Introduction

Aim of work

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Aim of this study is to discuss; first the role or gene therapy in the treatment of different diseases, including immunological inherited and infectious diseases, its advantage, disadvantage, and complication. Second to evaluate the role of antisense inhibition of gene expression by interfering with gene function.

Chapter 1

Review of literature

Human gene

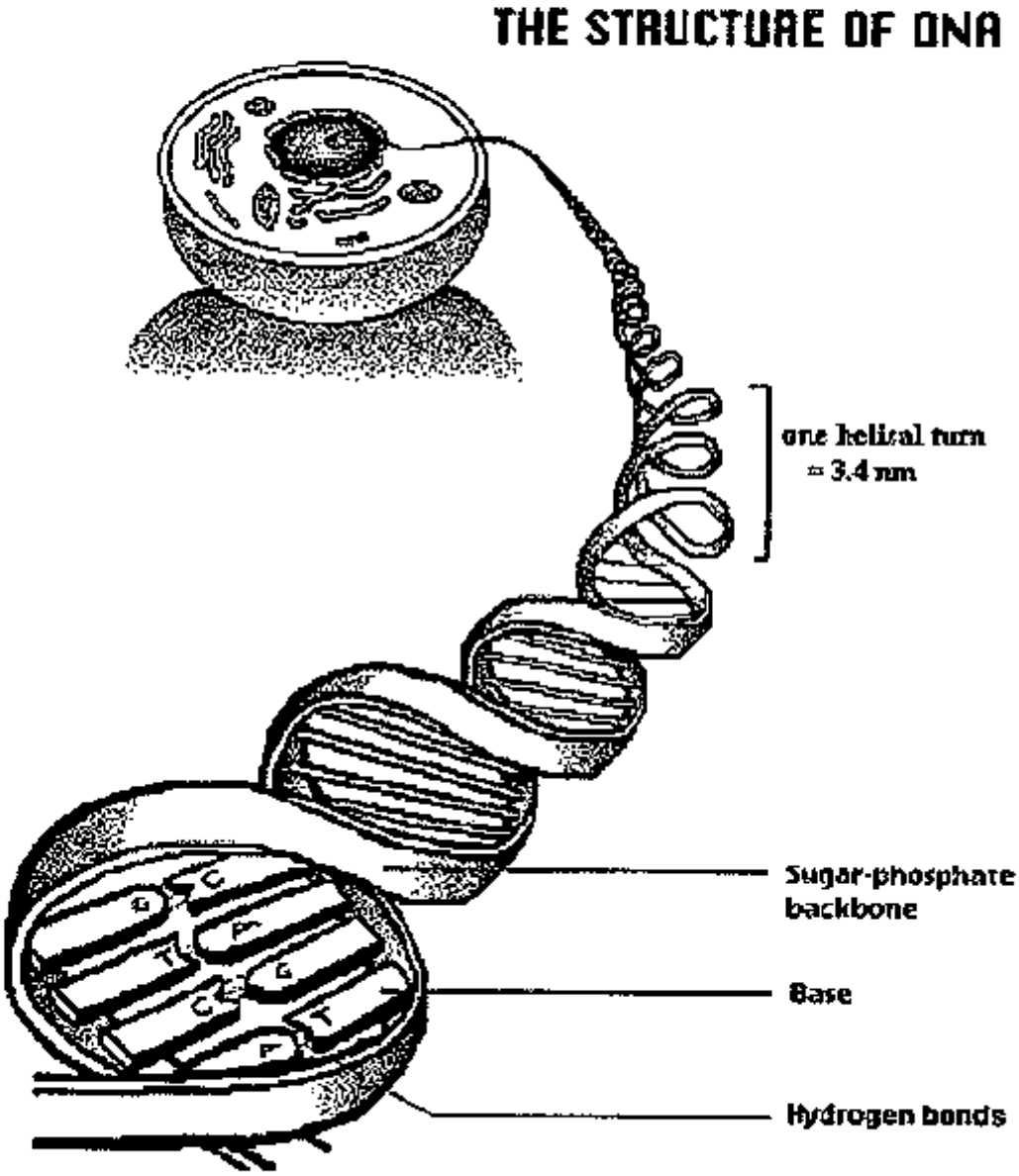
Each human somatic cell contains two copies of entire human genetic program or "genom", amounting to 6 billion base pairs (bp) of DNA.

DNA is a double stranded helix, each step of the helix comprising a base from one strand bonded to that from the other (a base pair). DNA is portioned into 46 (23 pairs) large fragments, each contained in a specific autosomal chromosome or the XorY Chromosomes.

The gene is the functional entity of information. Approximately 50,00 genes are thought to be encode in human DNA. The genes within a cell may be expressed at widely varying level. Some genes are responsible for the specialized function of a cell, like the globin genes of a red blood cell, other genes are considered to have a "house keeping" function, that is, genes that are needed for the maintenance of basic cellular functioning **(Darenell et al, 1990).**

It is known that only genes are located at a particular chromosome. Genes of closely related DNA sequence are located physically near each other; e.g. the alpha &beta globin gene clusters on chromosomes **(Dawkins, 1989).**

Fig (1) DNA structure **(Jacob et al, 1992)**.



electron microscope the chromosome has rounded, rather than irregular morphology.

Each somatic cell nucleus contains two sets of chromosomes, one of which has been inherited from each parent. Members of a pair of chromosome are called homologue. Chromatin is a name given to the material of the chromosome is made, i.e. a combination of DNA and histone proteins. Euchromatin stains lightly and is believed to contain genes, which are actively expressed. In contrast heterochromatin stains darkly and is believed to be made up largely of in^active unexpressed repetitive DNA. **(Lewin, 1997).**

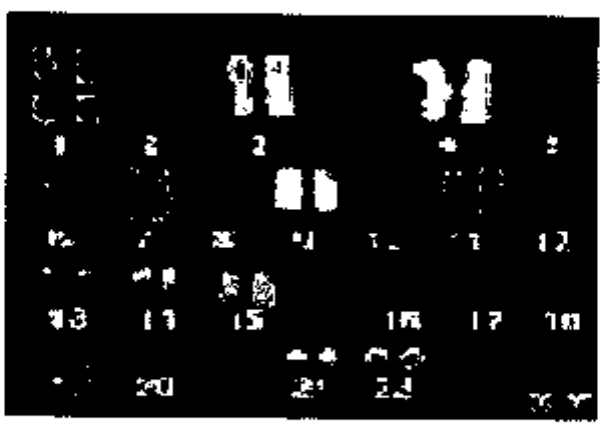


Fig.2 normal karytype **(Lewin, 1997).**

GENE STRUCTURE

Gene is functional unit of DNA from which RNA is copied (transcripted). Most genes implicated in human disease express a class of RNA that is translated by cellular machinery into protein messenger RNA (m-RNA). Genes range from between several hundred base pairs to more than 2 million base pairs of DNA.

A specialized nuclear enzyme, RNA polymerase, recognizes the begining or start sequence of gene, attaches to the double stranded DNA, and proceeds to copy one strand of the gene's DNA sequence into a single strand as it travels along the length of the gene. The enzyme recognizes another punctuation signal and falls off the RNA strand. The RNA strand is then processed **(Strachan & Read, 1996).**

The processing reactions involve additions of certain nucleic acid at both ends and removal of certain internal sequences. The processing reactions are necessary for the RNA to be transported from the nucleus to cytoplasm and for it to be used effectively by the protein synthetic machinery of the cytoplasm, which much translate this RNA into protein **(Alberts, et al., 1994).**

The most striking processing reaction involves the splicing out stretches of the RNA, each splicing event

Genetic diseases

Genetic abnormalities are a common cause of disease, handicap, and death among infants and children. Genetic disease accounts for primary diagnosis of 11 to 16 % of patients admitted to pediatric units of teaching hospitals. One percent of newborn infants have a hereditary malformation, and an additional 0.5 % have an inborn error of metabolism or an abnormality of the sex chromosome **(Gregory et al., 2000).**

Types of chromosomal mutations:

These can be divided into numerical and structural, with a third category consisting of different chromosome constitutions in two or more cell lines (table 1) **(Baird et al., 1988).**

1) Numerical abnormalities:

Numerical abnormalities involve the gain or loss of one or more chromosome or what is known as aneuploidy or the addition of one or more complete haploid complements or polyploidy. Loss of a single chromosome results in monosomy. Gain of one or two homologous chromosomes is referred to as trisomy and tetrasomy respectively **(Baird et al, 1988)**.

a) Triosmy

The presence of an extra chromosome is referred to as trisomy. Most cases of Down's syndrome is often known as trisomy 21. Other autosomal trisomies, which are compatible with survival to term, are Patau's syndrome (trisomy 13) and Edwards' syndrome (trisomy 18). Most other autosomal trisomies result in early pregnancy loss with trisomy 16 being a particularly common finding in first trimester spontaneous miscarriages. The presence of an additional sex chromosome (x or y) has only mild phenotypic effects.

Trisomy 21 is usually caused by failure of separation of one of the pairs of homologous chromosomes during anaphase of maternal meiosis I. This failure of the bivalent to separate is called non-disjunction **(Orel & Mendel, 1995)**.

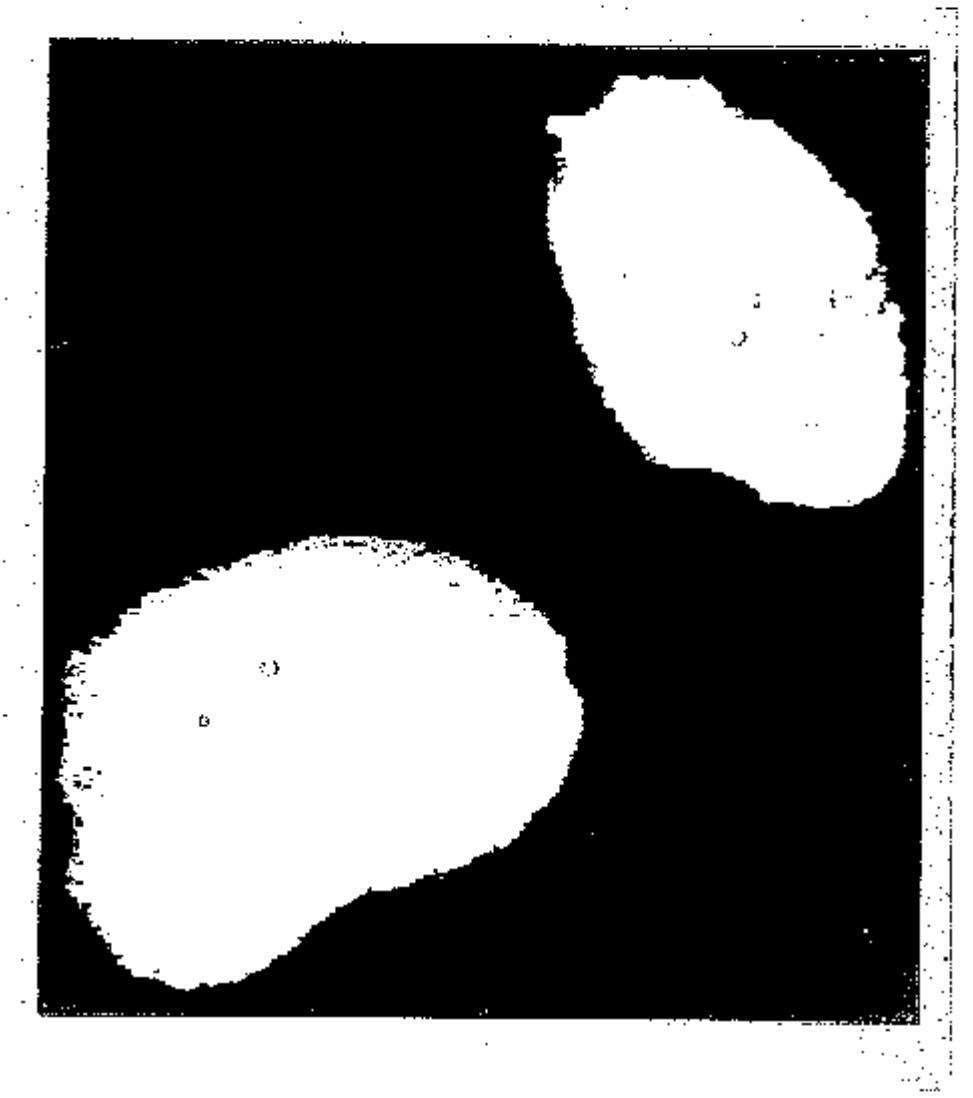


Fig. (3) Florescent insitu hybridization (FISH) of interphase nuclei with a chromosome 21 centromeric probe showing three signals consistent with triosmy 21 **(Orel & Mendel, 1995).**

fertilization after ovulation. In animals, it has been shown that an increased incidence of aneuploid embryos can result from lengthening of the interval between ovulation and fertilization. It has been suggested that this could account for the relationship between maternal age and the incidence of Down's syndrome, as with increasing age intercourse is likely to occur less frequently, with delayed fertilization therefore being more likely.

In some species, such as *Dorsophila,* non-disjunction is under genetic control. This could account for those occasional families, which seem to be prone to recurrent non-disjunction **(Rooney & Czaepulkowski, 1992).**

b) Monosomy:

The absence of a single chromosome is referred to as monosomy. Monosomy for an autosome is usually incompatible with survival to term, with the possible exception of a few very rare reported cases of monosomy 21. Absence of an X or a Y chromosome result in a 45, X Karyotype that causes a condition known as Turner's syndrome.

As with trisomy, monosomy can also result from disconjunction in meiosis **(Brown et al., 1997).**

in which the beak points are located at or close to the centromeres of two acrocentric chromosomes (Tjio & Levan, 1998).

Fig. (4) chromosome painting showing translocation involving chromosome 10 (blue) and 18 (red) (Tjio & Levan, 1998).

Deletions:

A deletion involves loss of part of a chromosome and results in monosomy of that segment of the chromosome. Usually a very large deletion will be compatible with survival to term and as a general rule any deletion resulting in a loss of more than 2% of the total haploid genome will be lethal (Vogel & Matusky, 1997).

Deletions are now recognized as existing at two levels. A microscopic or chromosomal deletion can be visualized under the microscope. Several deletion syndromes have been described such as the Wolf-Hirschhorn and cri du chat syndromes, which involve loss of material from the short arms of chromosomes 4and5 respectively. More recently submicroscopic microdeletions have been identified with the help of high-resolution prometaphase cytogenetics augmented by flurecent insitu hybridization studies. For example, it has been shown that several previously unexplained conditions such as the Prader-Willi and Angelman syndromes can be caused by microdeletions **(Schinzel, 1994)**