Genetic Disorders

TRANSMISSION PATTERNS OF SINGLE-GENE DISORDERS

- autosomal dominant,
- autosomal recessive,
- and X-linked.

Autosomal dominant disorders are manifested in the

- heterozygous state, so at least one parent is usually affected;
- both males and females are affected,
- and both can transmit the condition.
- When an affected person marries an unaffected one, every child has one chance in two of having the disease.
- Two major categories of nonenzyme proteins are affected in autosomal dominant disorders:
- Those involved in regulation of complex metabolic pathways that are subject to feedback inhibition: Membrane receptors such as the low-density lipoprotein (LDL) receptor provide one such example; in familial hypercholesterolemia, a 50% loss of LDL receptors results in a secondary elevation of cholesterol that, in turn, predisposes to atherosclerosis in affected heterozygotes.
- Key structural proteins, such as collagen and cytoskeletal elements of the red cell membrane (e.g., spectrin)

Autosomal Recessive Disorders

- Autosomal recessive traits make up the largest category of mendelian disorders.
- Because autosomal recessive disorders result only when both alleles at a given gene locus are mutated, such disorders are characterized by the following features:

(1) The trait does not usually affect the parents of the affected individual, but siblings may show the disease;

(2) siblings have one chance in four of having the trait (i.e., the recurrence risk is 25% for each birth); and

(3) if the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the affected individual is the product of a consanguineous marriage.

Autosomal recessive disorders include almost all inborn errors of metabolism.

X-Linked Disorders

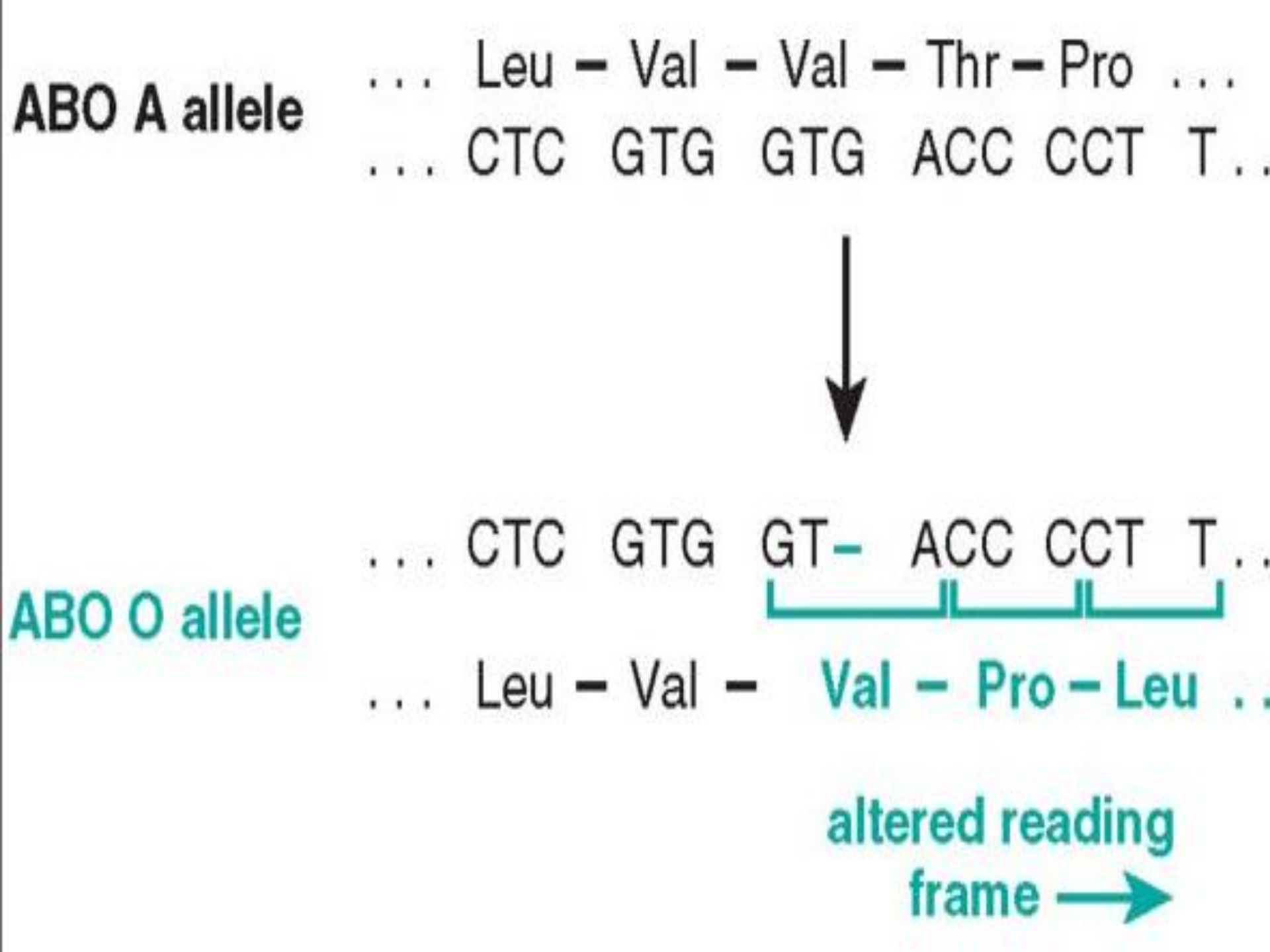
- *All sex-linked disorders are X-linked,*
- *and almost all are recessive*.
- Several genes are located in the "male-specific region of Y"; all of these are related to spermatogenesis. Males with mutations affecting the Y-linked genes are usually infertile, and hence there is no Y-linked inheritance.
- *X-linked recessive inheritance* accounts for a small number of well-defined clinical conditions.
- mutant genes on the X do not have corresponding alleles on the Y. Thus, the male is said to be *hemizygous* for X-linked mutant genes, so these disorders are expressed in the male.

MUTATIONS

- defined as a permanent change in the DNA.
- Mutations that affect germ cells are transmitted to the progeny and can give rise to inherited diseases. Mutations that arise in somatic cells do not cause hereditary diseases but are important in the genesis of cancers and some congenital malformations.
- Mutations may result in partial or complete deletion of a gene or, more often, **affect a single** base. For example, a single nucleotide base may be *substituted* by a different base, resulting in a *point mutation*. Less commonly, **one or two base** pairs may be *inserted* into or *deleted* from the DNA, leading to alterations in the reading frame of the DNA strand; hence these are referred to as *frameshift* mutations.

Point mutations within coding sequences

- A point mutation may alter the code in a triplet of bases and lead to the replacement of one amino acid by another in the gene product. Because these mutations alter the meaning of the sequence of the encoded protein, they are often termed ***missense*** *mutations*. If the substituted amino acid causes little change in the function of the protein, the mutation is called a "**conservative" missense mutation**. On the other hand, a "nonconservative" missense mutation replaces the normal amino acid with a very different one. An excellent example of this type is the sickle mutation affecting the β-globin chain of hemoglobin .Here the nucleotide triplet CTC (or GAG in mRNA), which encodes glutamic acid, is changed to CAC (or GUG in mRNA), which encodes valine. This single amino acid substitution alters the physicochemical properties of hemoglobin, giving rise to sickle cell anemia.


ABO A allele
. . . Leu – Val – Val – Thr – Pro . . .
. . . CTC GTG GTG ACC CCT T . .
. . . CTC GTG GT– ACC CCT T . .
ABO O allele
. . . Leu – Val – Val – Pro – Leu . .
altered reading frame

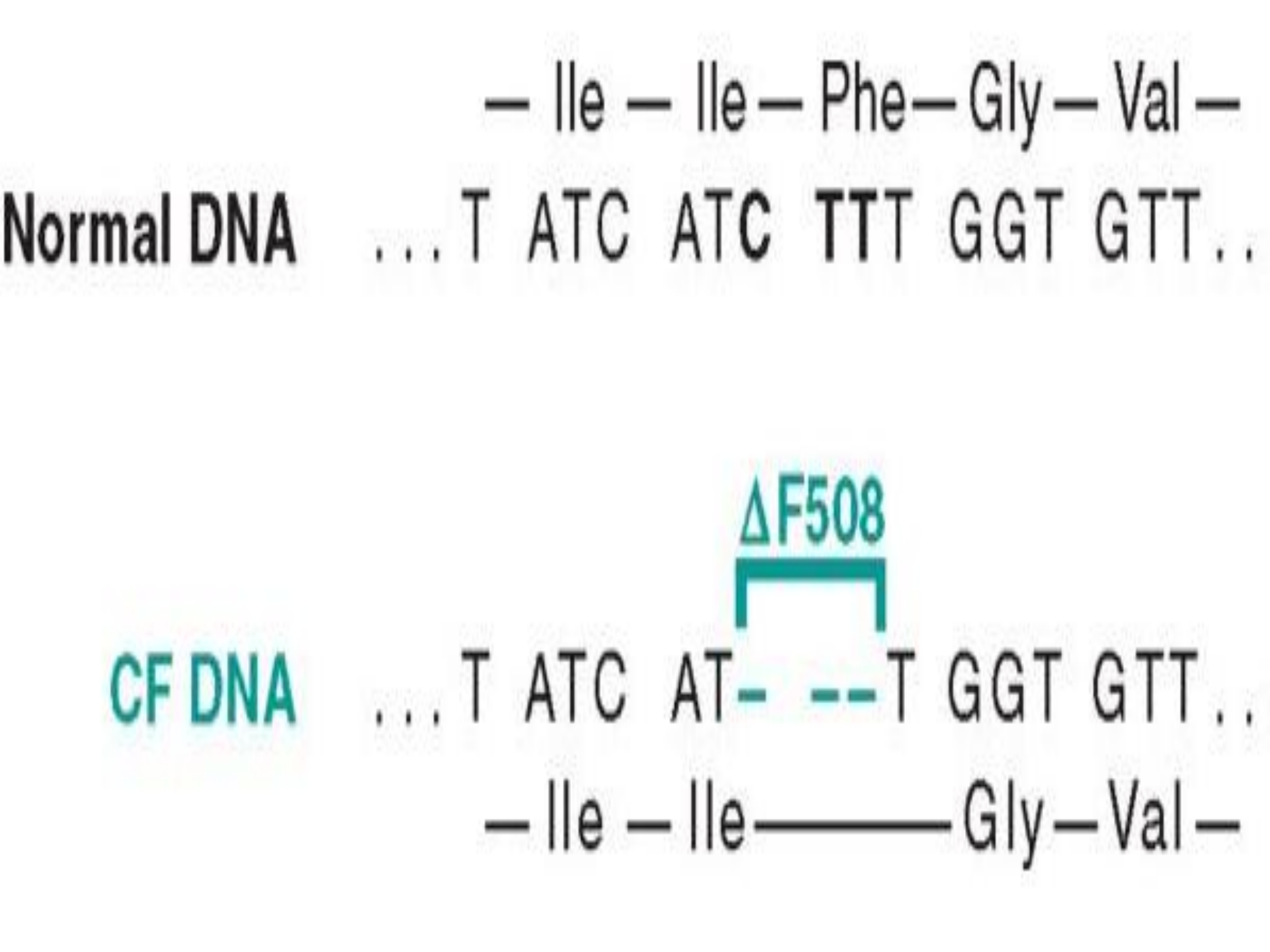
- Besides producing an amino acid substitution, a point mutation may change an amino acid codon to a chain terminator, or ***stop codon*** *(****nonsense mutation****)*. Taking again the example of β-globin, a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) if U is substituted for . This change leads to premature termination of β-globin gene translation, and the short peptide that is produced is rapidly degraded. The resulting deficiency of β-globin chains can give rise to a severe form of anemia called β^0-thalassemia.

Mutations within noncoding sequences

- Deleterious effects may also result from mutations that do not involve the exons. Recall that transcription of DNA is initiated and regulated by promoter and enhancer sequences. Point mutations or deletions involving these regulatory sequences may interfere with binding of transcription factors and thus lead to a marked reduction in or total lack of transcription. Such is the case in certain forms of hereditary anemias. In addition, point mutations within introns may lead to defective splicing of intervening sequences. This, in turn, interferes with normal processing of the initial mRNA transcripts and results in a failure to form mature mRNA. Therefore, translation cannot take place, and the gene product is not synthesized.

Deletions and insertions:

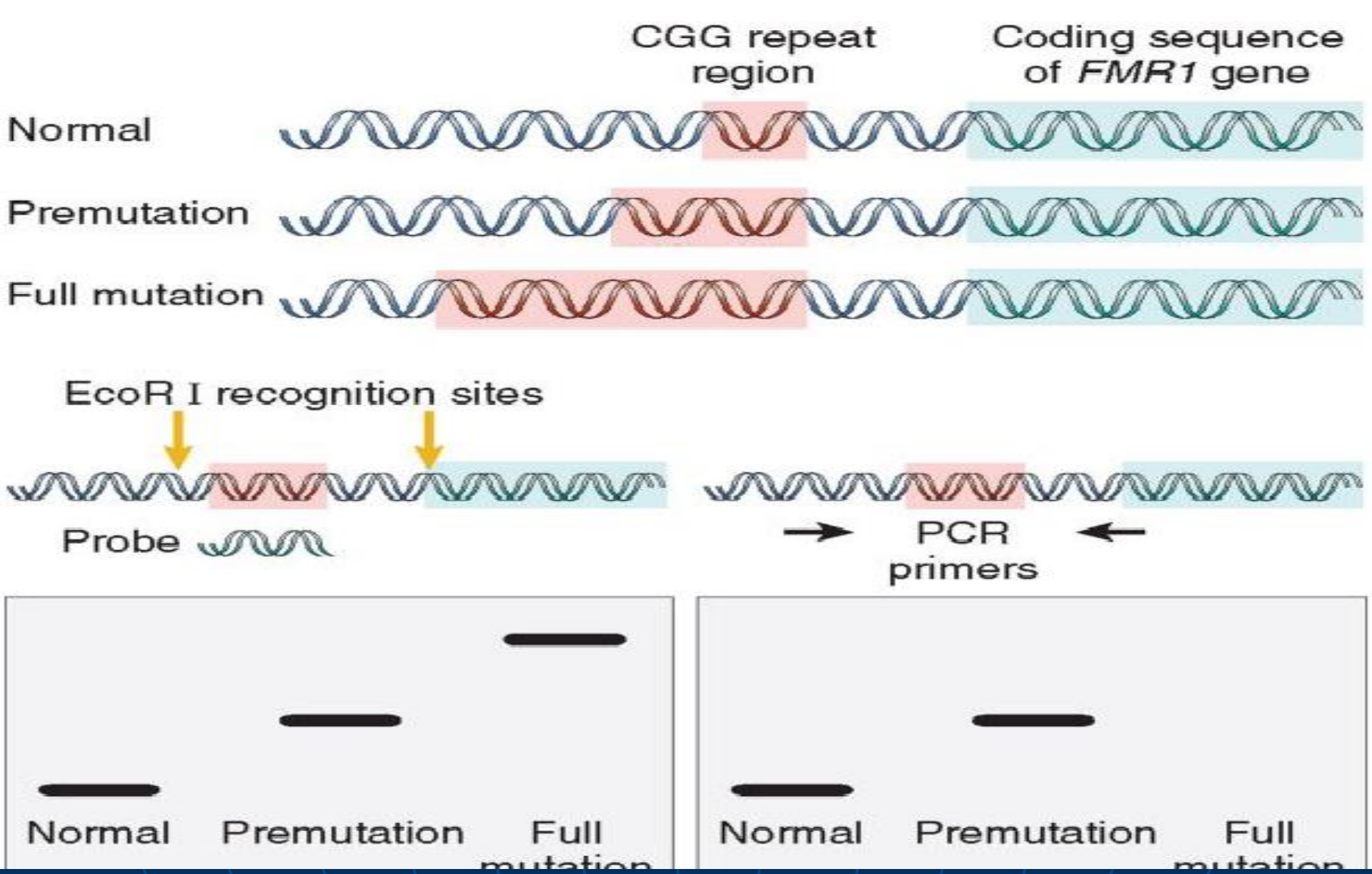
- Small deletions or insertions involving the coding sequence lead to alterations in the reading frame of the DNA strand; hence, they are referred to as ***frameshift mutations*****.** If the number of base pairs involved is three or a multiple of three, frameshift does not occur instead an abnormal protein lacking or gaining one or more amino acids is synthesized


– Ile – Ile – Phe – Gly – Val –
Normal DNA ...T ATC ATC TTT GGT GTT..
ΔF508
CF DNA ...T ATC AT- --T GGT GTT..
– Ile – Ile ——— Gly – Val –

Trinucleotide-repeat mutations

- Trinucleotide-repeat mutations belong to a special category of genetic anomaly. These mutations are characterized by amplification of a sequence of three nucleotides. almost all affected sequences share the nucleotides guanine (G) and cytosine (C). For example, in fragile-X syndrome, prototypical of this category of disorders, there are 250 to 4000 repeats of the sequence CGG within a gene called familial mental retardation 1 (*FMR1*). In normal populations the number of repeats is small, averaging 29. Such expansions of the trinucleotide sequences prevent normal expression of the *FMR1* gene, thus giving rise to mental retardation. Another *distinguishing feature of trinucleotide-repeat mutations is that they are dynamic* (i.e., the degree of amplification increases during gametogenesis).

- ***it should be noted that, uncommonly, mutations are beneficial, the human immunodeficiency virus (HIV) uses a chemokine receptor, CCR5, to enter cells; a deletion in the CCR5 gene thus protects from HIV infection.***



Southern blotting PCR

1.Single-Gene Disorders with Nonclassic Inheritance

Mitochondrial gene disorders:

- Mitochondria contain several genes that encode enzymes involved in oxidative phosphorylation .
- mtRNA is circular , double stranded structure without introns encoding 13 protiens. In addition mitochondria contain tRNA and rRNA for translation.

- It associated with maternal inheritance.(ova contain abundent mitochondria in their cytoplasm)
- During cell division, each mtRNA replicates but unlike the nuclear DNA , the mitochondria segregate passively to the daughter cells. This random segregation of mitochondria result in unpredictability in phenotype from individual to

- *Leber hereditary optic neuropathy* is a prototype of this type of disorder. It is a neurodegenerative disease that manifests as a progressive bilateral loss of central vision. Visual impairment is first noted between ages 15 and 35, and it leads eventually to blindness. Cardiac conduction defects and minor neurologic manifestations have also been observed in some families.

2.GENOMIC IMPRINTING

- We all inherit two copies of each autosomal gene, carried on homologous maternal and paternal chromosomes. In the past, it had been assumed that there is no functional difference between them. Studies over the past two decades have provided definite evidence that important functional differences exist between the paternal allele and the maternal allele. These differences result from an epigenetic process, called *imprinting.*
- *imprinting selectively inactivates either the maternal or paternal allele*. Thus, *maternal imprinting* refers to transcriptional silencing of the maternal allele, whereas *paternal imprinting* implies that the paternal allele is inactivated.
- Imprinting occurs in the ovum or the sperm, before fertilization, and then is stably transmitted to all somatic cells through mitosis.

- As with other instances of epigenetic regulation, imprinting is associated with differential patterns of DNA methylation at CG nucleotides. Other mechanisms include histone H4 deacetylation and methylation. genomic imprinting is best illustrated by considering two uncommon genetic disorders: Prader-Willi syndrome and Angelman syndrome.

- *Prader-Willi syndrome* is characterized by mental retardation, short stature, hypotonia, profound hyperphagia, obesity, small hands and feet, and hypogonadism.
- In 65% to 70% of cases, an interstitial deletion of band q12 in the long arm of chromosome 15, can be detected. *It is striking that in all cases the deletion affects the paternally derived chromosome 15*. In contrast with the Prader-Willi syndrome, patients with the phenotypically distinct Angelman syndrome are *born with a deletion of the same chromosomal region derived from their mothers*.

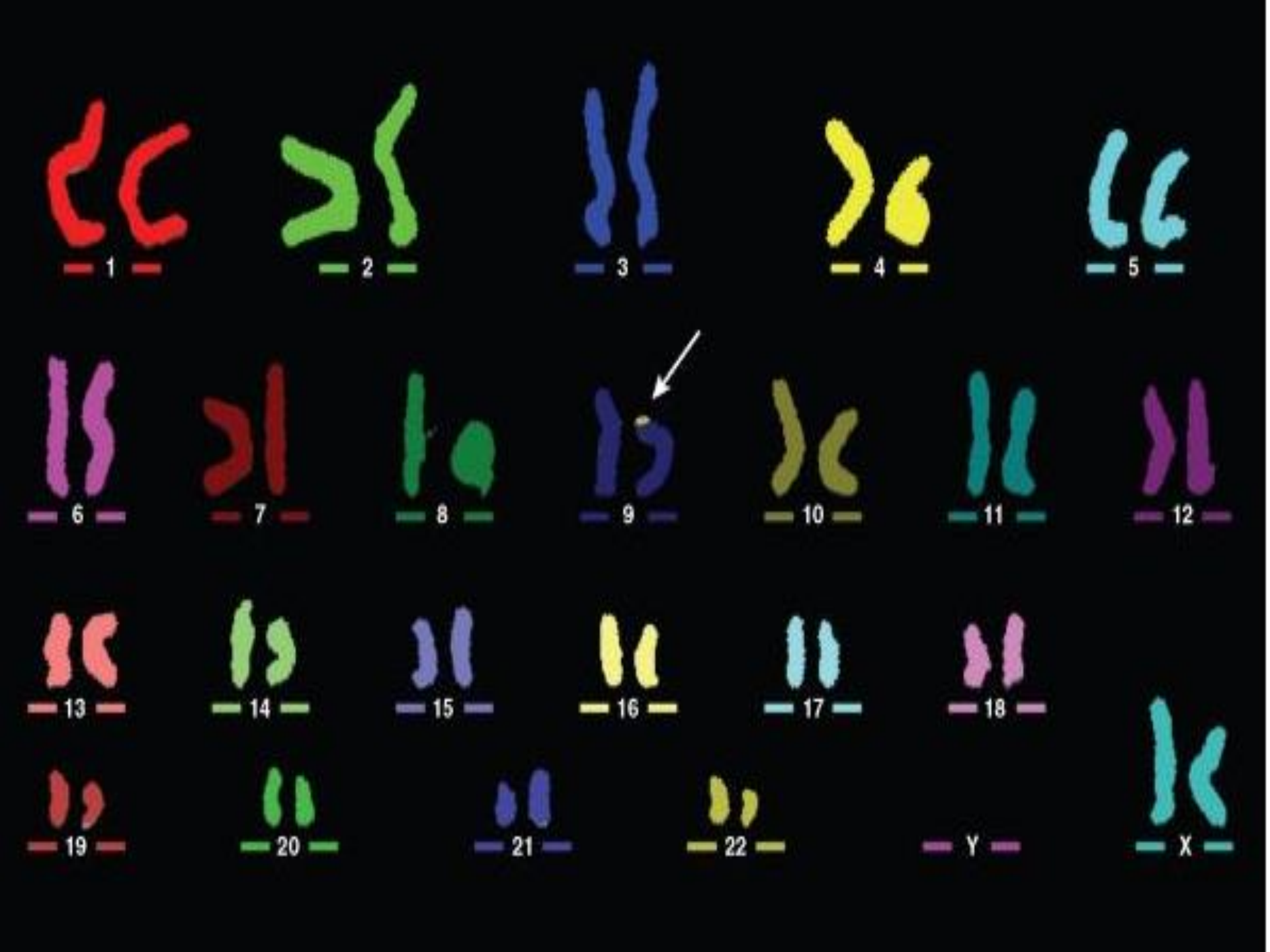
3.Triplet repeat mutation

- Increasing no. of long repeat sequence of three nucleotides whoch disrupt the gene function.
- Associated with neurodegenerative changes
- May be within exon or intron
- It cause signs and symptoms in earlier age a phenomenon called anticepation.

- Share the nucleotide C & G
- E.g. fragile X syndrome, huntington disease , myotonic dystrophy and friedreich's ataxia.
- Most of them inherited as AD or X-linked except the latter which is AR.

4. Gonadal mosaicism:

mutation occur in AD gene lead to AD disorder in family for first time (-ve family history). This mutation not occur in gametes but in undifferentiated cell of post-fertilization zygote. This cell and all of its descendants would carry the mutated gene but creating a cluster differ from non mutated cell this state called mosaicism (presence of 2 or more cell lines in the same individual. If this mutated cell form the testis or ovary in the future so called gonadal mosaicism.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