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The Egyptian Society for the Glaucomas

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Gene Therapy in Glaucoma

13-13

BY

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Genetics is the science of heredity.

Gr. genesis = origin

Thanks to J. Craig **Venter** who successfully mapped the human genetic code and gained a worldwide recognition in year 2000, thus paved a path to gene therapy.

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Let's start the "gene" story from its

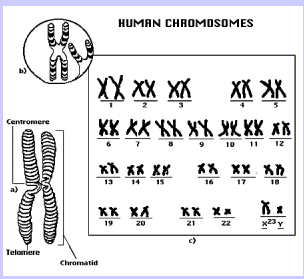
"tail"

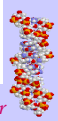
In summary:

In the human genome, each cell nucleus contains 46 chromosomes

22 pairs of autosomes

A single pair of sex chromosomes XX or XY





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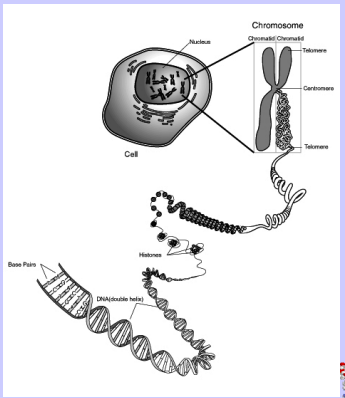
The DNA of these chromosomes has a double helix
Attached to it, the base pair of amino acids

Adenine-Thymine
Guanine-Cytosine



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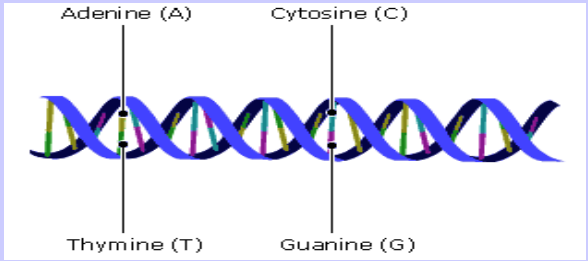
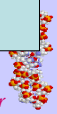


All human features, habits, diseases and others, are simply just a different arrangement of only these 4 amino acids



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Inside each cell nucleus there, are 46 chromosomes that carry 100,000 genes

The "gene" is the functional unit of hereditary, that occupies a specific place (locus) on a chromosome and it direct the formation of protein.

This protein determine the function of each cell .

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Only 0.1% is responsible for all the changes in human features,shapes,color or behavior

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When a copy is read, i.e. on reading gene information, this is called " gene expression". The gained knowledge is in the form of protein synthesized for different body cell functions.

Gene expression → Transcription
Translation

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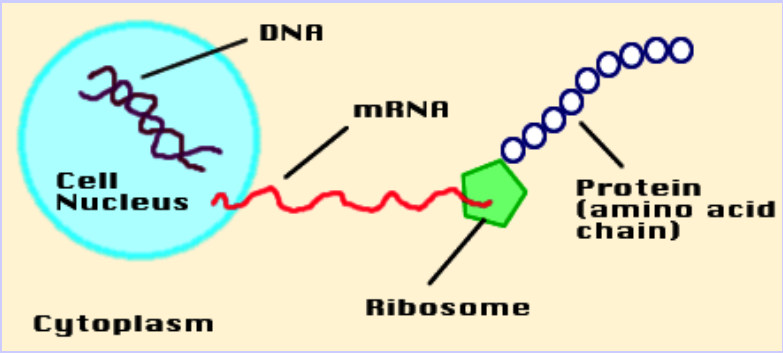

DNA → **mRNA** → **Protein**

Transcription Translation

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Cells can be totally different, both structurally and functionally , despite the fact that all carry the same genetic information (46 chromosomes). This means that

Inside each cell there is a large big libarary.

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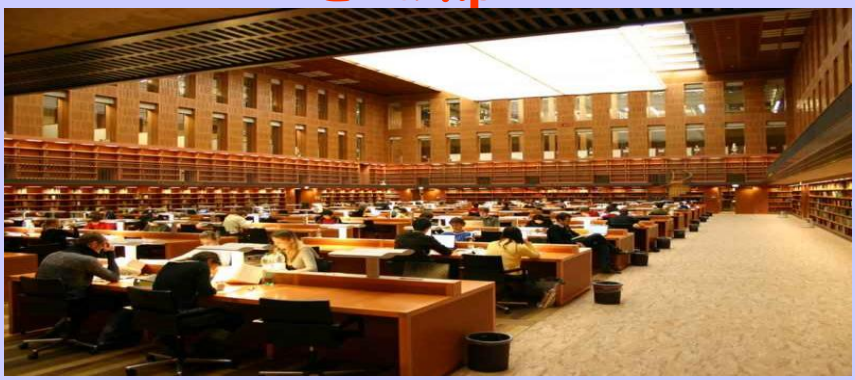
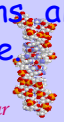
Example



E.g. a **physician** entering a library will search for the medical section, while the **architect** will search for the engenering section and accountant looks up the commerce section… etc. The big library contains all department but each to help, carry-on his job in life.



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A simple blood sample or buccal screening can give all the information about the eye, kidney, or any other body organ.

This is because all of them carry the same genetic information or the same big library.

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Hereditary errors can be:

-Transmitted early, from parent to child as in aniridia.

Or

-The defect is present in a gene that is activated later in life as in glaucoma.

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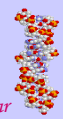
Thus the disease is a "defect" in **gene expression** whether during transcription or translation.



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Thus gene therapy is by:

-replacing the actual DNA of the gene (permanent effect)

-modifying m-RNA (temporary effect)

-replacing and blockage of proteins (temporary effect)

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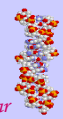
The **TIGR/MYOC gene** (trabecular meshwork glucocorticoid response/ Mycoline) **is the gene whose mutation is** strongly suggested to be **responsible for glaucoma**.

Mutation in **TIGR** were identified in juvenile glaucoma families and found to affect 3% of the general glaucoma patients.

Mutation of this gene can produce abnormal gene expression. This consequently affects the TM nature by changing the cytoskeleton or the internal structure of TM resulting in glaucoma.



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Human Genome Organization (HUGO/GDC) uses GLC as the general symbol for glaucoma.

The numbers 1,2,and 3 represent **open** angle, angle **closure**, and **congenital** glaucoma respectively. These are followed by "alphabetical letters" arranged in order according to the discovered gene in chronological order.

GLC1A = 1st gene to be discovered
GLC1F = 5th gene to be discovered

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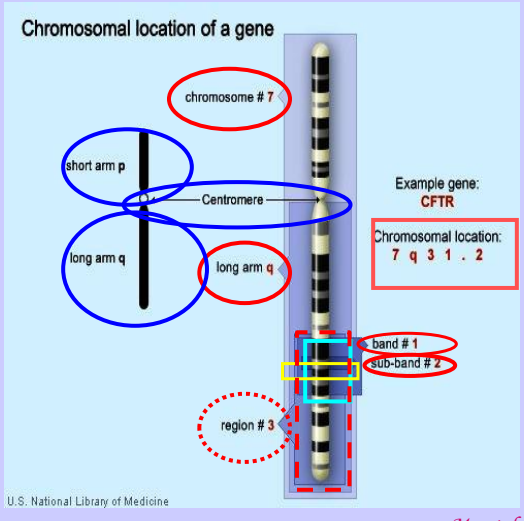
This is an example of Gene:CFTR ESG

Chromosomal location of this agene 7 q 3 1 - 2



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The discovered POAG genes are, one juvenile and 6 adult POAG and 3 primary congenital glaucoma.

The causative gene was only identified in 3 types:

TIGR
OPTN
WRD

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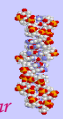
1- GLC1A : 1st gene to be discovered
location 1 q2 3- 25
phenotype JOAG
gene TIGR/MYOC

2- GLC1B (NTG) 2 q1 3

3- GLC1C (high pressure) 3 q2 1-24

4- GLC1D (high pressure) 8 q2 3



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5- GLC1E (NTG) 10 p1 5-14

gene OPTN

6- GLC1F 7q3 5

7- GLC1G (high and low pressure)

5q2 2

gene WRD36

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Primary congenital glaucoma (Buphthalmos)

GLC3A GLC3B

Developmental glaucoma
Axenfeld-Rieger syndrome
Aniridia
Peter's anomaly
Nanophthalmos/angle closure glaucoma

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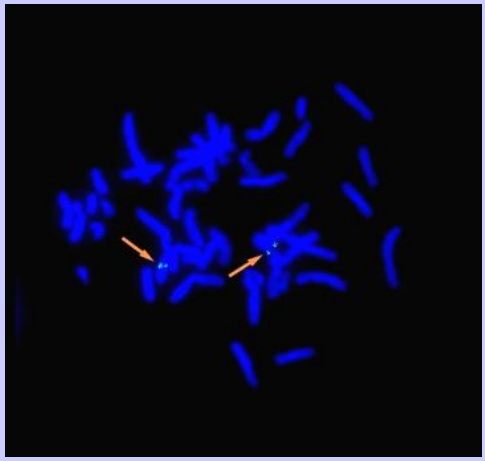

This slide demonstrate the location of a gene on a chromosome no. 13 as a blue dots

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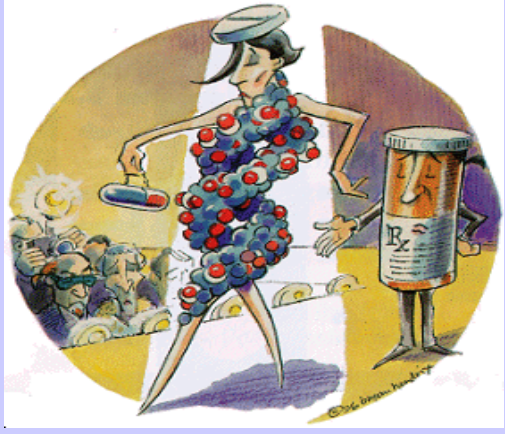
Genetics and Glaucoma Therapy



The medical treatment will be replaced by gene therapy

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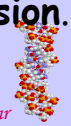
The current treatment which is now restricted to lowering IOP, may be guided by the knowledge of each person's genotype.

- Patients with **GLC1A** gene defect may respond best with **surgery**
- **Medical** treatment is effective in **GLC1C, GLC1D** and **GLC1F** gene
- Individuals with mutation of **GLC1B** or **GLC1E** (NTG) may require treatment of **ON perfusion**.



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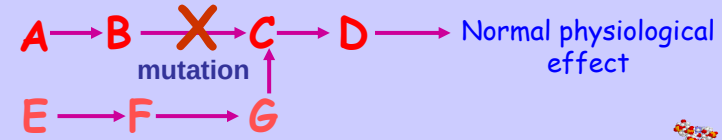
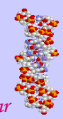
Future traditional treatment, will include both pharmacological and gene therapy, targeting ciliary epithelium and TM via topical or intracameral injection of adenovirus vectors.

Stromelysin is a pharmacological drug that bypass a gene defect in glaucoma.





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Genetic therapy of glaucoma

simulate transplantation surgery, i.e removal of mutant gene and replace it with a normal one.

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Several potential approaches, to transfer genetic material to TM cells exist.

They include **replacing** the mutant DNA or the gene as a permanent effect, or either **modifying** m-RNA = or **replacing and blockage** of protein as a temporary effect.

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Potential approaches for genetic glaucoma therapy includs.

1. Viral vector therapy (using the virus as a carier)
   - Retrovirus
   - Adenovirus
   - Herpes virus
2. Non-vector therapy by
   - Liposomes
   - Oligonuclutoide antisense
   - Recombinant proteins
   - Human artificial chromosomes
   - ribozymes

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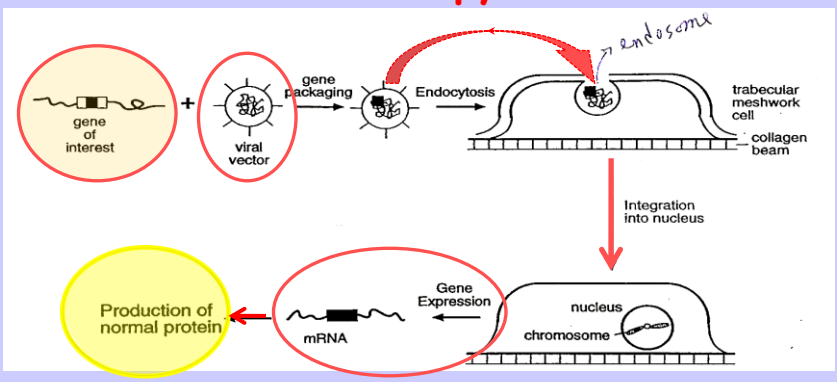
1. Viral vector therapy



The gene* of interest-is carried* by a viral vector to be-introduced *into the nucleus of the TM cell by a process called* endocytosis.-
This restores *the mutant gene to a normal one.*
Thus-normal gene expression with a normal mRNA and- protein production would be expected.

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2.Non-viral vector therapy:

Have more immediate potential and greater versatility and may be more accepted.

They can either replace defective genes, inhibit transcription, correct mutant m-RNA, or directly replace needed protein.

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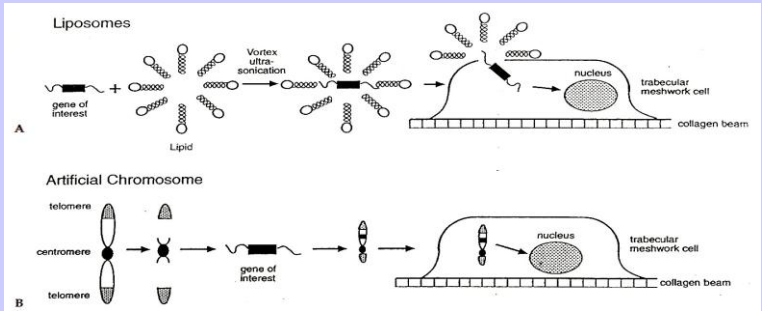

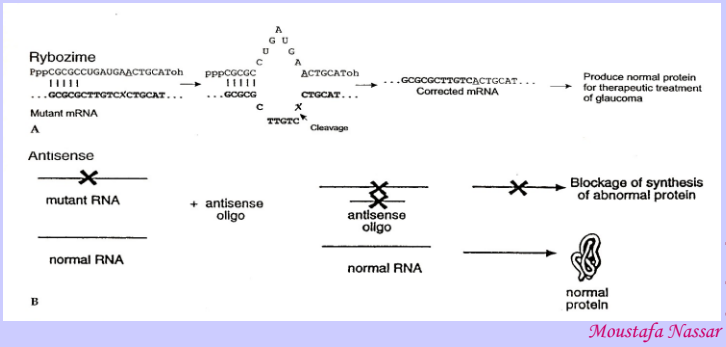

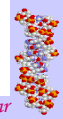

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Gene therapy in glaucoma

Gene therapy can replace or inactivate defective genes.

so as to help "individuals at risk of developing glaucoma " before irreversible damage to the optic nerve takes place.

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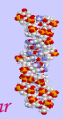


على اسم مصر
Thanks
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