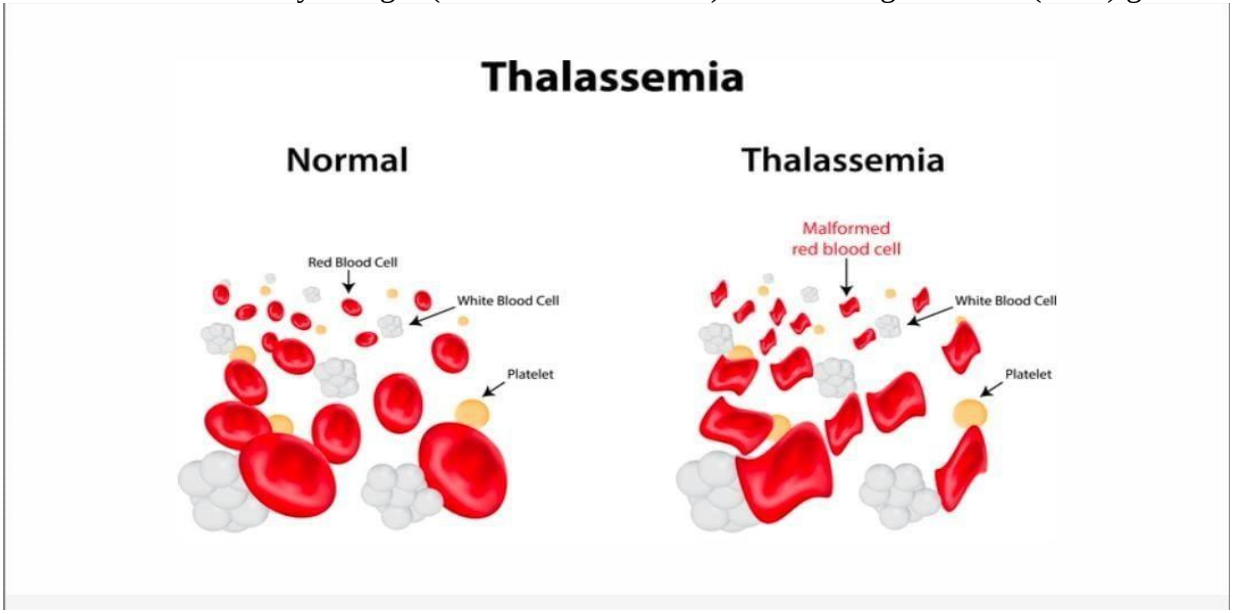


Figure-9

SYMPTOMS:

- ❖ Extreme tiredness
- ❖ Pale skin
- ❖ Shortness of breath
- ❖ A fast heartbeat
- ❖ Moodiness or irritability
- ❖ Slow growth
- ❖ Change in the shape of bones in the face and head.

DIAGNOSIS:

Hemoglobin analysis, for which various techniques likeHigh performance liquid chromatography (HPLC)

Electrophoresis

Chromatography

TREATMENT:

➢ The only FDA -approved gene therapy for beta thalassemia brings back normal red blood cells it works by putting functional copies of the abnormal gene into a patients own blood stem cells. The red blood cells are then able to make normal or near normal levels of hemoglobin.

SICKLE CELL ANEMIA

DEFINITION: Sickle cell disease is a genetic disorder in which red blood cells control into a sickle shape thecells die early leaving a shortage of healthy red blood cells [sickle cell anemia] and can block blood flow causing pain [sickle cell crises].

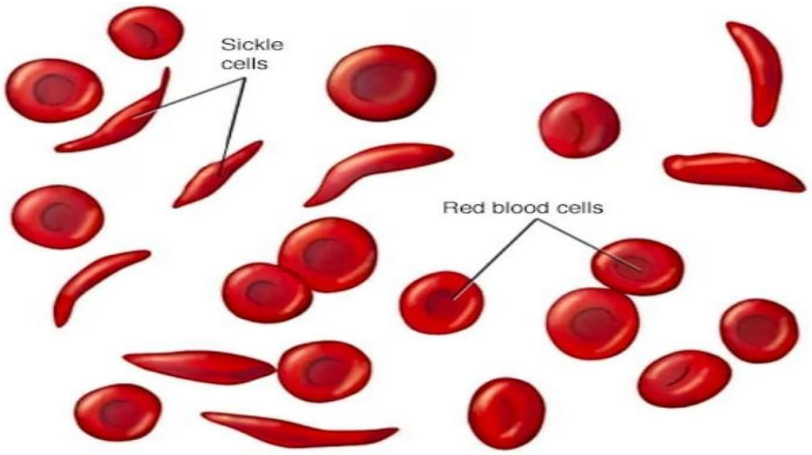


Figure-10

ETIOLOGY:

Caused by defect in a gene.

SYMPTOMS:

- ❖ Anemia sickle cells break apart easily and die
- ❖ Episodes of pain periodic episodes of extremely pain called pain crises are a major symptomsof sickle cell anemia
- ❖ Swelling of hands and feet
- ❖ Frequent infections
- ❖ Delayed growth or puberty
- ❖ Vision problems

DIAGNOSIS:

- o Blood test
- o Genetic test

TREATMENT:

- ➢ In case of LYFGENIA the gene therapy is specifically designed to treat the underlying cause of sickle cell disease by adding a functional gene that does not form into the crescent shape associated with the disease.

FRAGILE X SYNDROME

DEFINITION:

Fragile x syndrome is a genetic disorder FXS is caused by changes in a gene called fragile x syndrome messenger ribonucleoprotein 1 FMR1 usually makes a protein called FMRP that is needed for brain development.

ETIOLOGY:

It is caused by a change to a gene on the X chromosome called FMR1 gene this gene produces a protein that helps the brain functioning normally if the gene is changed or altered in any way it cannot produce its normal protein which can result in fragile x syndrome

SYMPTOMS:

- ❖ Intellectual disability
- ❖ Autism spectrum disorders
- ❖ Abnormal facial features
- ❖ Prominent forehead
- ❖ Large ears

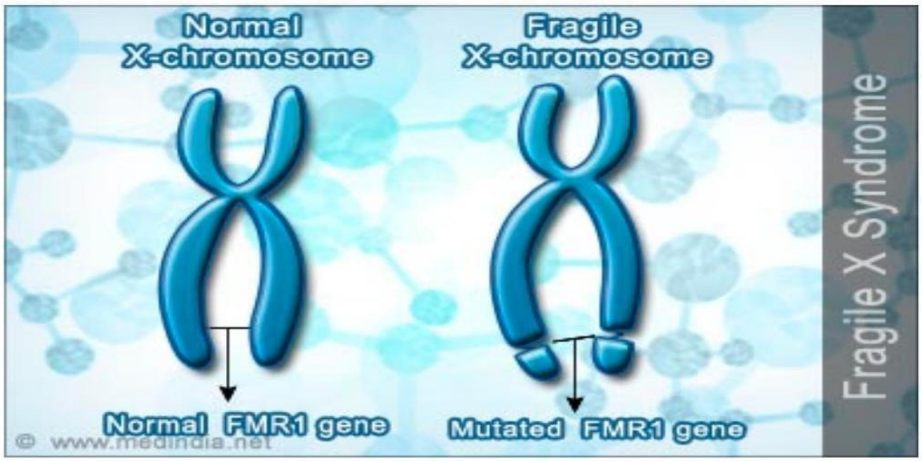


Figure-11

DIAGNOSIS:

- ❖ Testing a person`s DNA from a blood test.

TREATMENT:

➢ Gene therapy is a therapeutic approach to treat fragile x a functioning FMR1 gene is delivered to cells using a harmless modified adeno -associated viral vector to induce the expression of FMRP protein

➢ Reactivation of FMR1 gene expression is promising strategy for fragile x syndrome therapy the FMR1 gene is subjected to complicated alternative splicing that effects the presence of exons 12 and 14 as well as the choice of acceptor sites in exons 15 and 17.

HEART FAILURE

DEFINITION:

A chronic condition in which the heart doesn`t pump blood as well as it should.

Heart failure can occur if the heart cannot pump blood (systolic) or fill (diastolic) adequately.

ETIOLOGY:

Heart failure is caused by coronary artery disease.

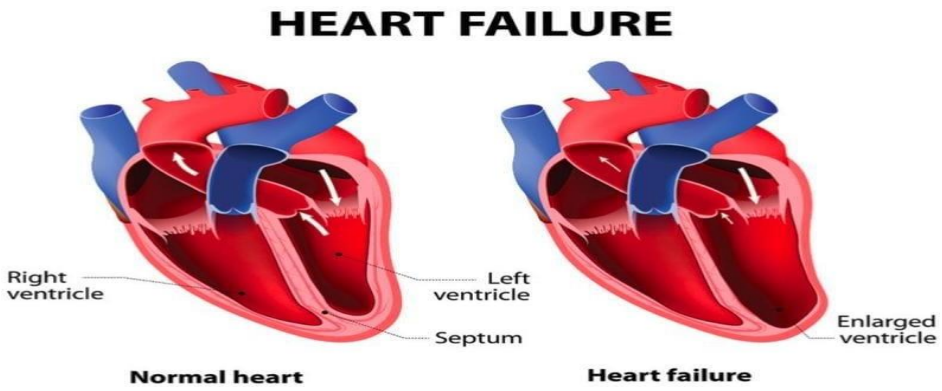


Figure-12

DIAGNOSIS:

Echocardiogram is a test to diagnosis the heart failure.

SYMPTOMS:

- Short of breath
- Tired
- Swollen ankles
- Loss of appetite
- Coughing

- Dizziness
- Sleep disturbance

TREATMENT:

Loss of function variants result in a diminished level of function proteins, which can potentially be addressed through gene replacement therapy. This approach involves introducing a functional transgene into the affected cells, allowing for the restoration of the proper expression of functional protein.

AIDS (Auto immune disorder)

DEFINITION:

HIV causes AIDS and interferes with the body`s ability to fight infections.

The virus can be transmitted through contact with infected blood, semen or vaginal fluids.

ETIOLOGY:

Caused by the human immunodeficiency virus, also called HIV.

SYMPTOMS:

- Rapid weight loss
- Tiredness
- Diarrhea
- Pneumonia
- Sores of the mouth, anus, or genitals.

DIAGNOSIS:

- ELISA (Enzyme linked immunosorbent (assay).
- Antigen antibody test performed by a lab on blood from a vein can usually detect HIV 18 to 45 days after exposure.

TREATMENT:

➢ In this therapy can be achieve in two ways: by preventing de novo infection of susceptible cells by inserting a therapeutic gene before the cell is exposed to the virus and by suppressing ongoing replication in chronically infected cells.

METHODS OF GENE THERAPY

5. METHODS OF GENE THERAPY

GENE THERPY

- Employes a high -pressure delivery system to shoot tissue with gold or tungsten particles thatare coated with DNA

MICROINJECTIONS

- Process of using a glass micropipette to insert microscopic substances into a single living cell
- Normally performed under a specialized optical microscopic setup called micromanipulator

CHEMICAL METHODS USING DETERGENT MIXTURES

❖ Certain charged chemical compounds like calcium phosphates are mixed with functional DNA of desired functions

❖ The mixture is introduced near the vicinity of recipient cells

❖ The chemicals disturb the cell membrane widens the pore size and allows DNA to pass through the cell

LIPOFECTION

- It is a technique used to inject genetic inject genetic materials into a cell by means of liposomes
- Liposomes are artificial phospholipid vesicles used to delivery used to deliver a variety of molecules including DNA into the cells

DISADVANTAGES

➢ Long lasting therapy is not achieved by gene therapy due to rapid dividing of cells benefitsof gene therapy is short lived

➢ Immune responses to transferred gene stimulates a potential risk to gene therapy

➢ Viruses used as vectors for gene transfer many cause toxicity immune responses and inflammatory reactions in the host

➢ Disorders caused by defects in multiple genes cannot be treated effectively using genetherapy

5.2.-ADVANTAGES

➢ Gene therapy has the potential to eliminate to eliminate and prevent hereditary disease suchas cystic fibrosis ADA-SCID etc.

➢ It is a possible cure for heart disease AIDS and cancer

➢ It gives someone born with a genetic disease a chance to life

➢ It can be used to eradicate diseases from the future generations.

9. GENE THERAPY SUCCESSES

Researches have been working for decades to bring gene therapy to the clinic yet very few patients have received any effective gene therapy treatments but the doesn't mean gene therapy is an impossible dream even though gene therapy has been reach patients its future is very encouraging decades of research have taught us a lot about designing safe and effective vectors targeting different types of cells and managing and minimizing immune responses in patients .we have also learned a lot about the disease genes themselves today many clinical traits are under ways where researchers are carefully testing treatments to ensure that any gene therapy brought into the clinical is both safe and effective .

Below are some gene therapy success stories success represent a variety of approaches different vectors different target cells populations and both in vivo and ex vivo approaches to treating a variety of disorders

IMMUNE DEFICINENCES

Several inherited immune deficiencies have been treated successfully with gene therapy most commonly blood cells are used to deliver working copies of the defective genes after the genes have been delivered the stem cells are returned to the patient because the cells are treated outside the patients body the virus will infect and transfer the gene to only the desired target cells

RECENT DEVELOPMENTS

- In a new gene therapy method developed by university of Florida in January 2012 researchers found treatment for a common form of blindness [x -linked retinitis pigmentosa] that strikes both youngsters and adults.
- A gene therapy called NLX-P101 dramatically reduces movement impairment in Parkinson`s patient according to results of a phase 2 study published on march ,2011 in the journal Lancet Neurology.

10. EVOLUTION OF GENE THERAPY:

Gene therapy 1.0: First introduction of corrected genes.Gene therapy 2.0: Improved viral vectors.

Gene therapy 3.0: Gene editing and base editing.

11. CONCLUSION:

- Theoretically gene therapy is the permanent solution for genetic diseases
- But it has several complexities at its current stage it is not accessible to most people due toits huge cost
- A breakthrough may come anytime and a day may come when almost every disease will have a gene therapy

- Gene therapy has the potential to revolutionize the practice of medicine.

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