In the Name of God
The Most Merciful, The Most Beneficient

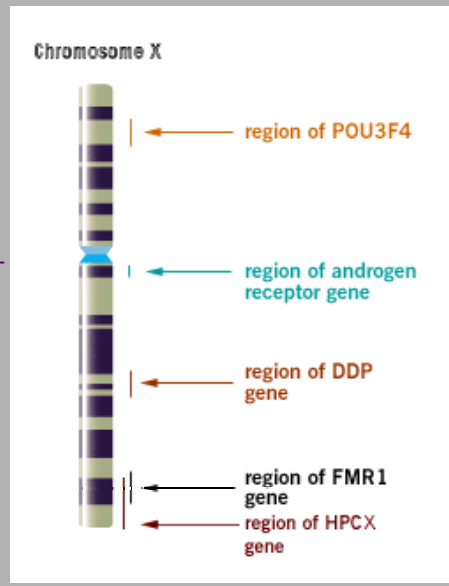
Spectra of Etiological Factors in Human Genetic Diseases

Diverse

Environmental

Environmental + Genetic (Multifactorial)

Genetic



GENETIC DISORDERS

- A major cause of chronic diseases in human populations.
- Require long-term care and management.
- Implicit a significant:
  - Economic burden.
  - Social burden.
  - Psychological trauma on the patient, family and the health care services.

Mutagenesis & Mutations

Mutations

A permanent change in the base sequence or arrangement of bases in the DNA

- **Have no effect**
  - **No a.a change**
    (Change in the third position of the triplet will not have effect)
- **Produce a harmful effect**
  - **Genetic disease**
- **Produce a beneficial effect**
  - **Resistance against Environmental factors**

Mutagens—Substances that produce mutations

Chemicals:

- **Mustard gas**
- **Nitrous acid (HNO_2)**
- **Hydroxylamine (NH_2OH)**
- **Alkylating agents:**
  - **Dimethyl Sulfate.**
- **Interchelating agents:**
  - **Acridine dyes.**
  - **Ethidium bromide.**
- **Dyes**
- **Caffeine**

- **Ionizing Radiation: - UV, γ , X rays.**
- **Spontaneous.**

Types of Mutation

Genomic Mutation

Missegregation of Chromosome pairs

e.g. Down's Syndrome

Chromosomal Mutation

Structurally abnormal chromosome

e.g. Cleftlips cleft palate

Gene Mutation

- Substitution
- Addition.
- Deletion.

e.g. Sickle cell anemia.
Hb-constant spring

Genetic Disorders

Mutations in the:

* Genome,
* Chromosome or
* Gene

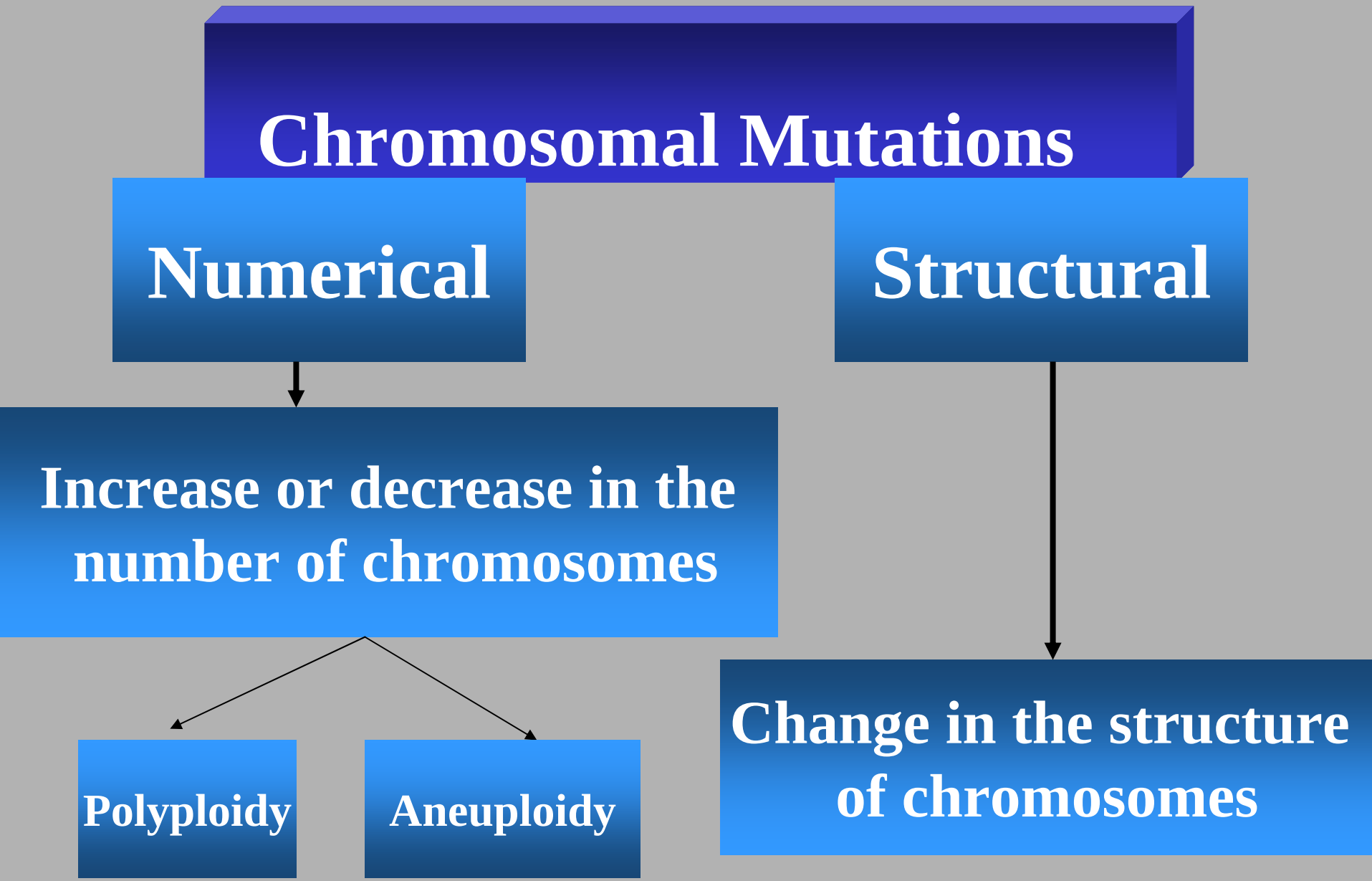
- Decrease or increase in the amount of genetic material
- Abnormal gene

- Increase or decrease in the amount of gene products (proteins).
- Decrease in the amount of one protein.
- Defective function of the protein.
    - Increased function.
    - Decreased or complete loss of function.

Genetic Disease

Estimated frequencies of different types of Mutation

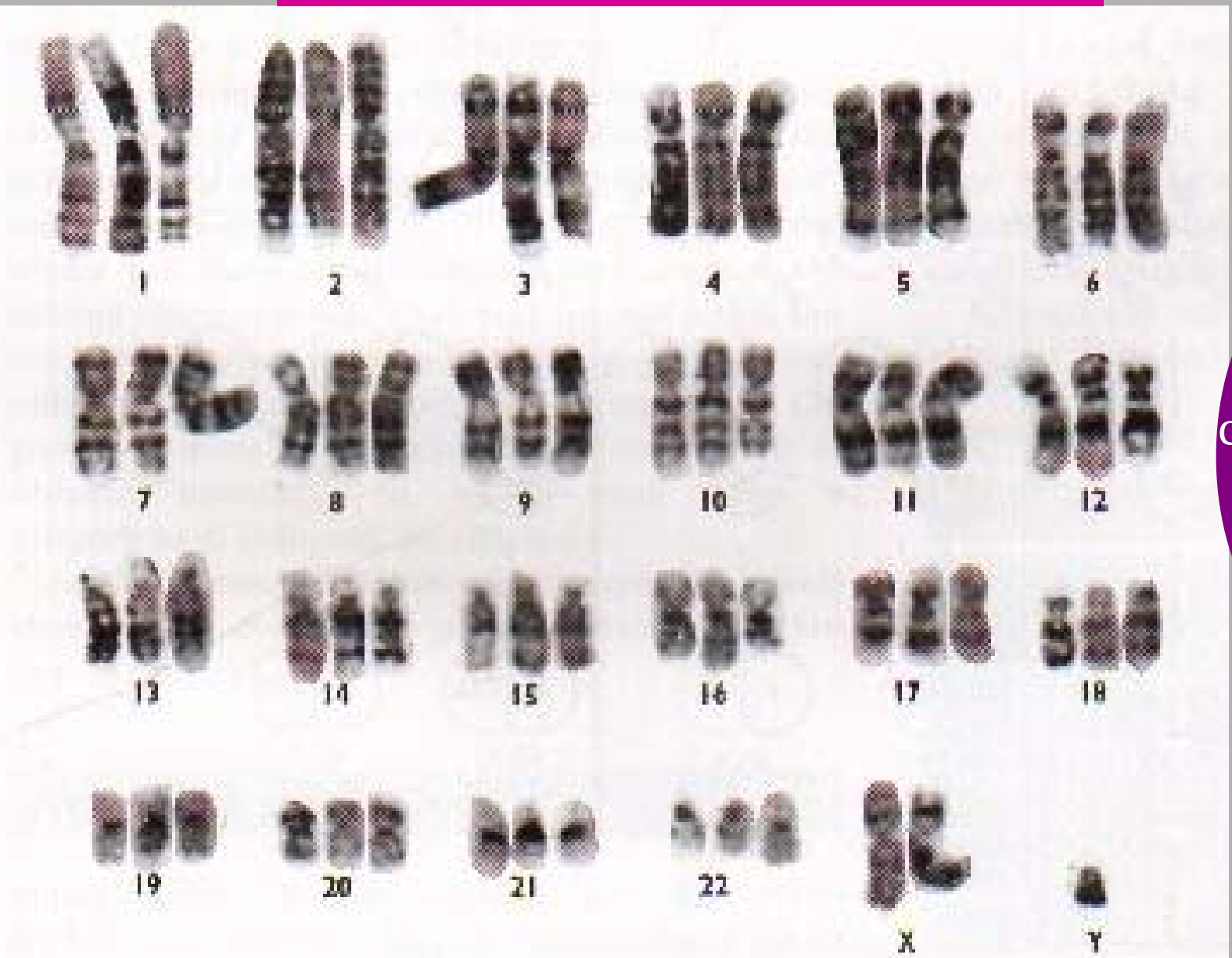
Mutation	Mechanism	Frequency "approximate"
(1) Genome mutation	Chromosome	10^{2}/ cell division
(2) Chromosome mutation	missegregation	$6x10^{-4}$/ cell division
(3) Gene mutation	Base pair mutation	10^{-10}/base pair/cell division
		10^{-5}/ 10^{-6}/ locus/generation


Chromosomal Mutations
Numerical
Structural
Increase or decrease in the number of chromosomes
Change in the structure of chromosomes
Polyploidy
Aneuploidy

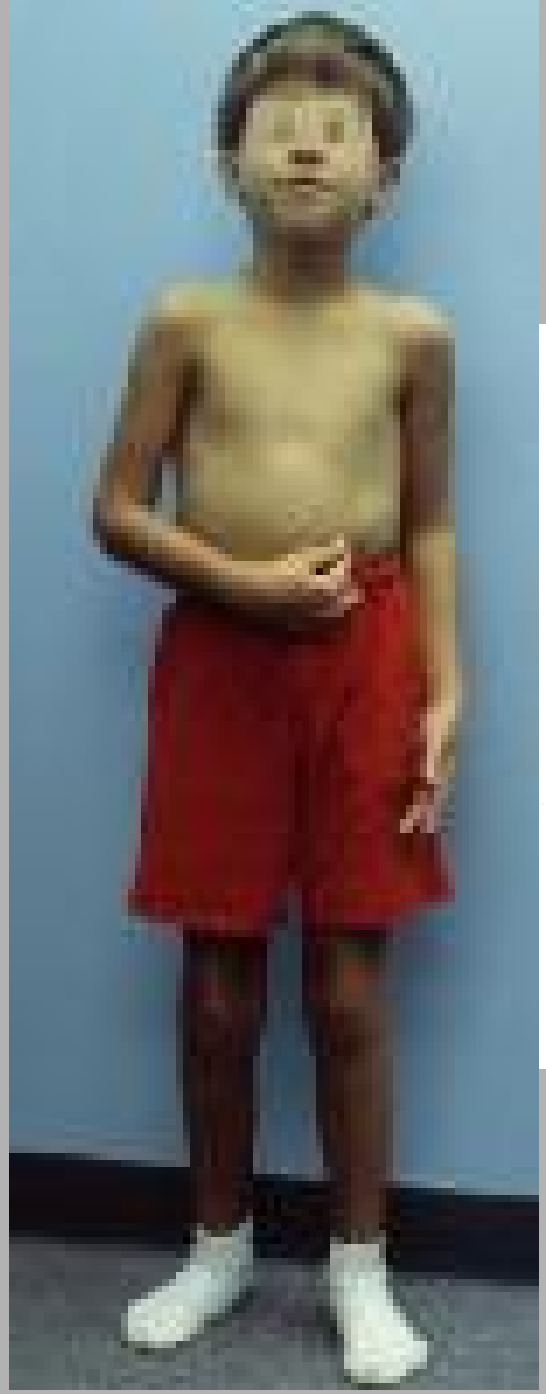
Examples of Numerical Chromosomal Aberrations

Karyotype	Example
92, XXYY	Tetraploidy
69, XXY	Triploidy
47, XX+21	Trisomy 21(Down Syndrome)
47,XX+18	Trisomy 18
47, XX+13	Trisomy 13
47,XXY	Klienfelter Syndrome
47,XXX	Trisomy X
45, X	Turners Syndrome

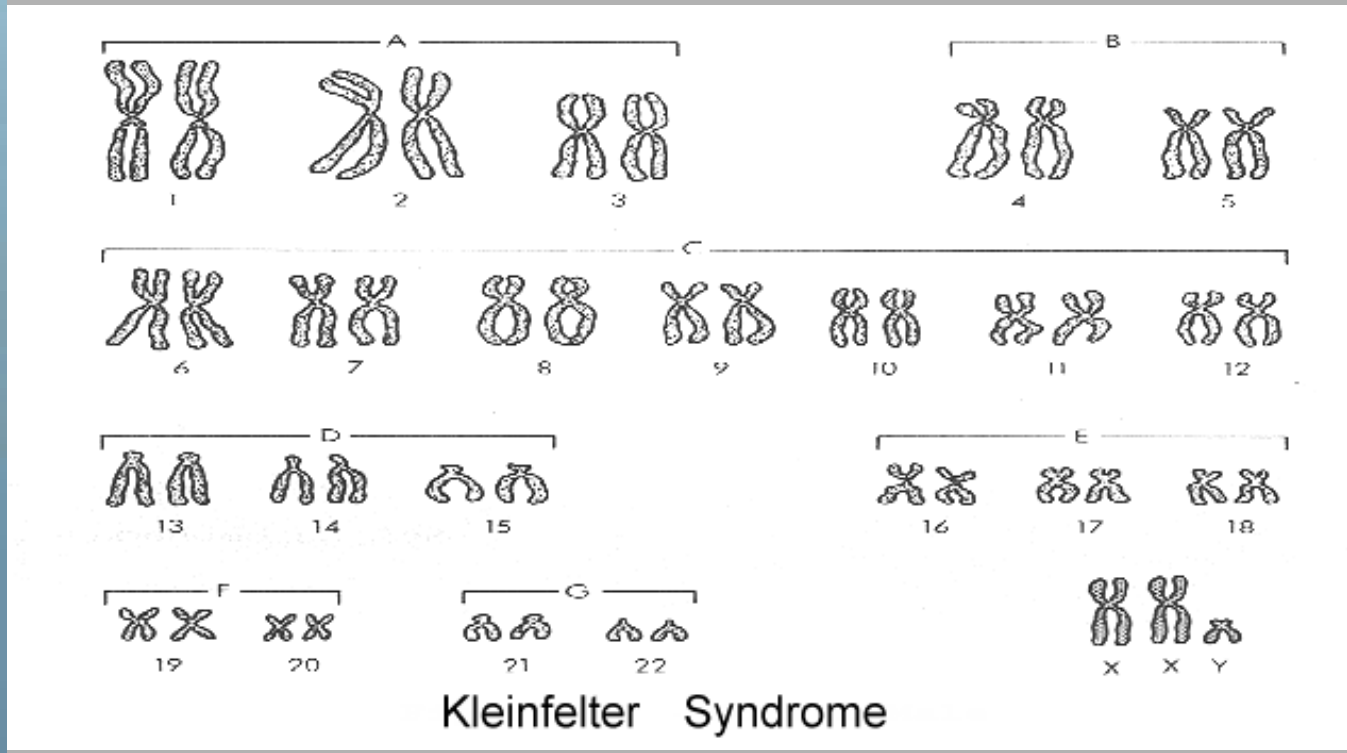
Triploidy (69, XXY)



Not compatible with life

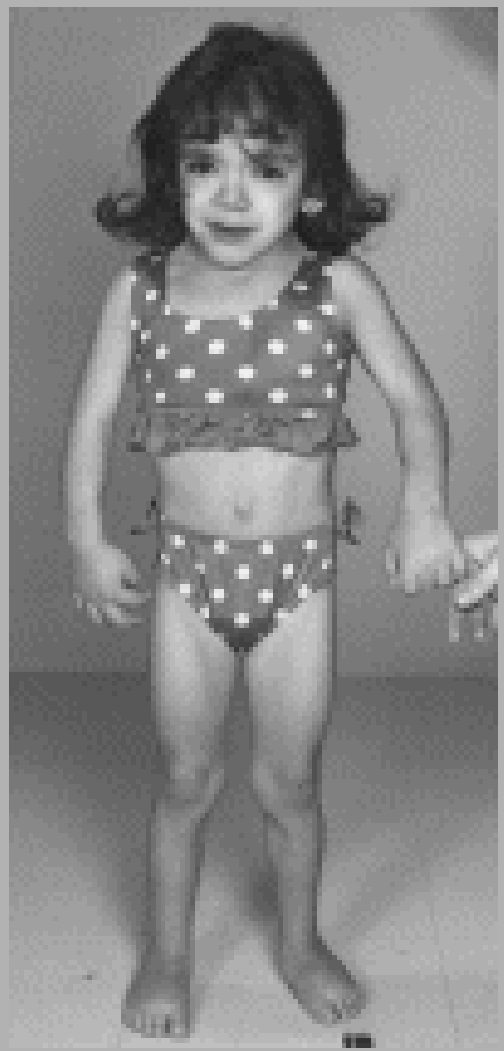


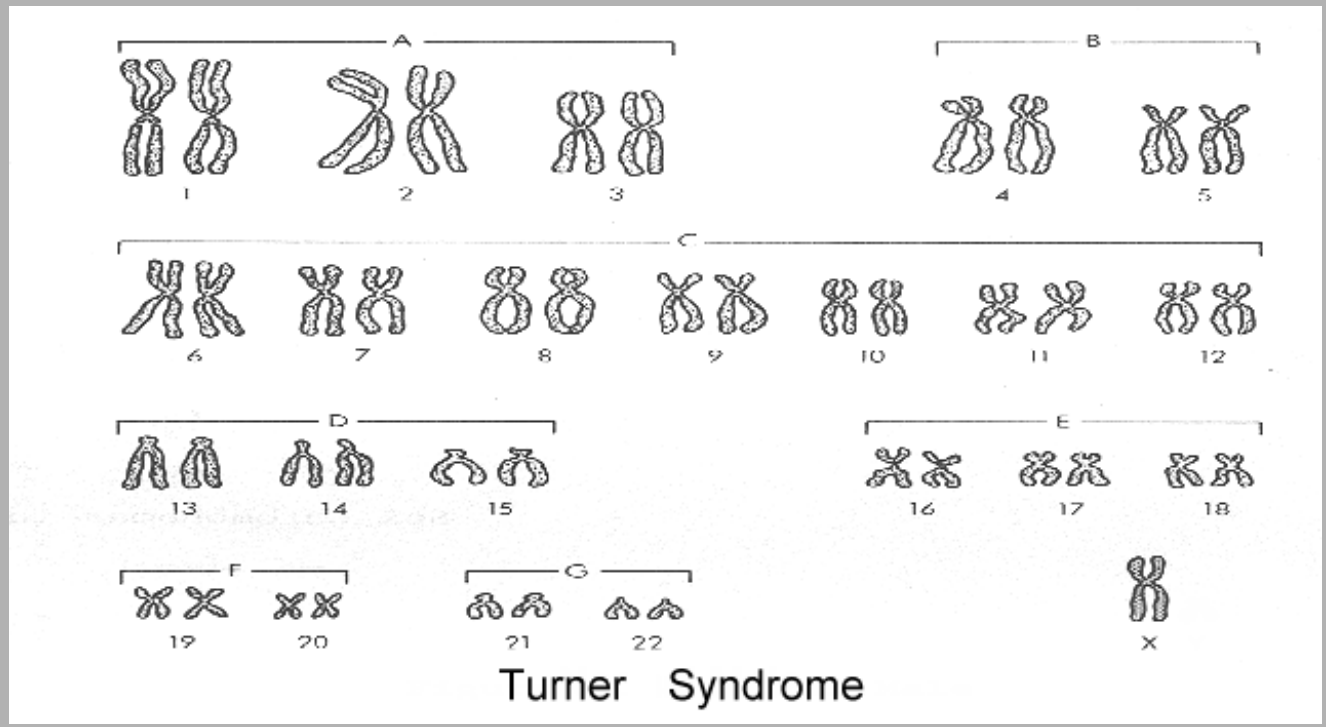
Klinefelter Syndrome



47,XXY

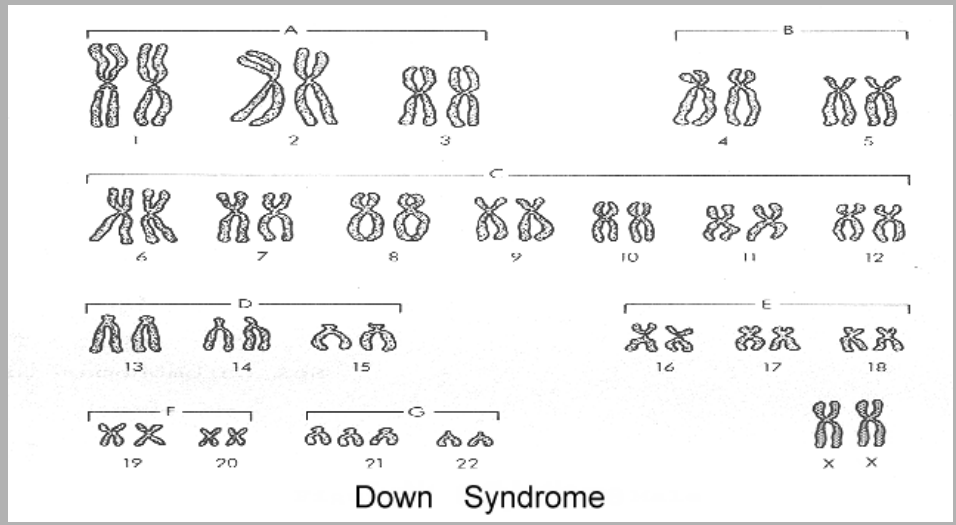
Turner Syndrome



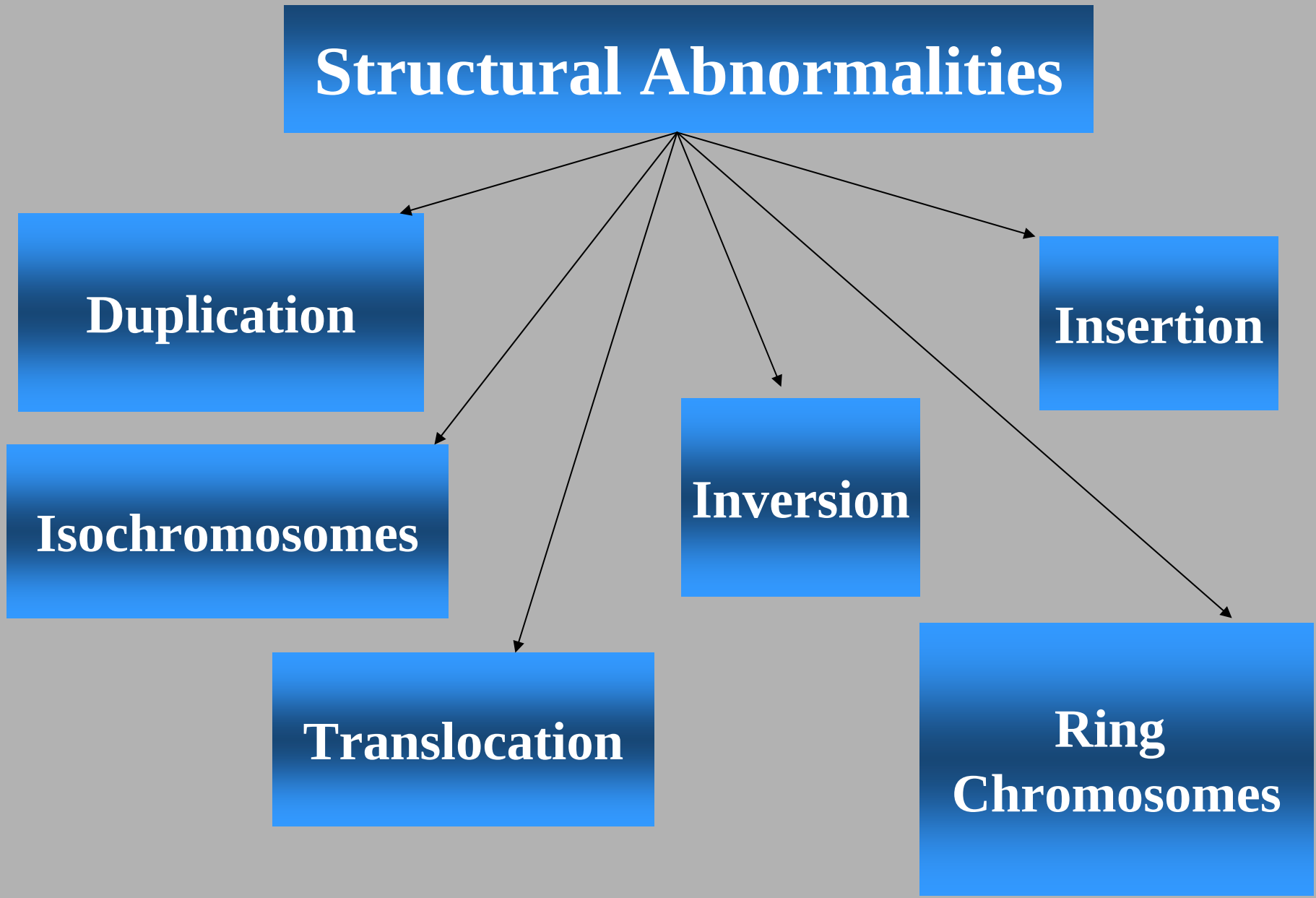


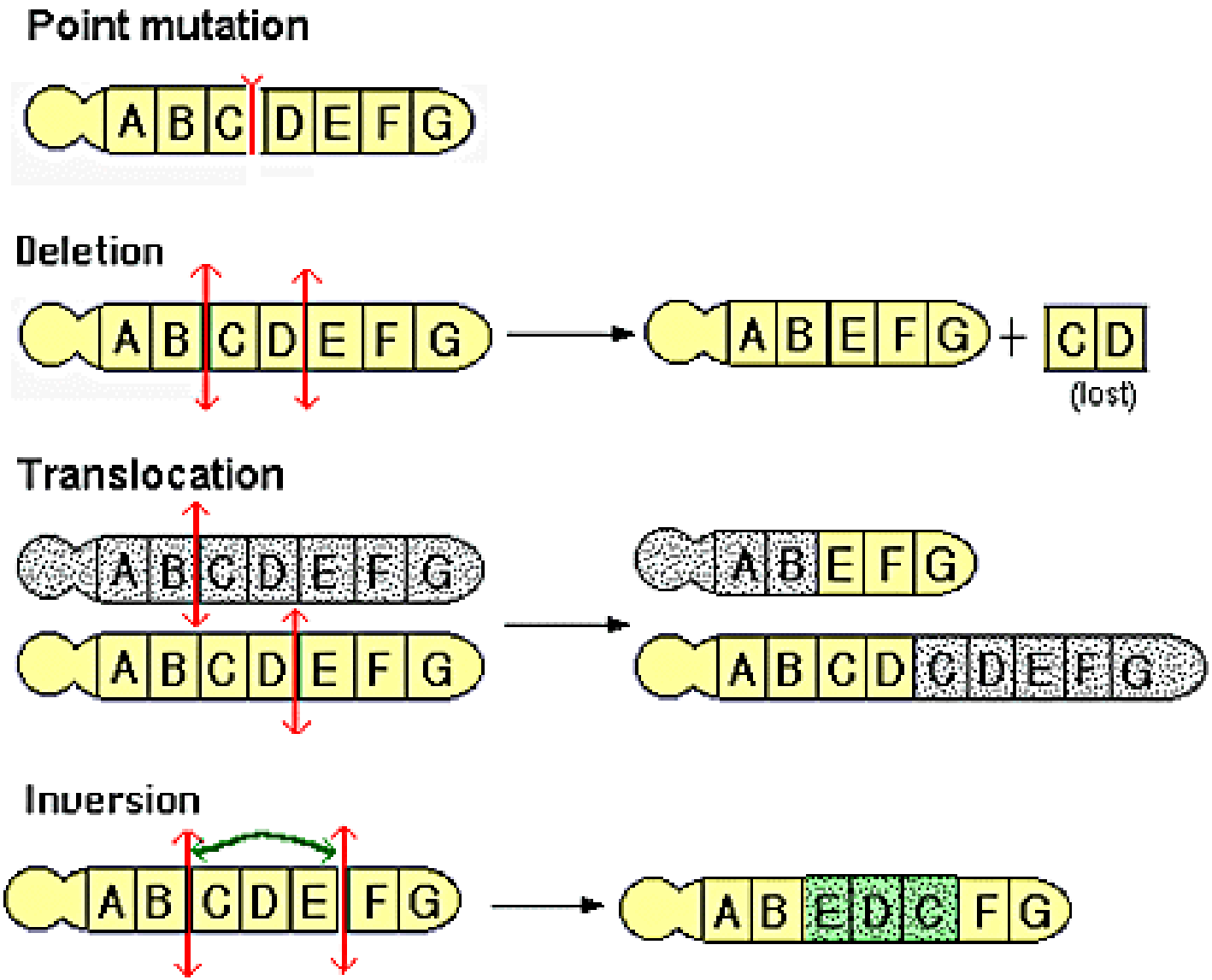
45, X

Down's Syndrome



Down Syndrome

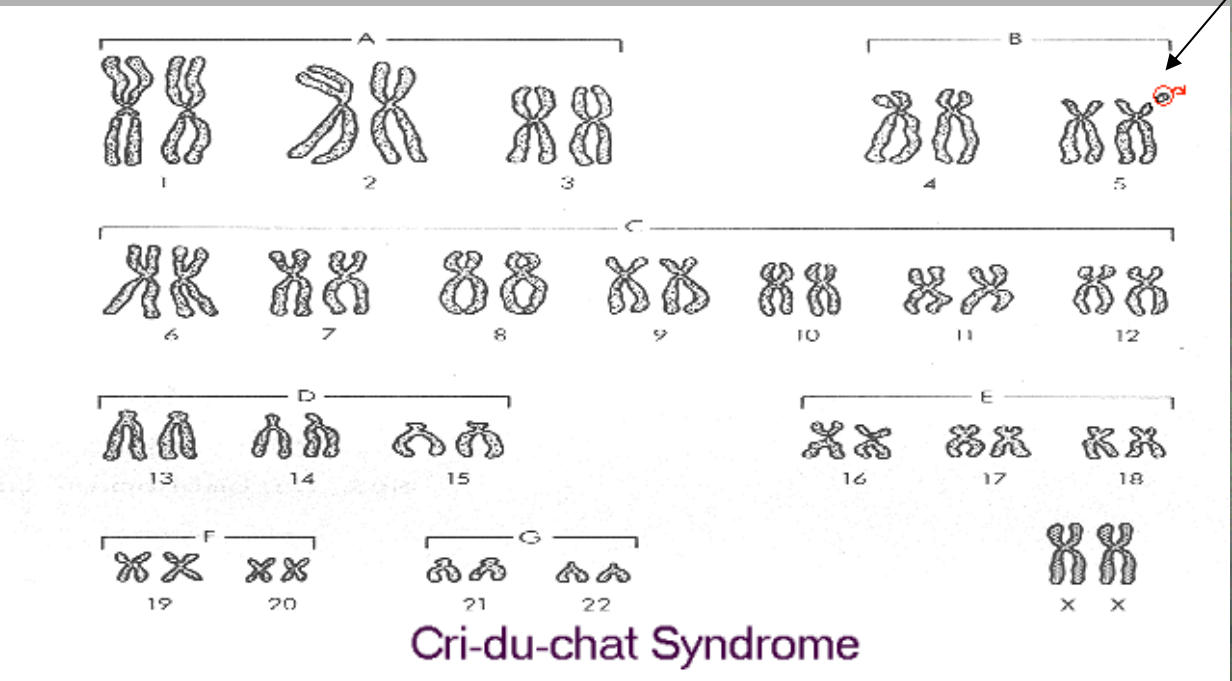

Structural Abnormalities
Duplication
Insertion
Isochromosomes
Inversion
Translocation
Ring Chromosomes



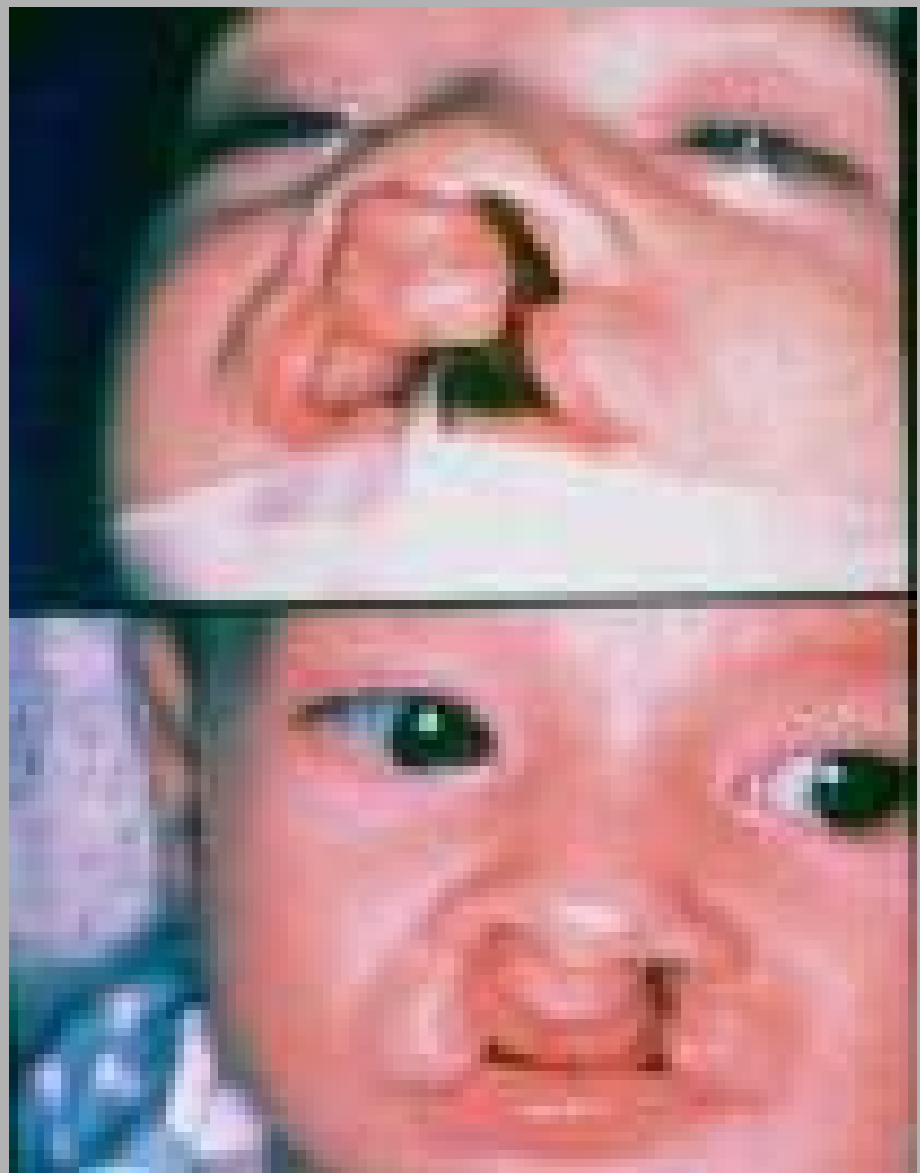
Mutations of Chromosomes

Deletion in Cri du chat syndrome

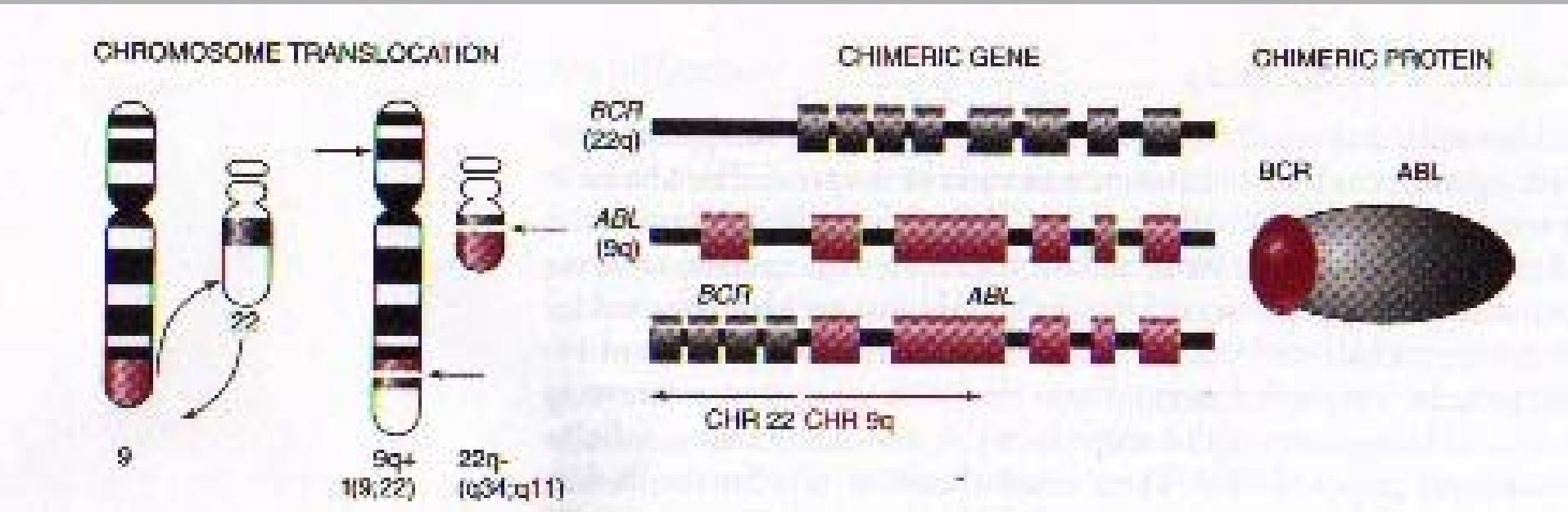
Deletion in Chr.5



Cleft lip and cleft palate



The Philadelphia Chromosome*



* Mutation found in all cases of chronic myeloid leukemia
* The ABL & BCR fuse due to translocation and form an oncogene

Single Gene Mutations

Single Gene Disorders

Gene

Mutation

- **Substitution**
- **Addition**
- **Deletion-Partial or complete**

Mutated gene or loss of gene

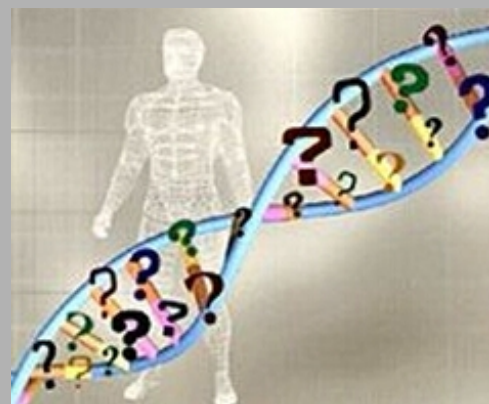
Transcription

Altered mRNA or loss of mRNA

Translation

Altered protein or loss of protein

Genetic disease

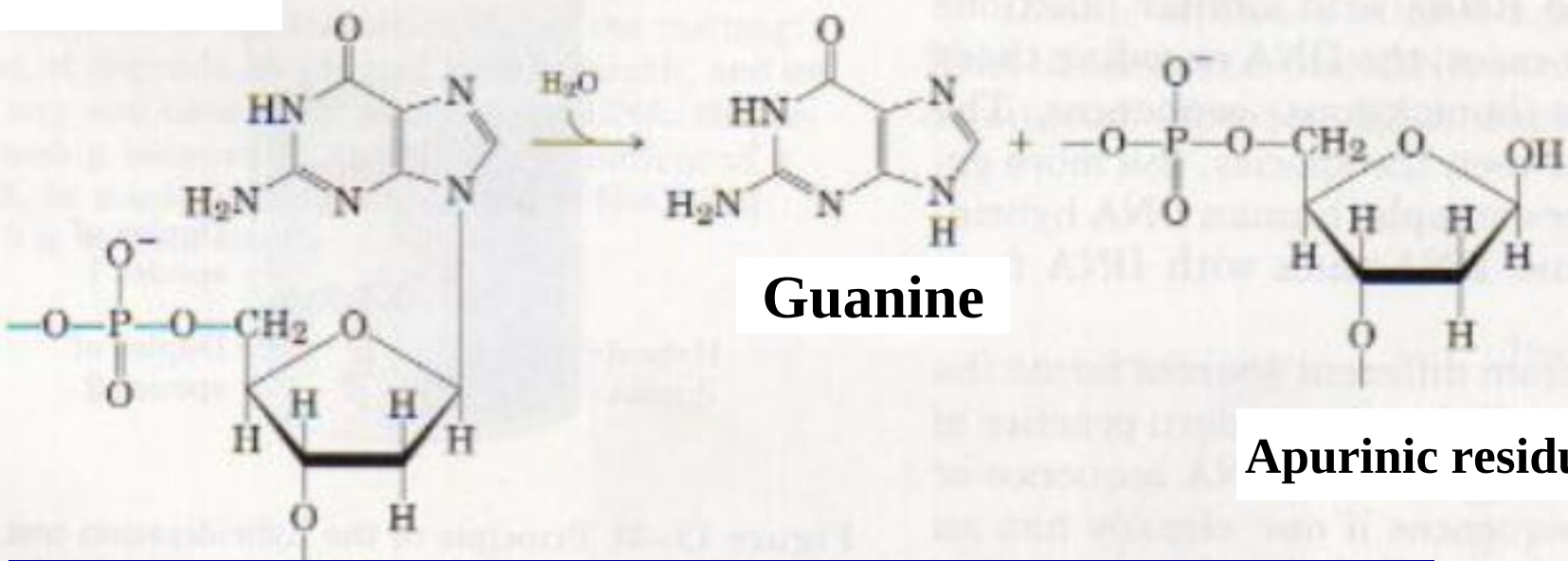


Types of damage to DNA

- **Single base alterations:**
  - Depurination
  - Deamination of C to U
  - Deamination of A to hypoxanthine
  - Alkylation of base
  - Insertion or deletion of nucleotide
  - Base-analog incorporation
- **Two base alterations**
  - T-T dimer by UV light
- **Chain breaks**
  - Radioactive disintegration of backbone element
- **Cross-linkage**
  - Between bases in same or opposite strands
  - Between DNA and protein molecules

Depurination

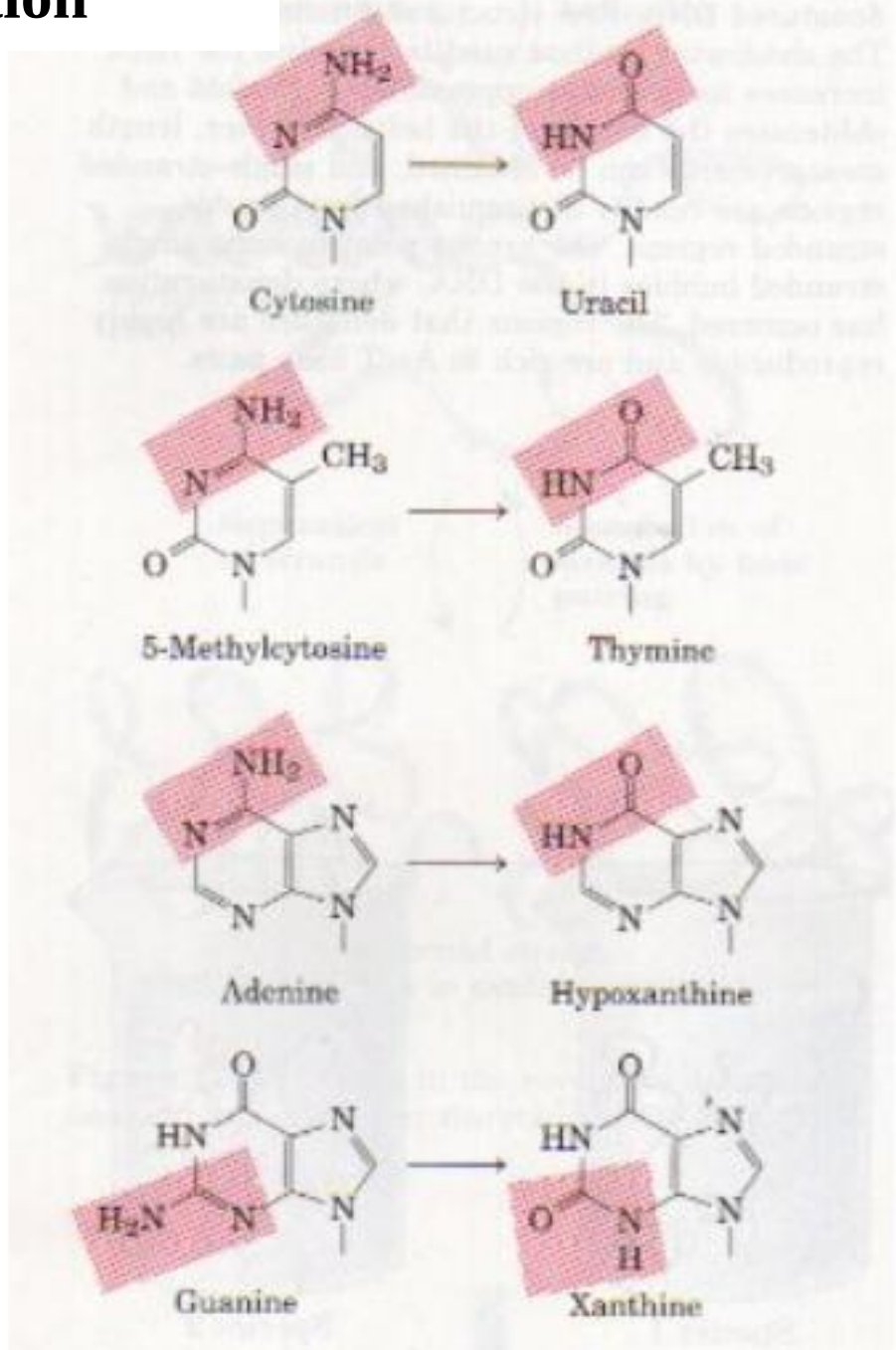
Guanosine residue In DNA



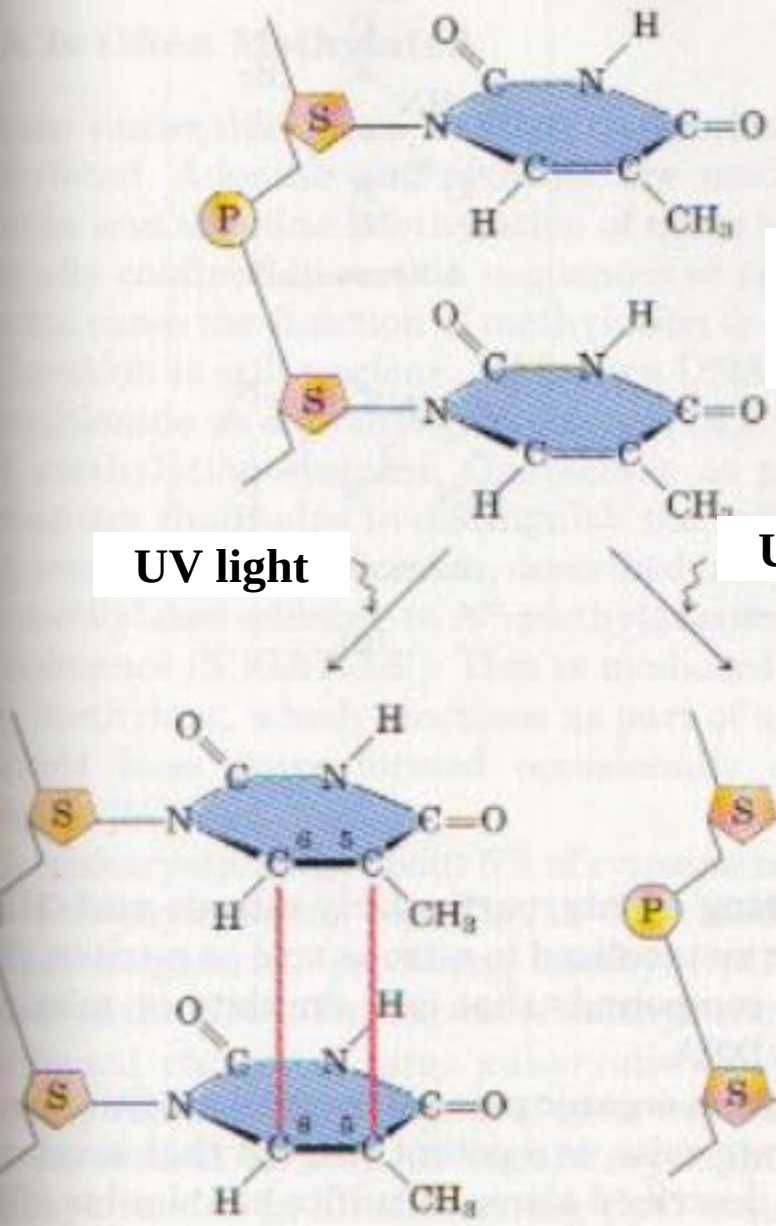
Purine is lost by hydrolysis of the N-glycosyl bond. Removal of pyrimidines can also occur but at much slower rate then depurination.

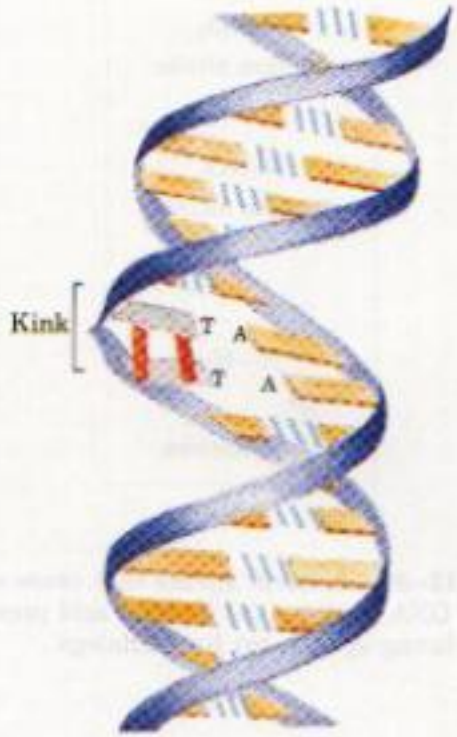
In mammals one in 10^5 purines are lost every 24 hrs.

Deamination

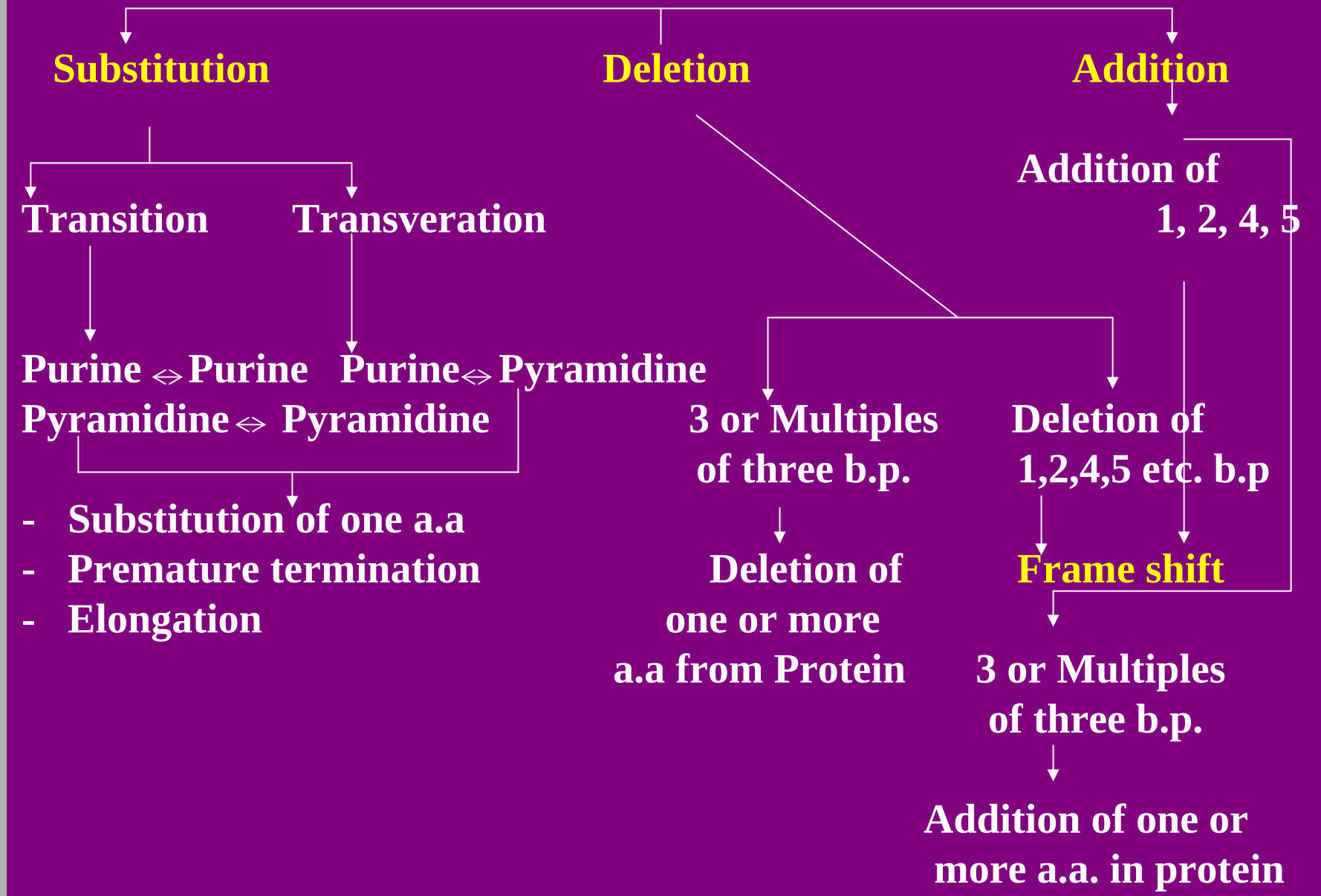


Formation of Thymine Dimer





Gene Mutations



Types of mutation:

(a) Transition:

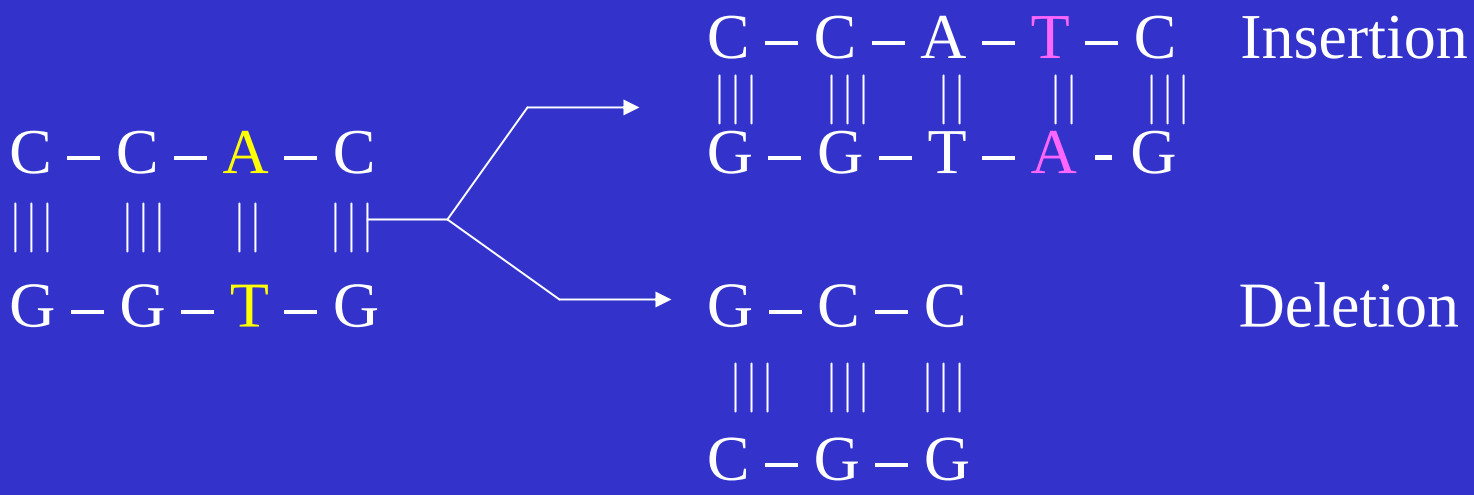
A purine – pyramidine base pair is replaced by another purine – pyramidine base pair.

(b) Transversion:

A purine – pyramidine base pair is replaced by pyramidine - purine base pair.

(c) Frame Shift:

Due to insertion and deletion.



Wild type allele:

M D D Q S R M L Q T L A G V N L

atggacgatcaatccaggatgctgcagactctggccggggtgaacctg

silent (third base pair) mutation:

M D D Q S R M L Q T L A G V N L

atggacgatcaatccaggatgctgcaaactctggccggggtgaacctg

point mutation (missense):

M D D Q S R M L K T L A G V N L

atggacgatcaatccaggatgctgaagactctggccggggtgaacctg

point mutation (nonsense):

M D D Q S R M L stop

atggacgatcaatccaggatgctgtagactctggccggggtgaacctg

frameshift leading to premature termination:

M D D Q S R M L R L W P G stop

atggacgatcaatccaggatgctgagactctggccggggtgaacctg

Phenylketonuria

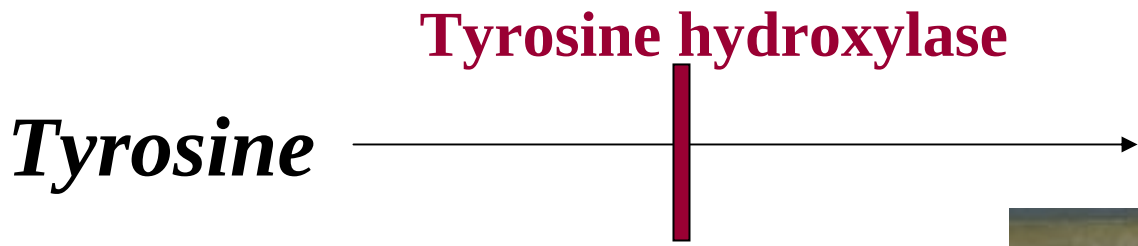
Deficiency of

Phenylalanine hydroxylase

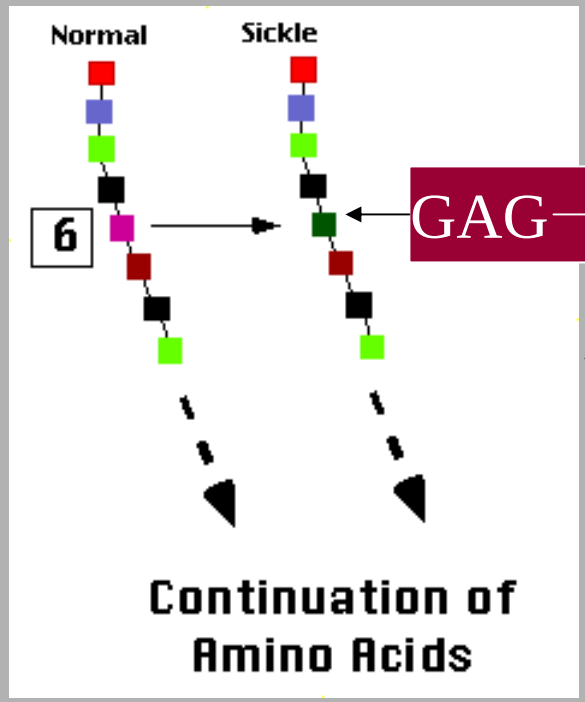
Phenylalanine ***Tyrosine***

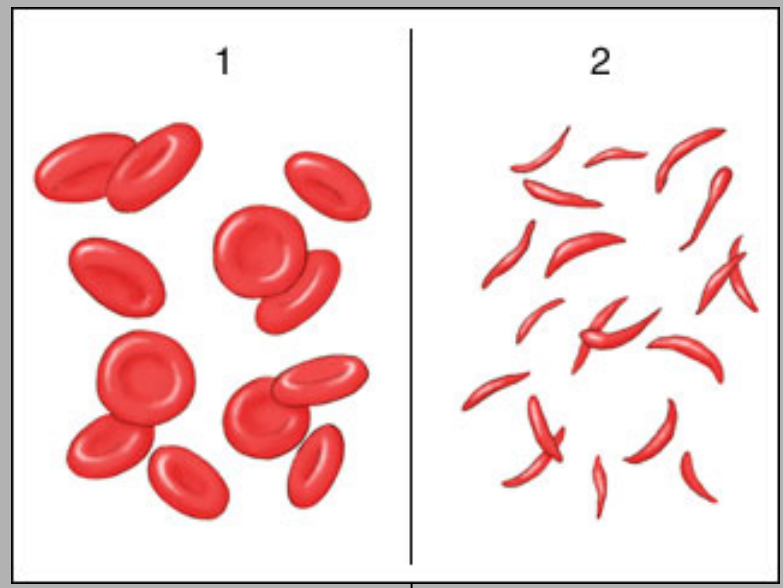
Tetrahydrobiopterin ***Dihydrobiopterin***

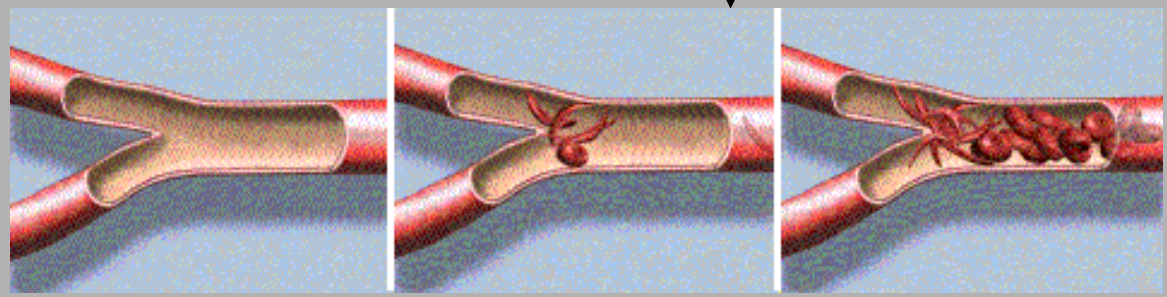
Albanism



Sickle cell Mutation







EXAMPLES OF TRINUCLEOTIDE REPEATS LEADING TO DISEASES

(CGG)	Fragile X syndrome
(CAG)	Huntington’s chorea
(CTG)	Myotonic dystrophy
(CAG)	Spinobulbar muscular atrophy
(CAG)	Kennedy’s disease

Gene Mutation affection rate of Protein Synthesis

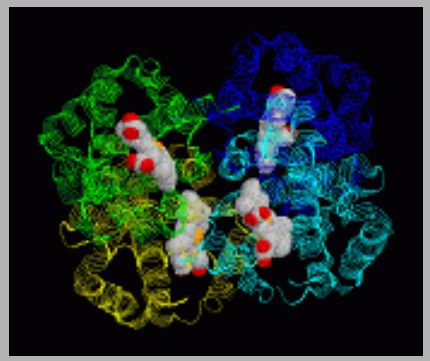
. Mechanisms:

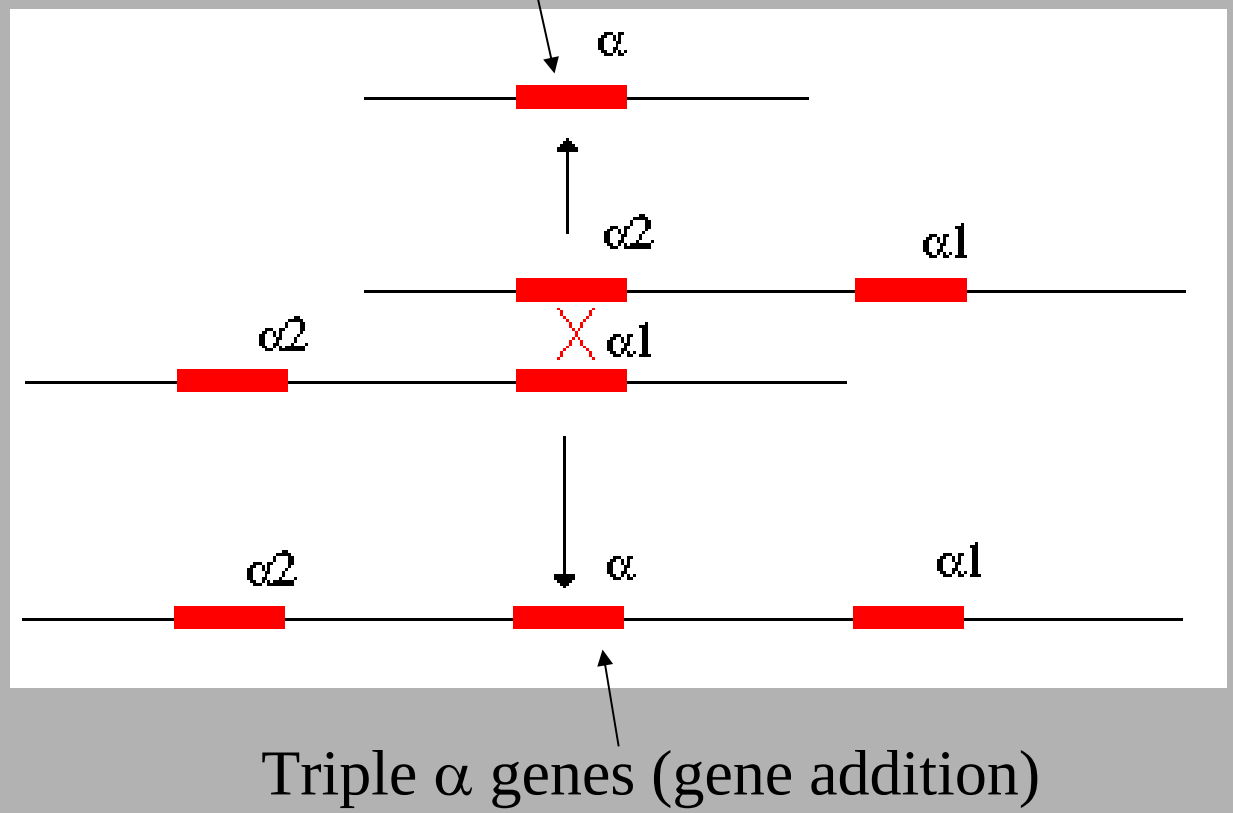
- Gene deletion
  - Partial
  - Complete
- Defective gene expression
- Defective mRNA.

- **The Rate of Protein Synthesis:**
  - Maybe decreased or completely stopped.
- **The Synthesized Protein is structurally normal**

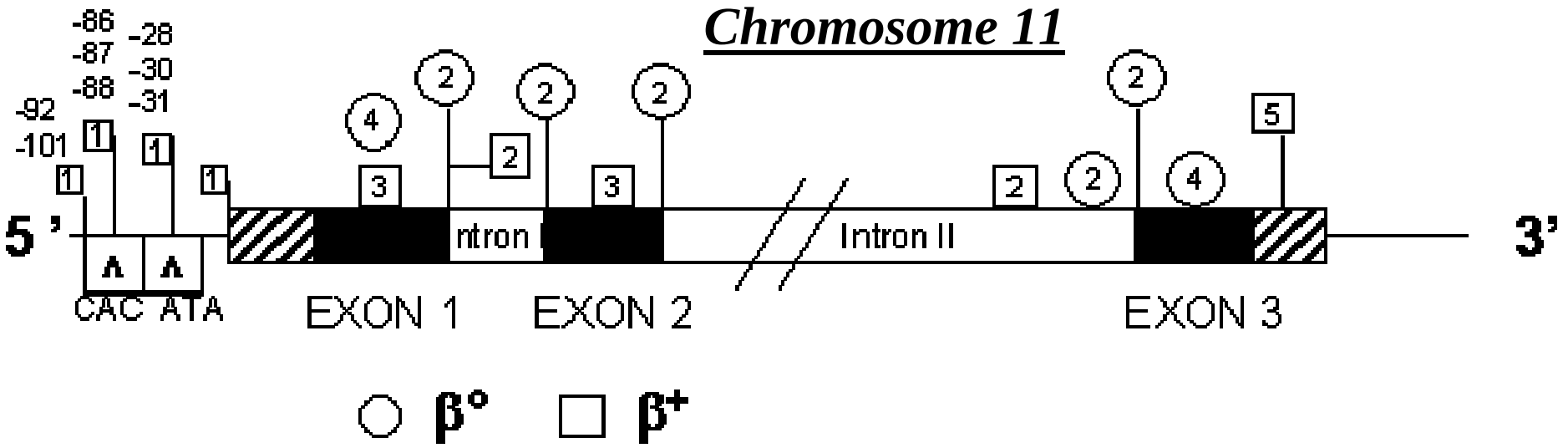
Alpha thalassaemia

Haemoglobin





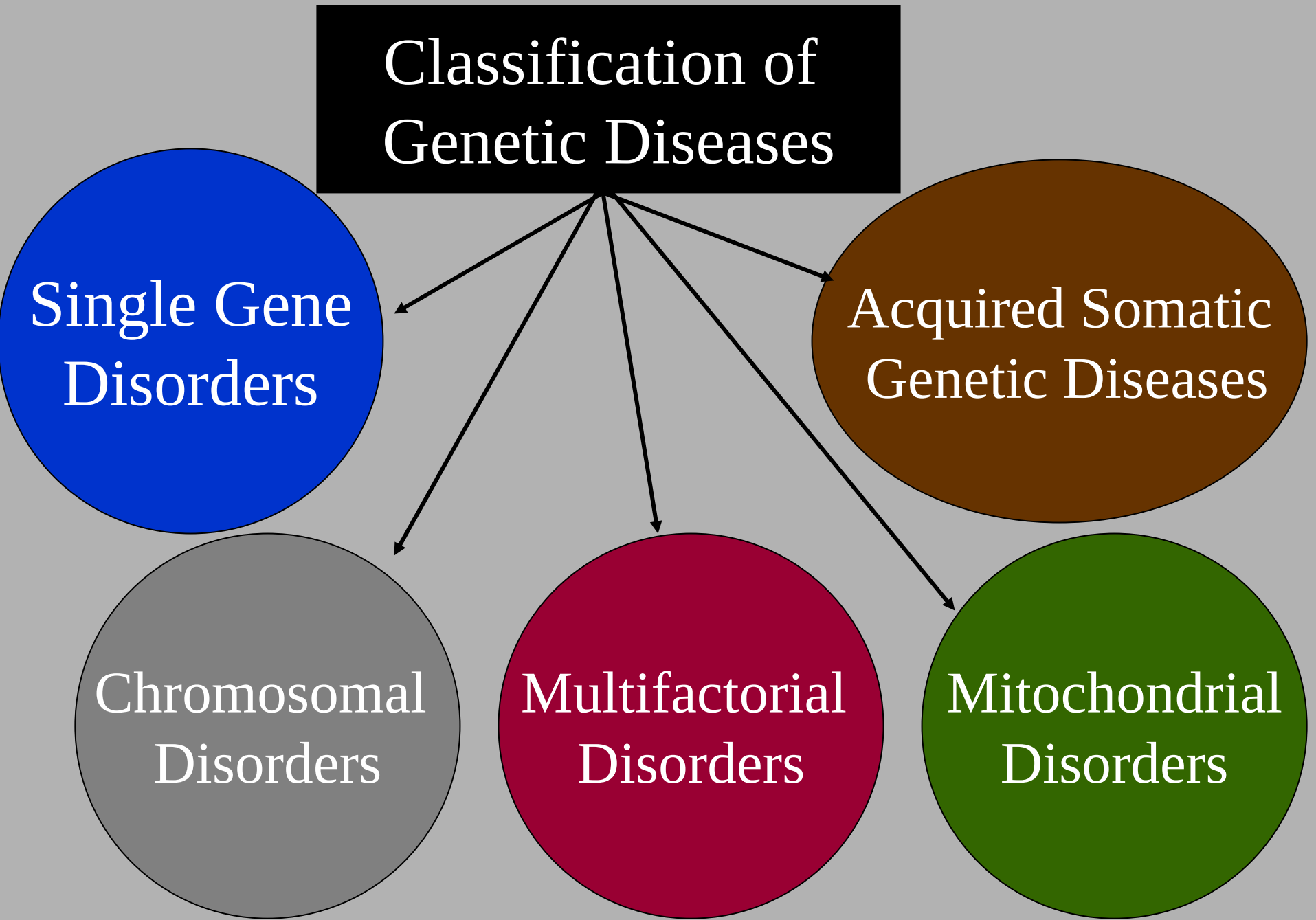
Mutations affecting the β-Globin gene.



1. Mutations affecting transcription initiation
2. Mutations affecting RNA splicing
3. Mutations affecting translation initiation
4. Non-sense Mutations.
5. Mutations of polyadenylation site.

Mechanisms of DNA repair

Mechanism	Problem	Repair
Mismatched repair	Copying error	Methyl directed strand cutting, exonuclease digestion, and replacement
Base excision repair	Spontaneous, chemicals, or radiations damage to a single base	Base removed by N-glycosylase, a basic sugar removal, replacement
Nucleotide excision repair	Spontaneous, chemicals, or radiation damage to a DNA segment	Removal of an approx. 30 nucleotide oligomer and replacement


Classification of Genetic Diseases
Single Gene Disorders
Acquired Somatic Genetic Diseases
Chromosomal Disorders
Multifactorial Disorders
Mitochondrial Disorders

Examples of Single Gene Disorder and associated clinical presentation

Disorder	Inheritance	Clinical presentation
Sjogren-Larsson syndrome	AR	Mental retardation, speech and hearing defects. Inability to walk.
Phenylketonuria	AR	Mental retardation
Lesch-Nyhan syndrome	AR	MR, self mutilation tendency
Duchenne Muscular Dystrophy	XR	Muscle weakness, Inability to walk, Low IQ, Speech impaired
Hunter syndrome	XR	Behaviour problems. Mental retardation. Hearing impairment.
Huntington Disease	AD	Dementia, psychiatric distur-bance, Choreiform movement
Achondroplasia	AD	Short, abnormal stature (short limbs, with normal length trunk
Congenital blindness	AR & AD	Partial or complete blindness
Fragile X Syndrome	XR	Mental retardation
Albinism	AR	No skin pigmentation, low vision


Thank you
for listening