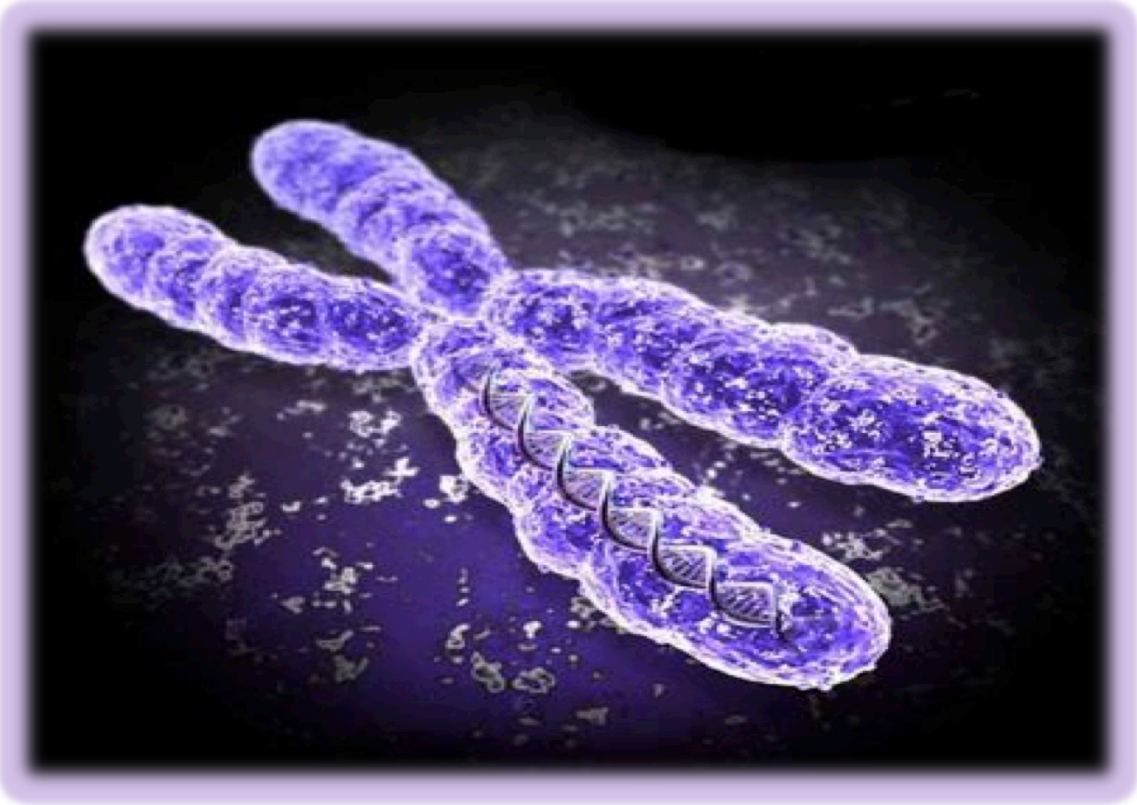
EFFECT OF GENETIC FACTORS ON PERIODONTAL DISEASES



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Introduction

- Genetics is defined as the science of heredity; it is concerned with the physical and chemical properties of the hereditary material, how this material is transmitted from one generation to next and how the information it contains is expressed during the development of the individual.

- Involvement of periodontal tissues is seen in a number of genetic disorders. In some, supporting tissues of teeth are involved, while in others, they are affected as a consequence of the primary genetic disorder.

- In others, the gingival or periodontal disorder is associated with the involvement of other body systems; at other times they will be the only manifestation of the genetic disorder.

Gregor Mendel (1823 – 1884)

DEFINITIONS

GENE

- Biological unit of heredity.
- Gene hold the information to build and maintain their cells and pass genetic traits to offsprings
- In cells, a gene is portion of DNA
- Gene consists of a long strand of DNA that contains a promote region, a coding and a non coding sequence.

GENOME:- The total set of genes in an organism

GENOTYPE:- Genetic composition of an organism

PHENOTYPE:- Collection of traits or characteristics

HOMOZYGOUS:- Identical alleles on homologus chromosomes at a given locus.

HETEROZYGOUS:- Different alleles on homologus chromosomes.

GENETIC MARKER:- Refers to any gene or nucleotide sequence that can be mapped to a specific location or region on a chromosome. Any marker which is sufficiently polymorphic or variable in the population can be used to map or locate disease alleles.

LOCI

- Specific locations on chromosomes.

ALLELE

- Is one member of a pair or series of different forms of a gene.
- Homozygous-an organism in which 2 copies of genes are identical i.e. have same alleles
- Heterozygous-an organism which has different alleles of the gene

NUCLEOTIDE

- Group of molecules that when linked together, form the building blocks of DNA and RNA; composed of phosphate group, the bases: adenosine, cytosine, guanine and thymine and a pentose sugar. In case of RNA , thymine base is replaced by uracil.

CODON

- Series of three adjacent bases in one polynucleotide chain of a DNA or RNA molecule which codes for a specific amino acid.

GENETIC CODE

- The sequence of nucleotides in a DNA or RNA molecule that determines the amino acid sequence in the synthesis of proteins.

Mutations

Permanent changes in the DNA.
Those that affect germ cells are transmitted to the progeny. Mutations in the somatic cells are not transferred to the progeny but are important in the causation of cancer and some congenital diseases.

TYPES OF MUTATIONS

1. POINT MUTATION:

A single nucleotide base gets replaced by another

MISSENSE MUTATION

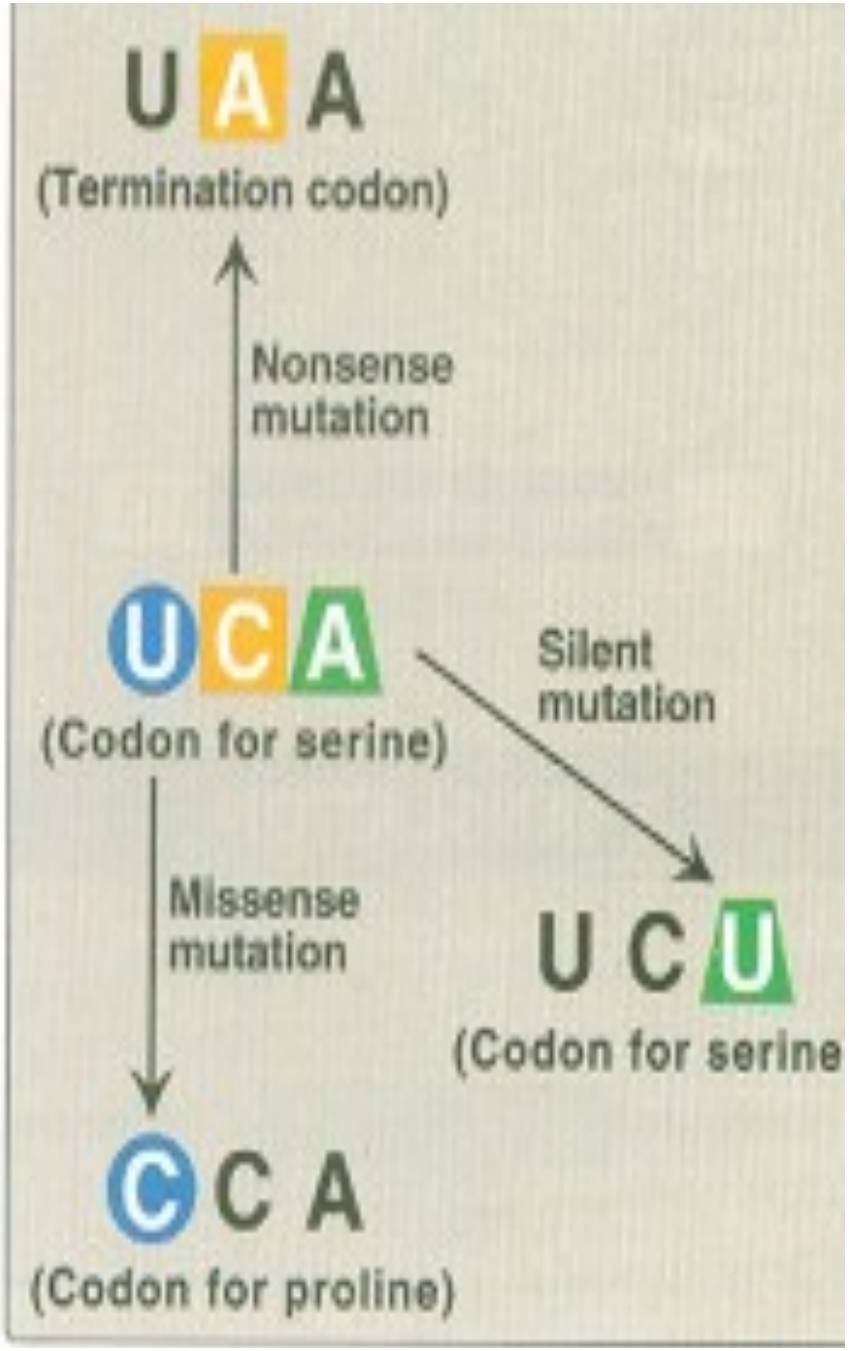
- The new base alters a codon resulting in a different amino acid

NONSENSE MUTATION

- The new base changes a codon that specified an amino acid into one of the stop codons & can truncate the protein

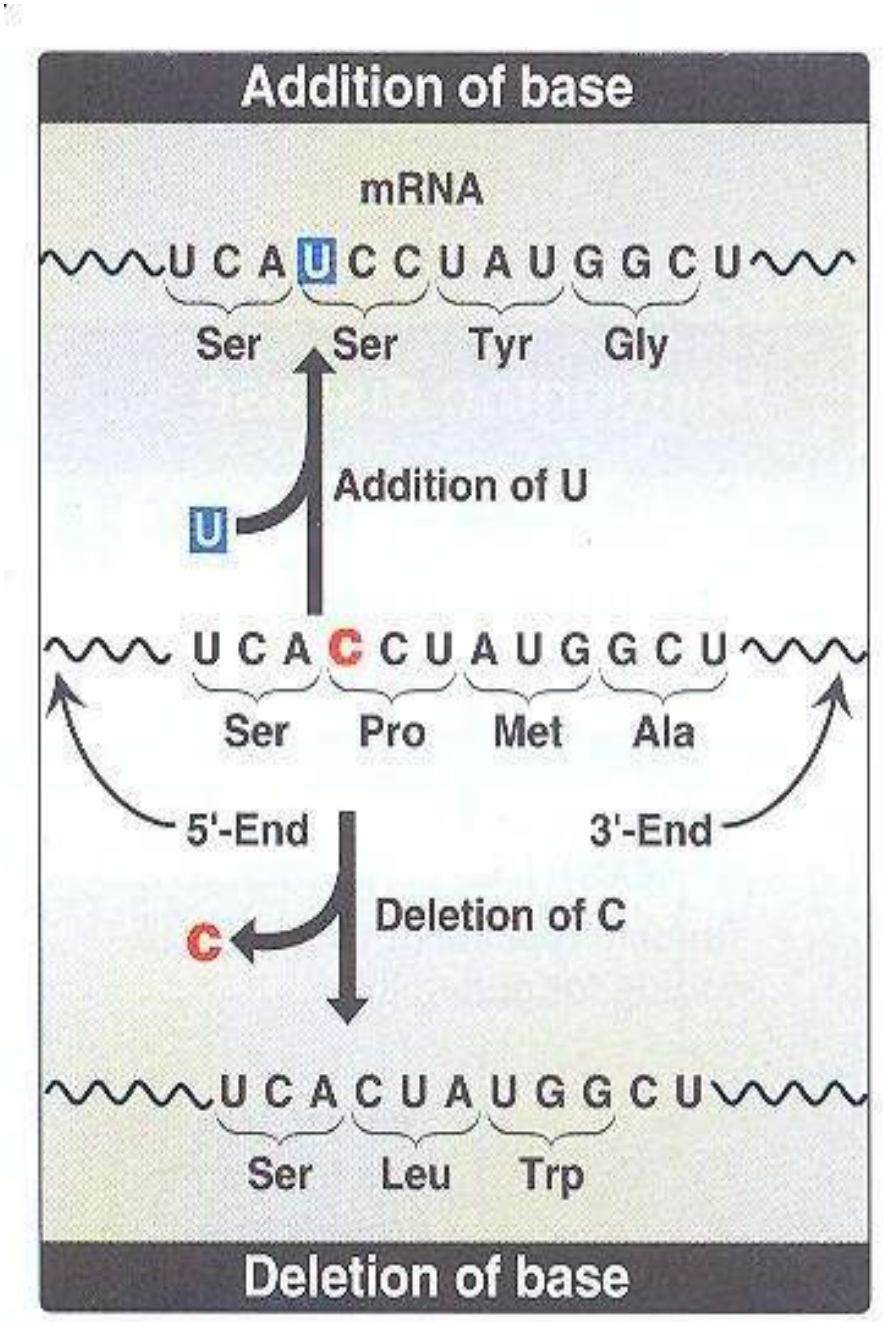
SILENT MUTATION

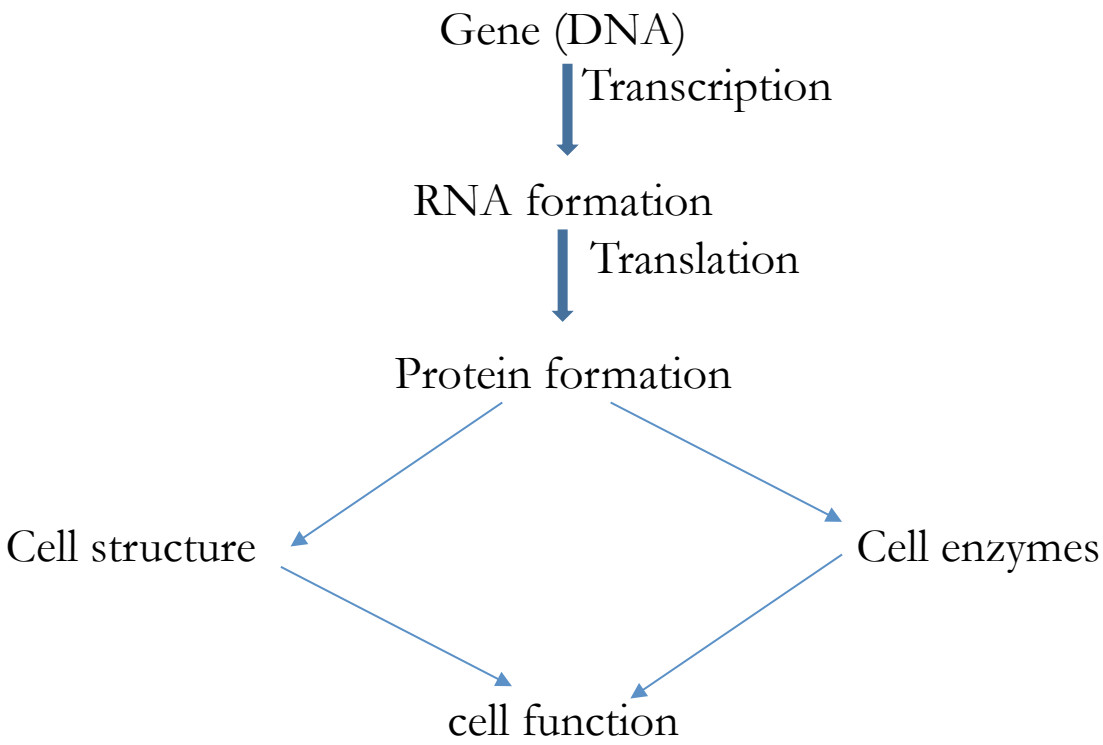
- Causes no change in final protein product



2. Frameshift Mutations:

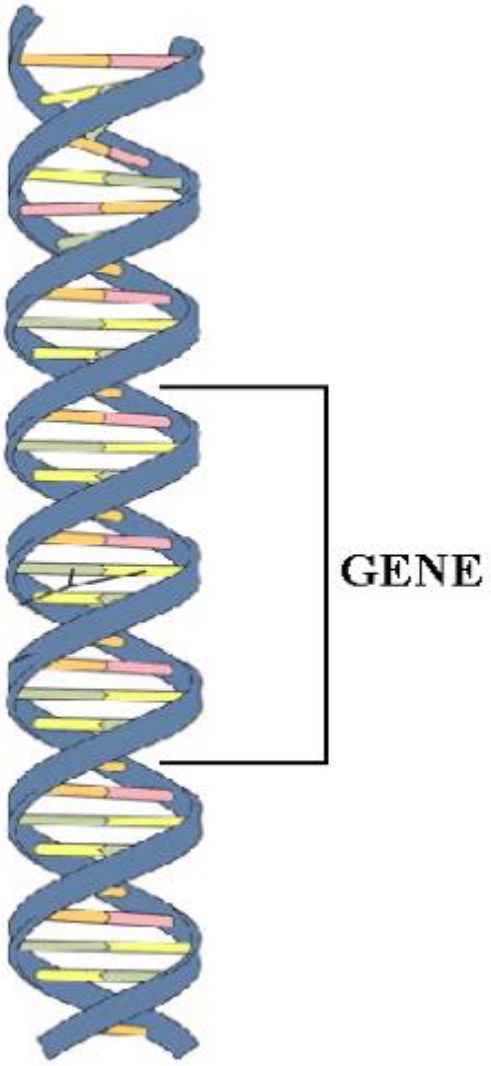
Insertion or deletion of one or two base pairs
alters the reading frame of the DNA strand.




Gene (DNA)
Transcription
RNA formation
Translation
Protein formation
Cell structure
Cell enzymes
cell function

DNA and Translation

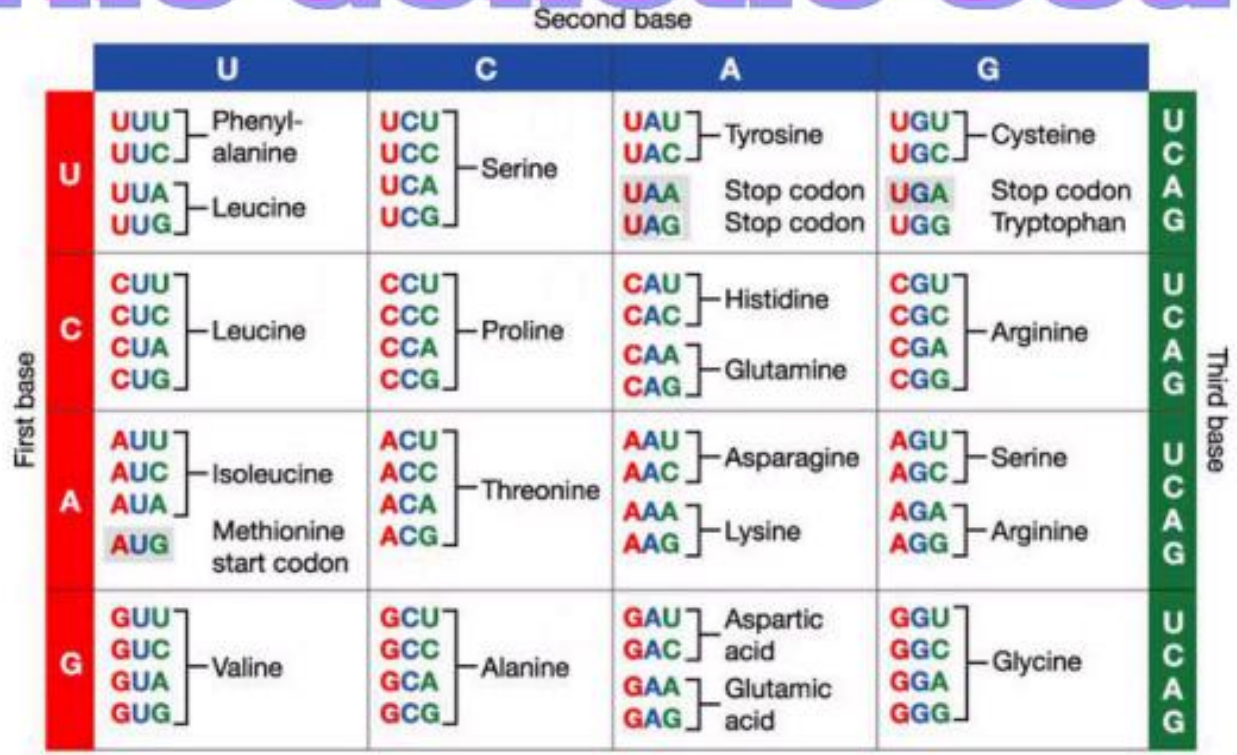
- **Gene**: section of DNA that creates a specific protein
  - Approx 25,000 human genes
- Proteins are used to build cells and tissue
- Protein synthesis involves two processes:
  1) Transcription
  2) Translation



Transcription Review

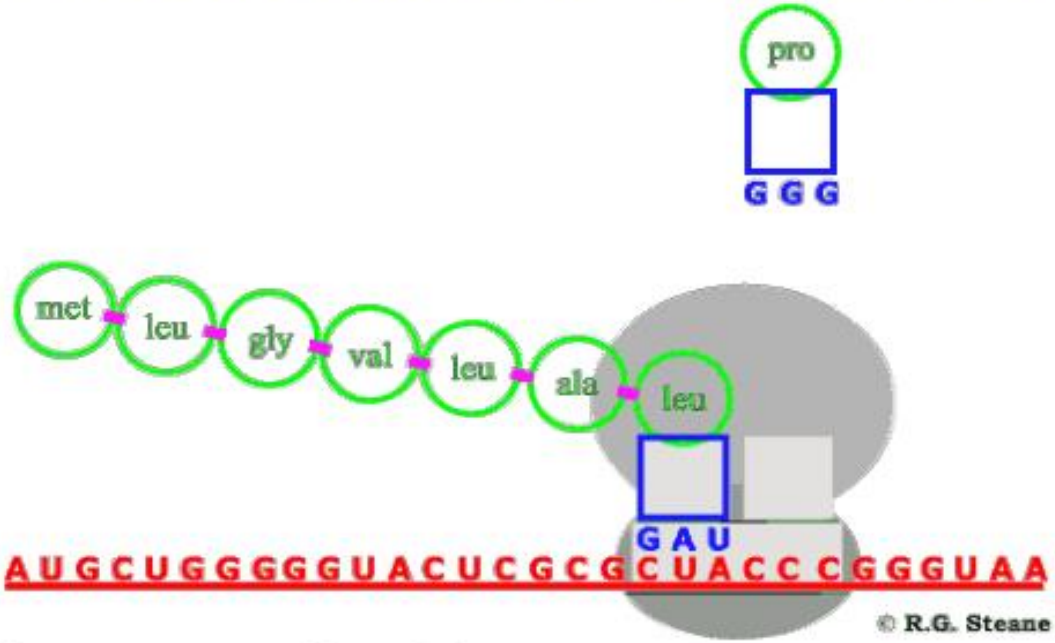
- **Transcription takes place in the nucleus**
  - **1) DNA double helix is broken apart**
  - **2) mRNA nucleotides match up**
  - **3) Finished mRNA detaches, and moves to a ribosome**

The Genetic Code



- **Codon**: Combination of 3 mRNA nucleotides
- Each mRNA codon matches with 1 of 20 amino acids
- Codon AAA = **Lysine**
- Codon GUU = **Valine**
- Codon AUG = **Methionine (Start)**
- Codons UAA or UAG or UGA = **Stop**

Translation Overview



- **Defined**: Process of making proteins
  - **Step 1**: mRNA enters ribosome
  - **Step 2**: Ribosome reads one mRNA codon at a time
  - **Step 3**: tRNA delivers amino acids until a protein is created

Translation Details

- Translation begins when the mRNA codon "AUG" is reached
- Each mRNA codon matches with a specific amino acid
  - AUG = methionine
  - GCU = alanine
- tRNA carries over the proper amino acid
  - tRNA anticodon matches with the mRNA codon
- One by one, amino acids are linked together
- Translation ends when a "stop" codon is reached
- End result: Polypeptide (protein)

TYPES OF GENETIC DISORDERS

GENETIC DISORDERS

1) SINGLE GENE (MONOGENIC / MENDELIAN) DISORDERS

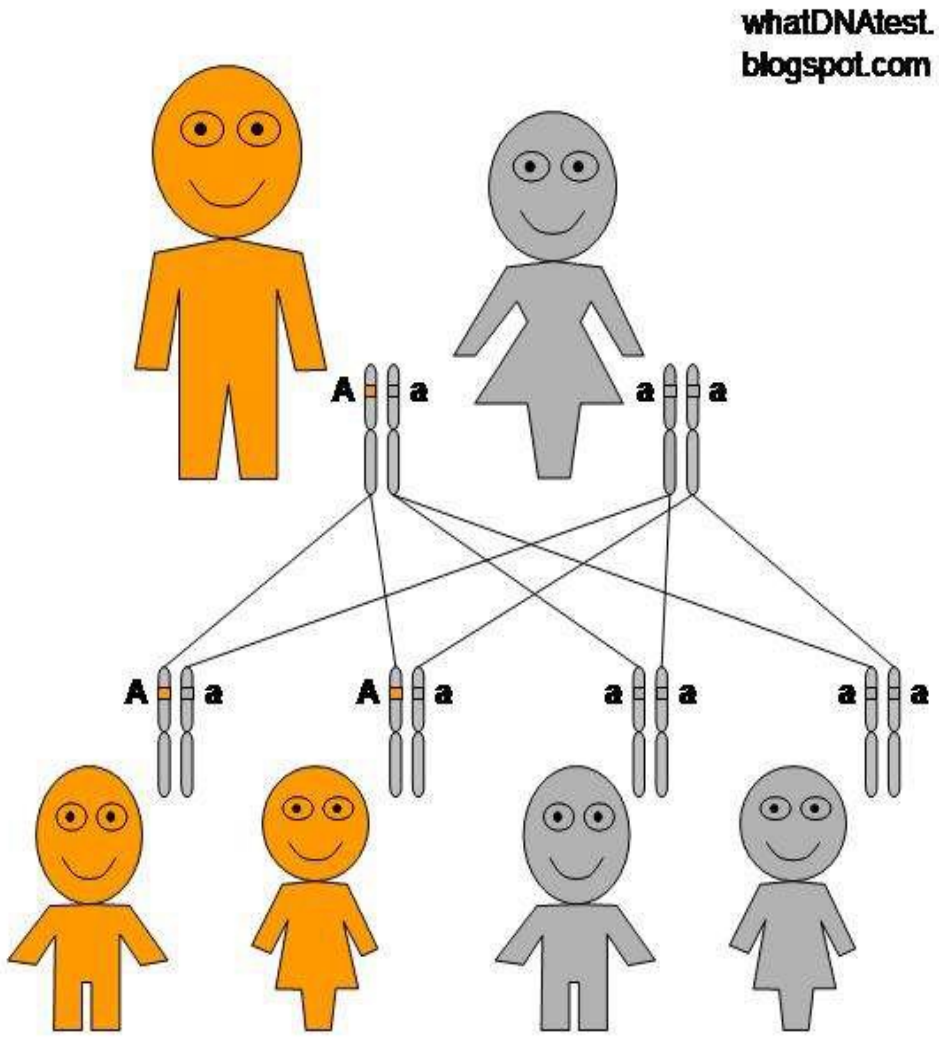
2) NON-MENDELIAN /COMPLEX DISORDERS

SINGLE MENDELIAN DISEASES

- Follow predictable and generally simple patterns of transmission.
- In most cases a single gene locus is the major determinant of the clinical disease phenotype.
- These diseases follow a classic Mendelian mode of inheritance (autosomal-dominant, autosomal-recessive, or X-linked).

A) Autosomal dominant disorders

- Caused by mutation of genes located on one of the autosomes
- Individuals may have a "normal" copy & an "abnormal" copy.
- One of the 2 copies is abnormal – disease is produced
- 50% chance that each offspring will develop the disease.



e.g. Hereditary gingival fibromatosis; Cleidocranial Dysplasia; Dentinogenesis Imperfecta; Hypophosphatasia
Dentin Dysplasia

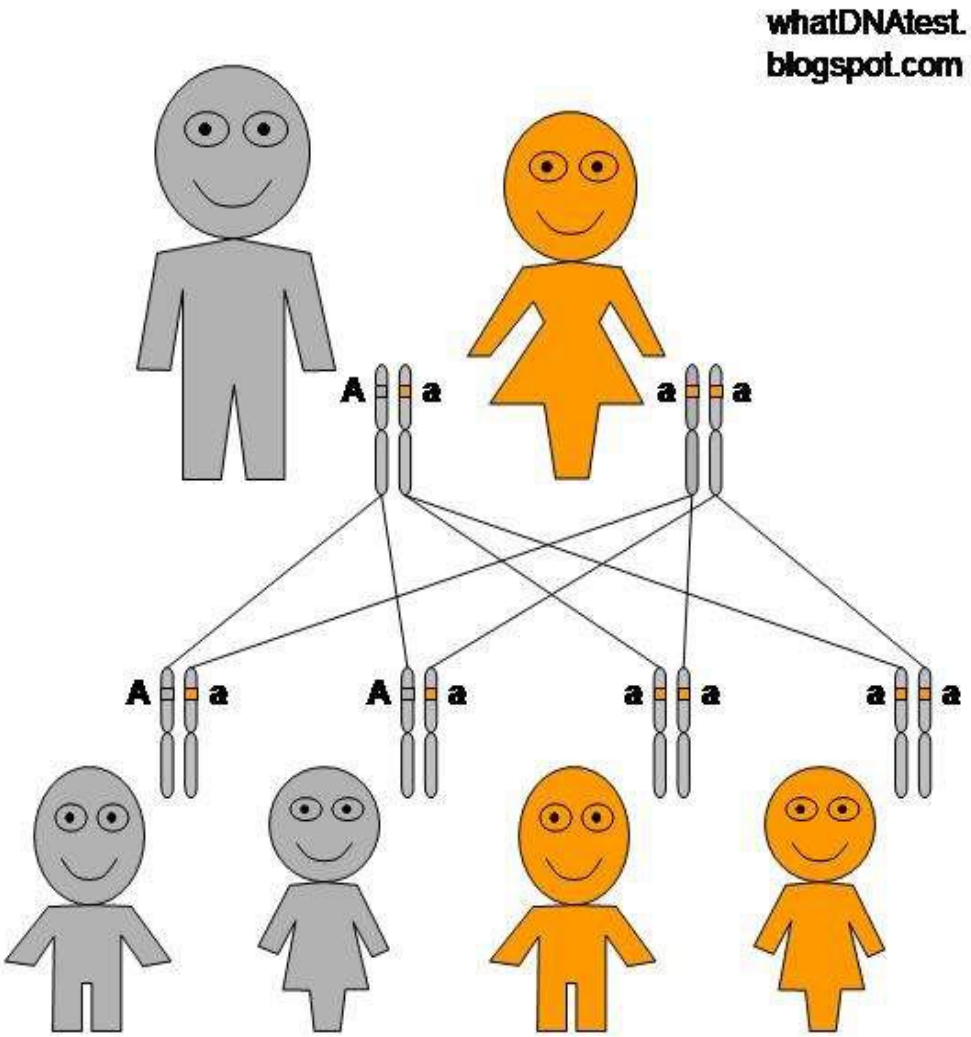
B) Autosomal recessive disorders

• 2 alleles of an abnormal gene are necessary for disease expression.

• Affected individuals are homozygous
for the disease gene.

• Heterozygotes have a single abnormal gene – Carriers.

e.g. Ectodermal dysplasia;
Thalassemia;
Sickle cell anemia



C) X-linked disorders

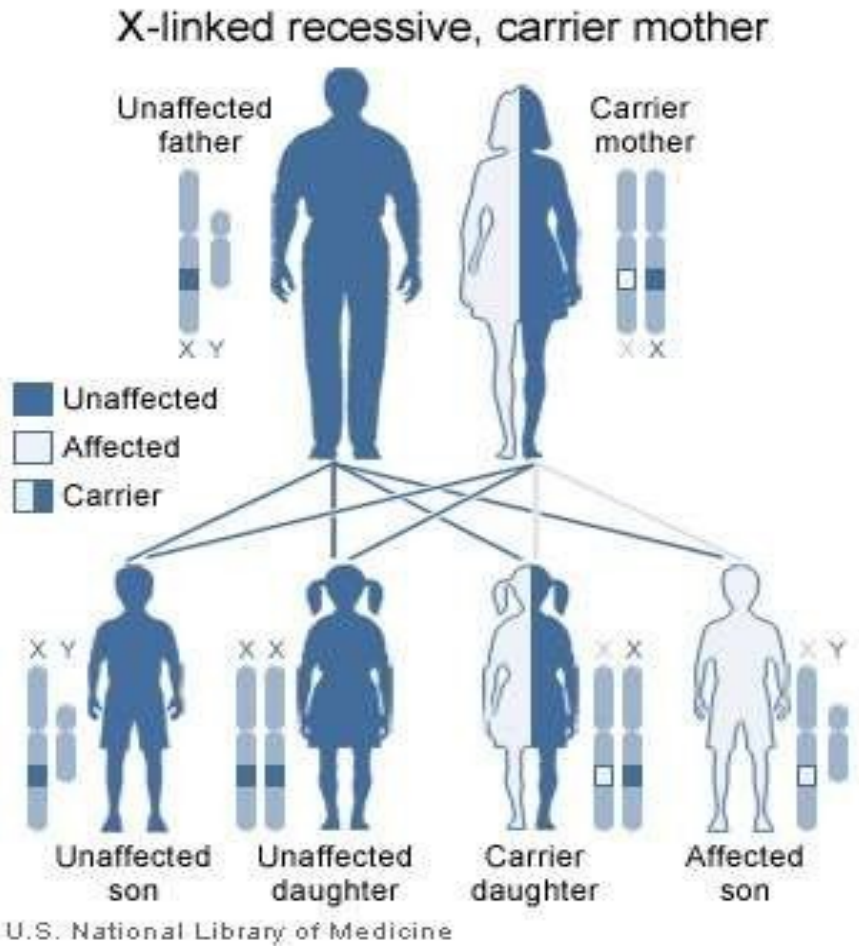
- Usually expressed only in males.
- Rarely, due to random X-inactivation, a female will express disease, called manifesting heterozygotes.

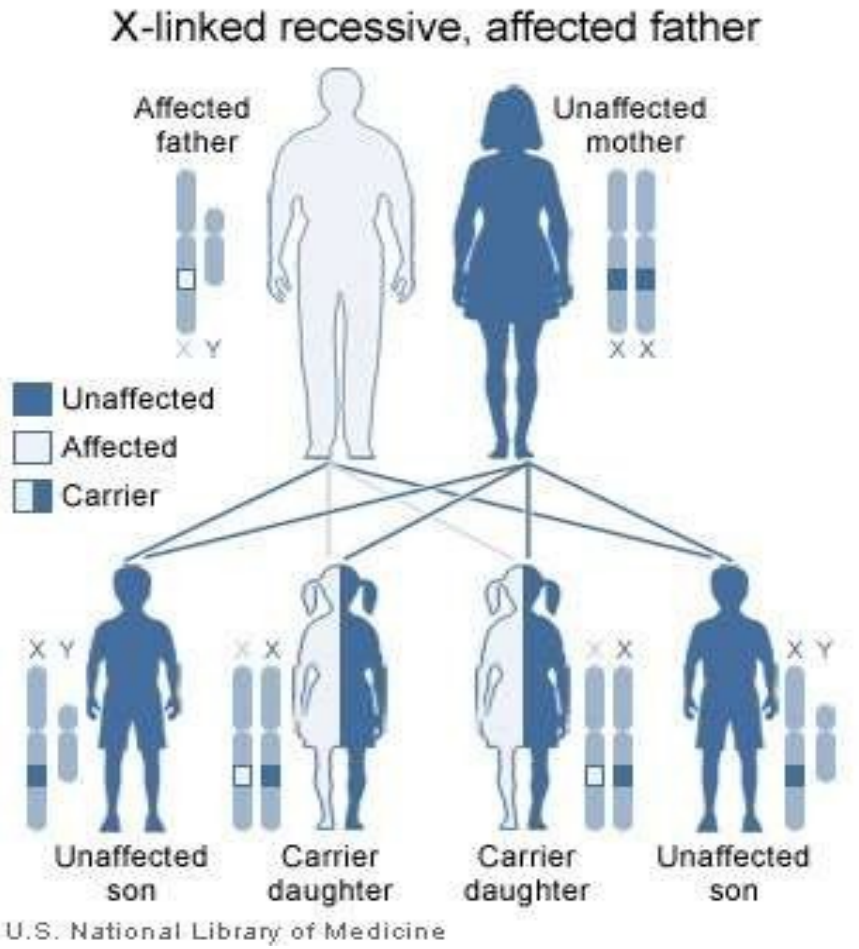
Pattern Of Inheritance:

- Disease usually passed on from carrier mother.
- Expressed in male offspring, females are carriers.
- Skipped generations are commonly seen.
- In this case, Recurrence risk is half of sons are affected, half of the daughters are carriers.

Recurrence risk:

- All the daughters are heterozygous carriers and all the sons are homozygous normal.





COMPLEX GENETIC DISEASES

- Complex diseases do not typically follow a simple pattern of familial distribution or transmission.
- Much more prevalent, and usually occur with a frequency of greater than 1% of the population.
- "complex traits" are the result of the interaction of alleles at multiple different gene loci. Additionally, environmental factors are etiological and important in the development of complex disease .
- Individual genetic variants are less disruptive and usually function within normal range.

METHODS OF GENETIC ANALYSIS

- Segregation analysis
- Twin studies
- Linkage analysis
- Association studies

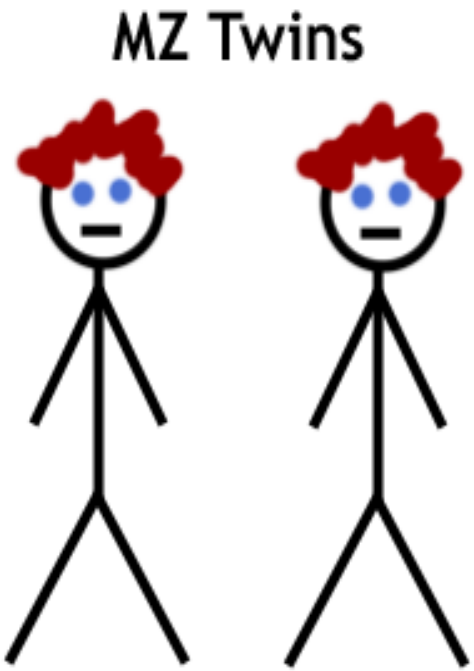
SEGREGATION ANALYSIS

- In segregation analysis, the observed pattern of disease in families is compared with patterns expected under various models of inheritance.

- The transmission across generations depends on whether the disease alleles lie on autosomes or sex chromosomes, dominant or recessive, fully penetrant or partially penetrant.

Twin studies

Dizygous twins on average share 50% of their genes in common.



Monozygous twins are genetically identical

- The relative influence of genetic and environmental factors on complex disease can be estimated using twin study
- The twin data is used to estimate heritability which is the proportion of phenotypic variation attributed to genetic variance.

Linkage analysis

Technique used to localize the gene for a trait to a specific chromosomal location.

Genetic linkage studies are based on the fact that alleles at gene loci in close proximity on the same chromosome tend to be passed seperately from generation to generation (i.e. segregate), as a unit.

Association studies

Genes contributing to common, complex diseases such as periodontitis have proved to be more difficult to isolate.

In the absence of specific genetic models, the etiology of complex diseases is often conceptualized due to multiple factors— several genetic loci interacting with each other to produce an underlying susceptibility, which in turn interacts with additional environmental factors to produce an actual disease state.

Polymorphism	Gene
IL-1A (+4845) and IL-1B (+3954)	IL-1 gene
IL-4 promotor and intron polymorphisms	IL-4 gene
FcγRIIIb-NA2 allele (and possibly FcγRIIIa-158F)	Fc receptor gene polymorphisms
Gc locus chrom 4q	unknown
fMLP receptor	*N*-formyl peptide receptor polymorphisms
VDR gene	vitamin D receptor polymorphism

IL-1, interleukin-1.

1.)IL-1 Gene Polymorphism

Interleukin-1 gene complex (IL-1A and IL-1B genes) which control levels of the multifunctional cytokine IL-1.

The Polymorphisms of the interleukin (IL)-1 gene have been proposed as potential genetic markers for periodontal diseases. Many investigators have reported a positive association between periodontitis and the presence of specific polymorphism of the IL-1 gene.

Il-1 and Smoking

Smokers bearing the genotype-positive IL-1 allele combination may be at an increased risk of developing periodontitis.

STUDIES concluded that the IL-1 gene cluster combined with smoking was associated with an increased risk of attachment loss.

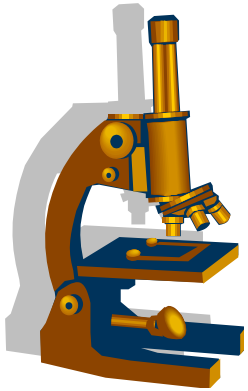
In this population, non-smoking subjects were not at increased risk, even if they are genotype-positive.

IL-1 and GTR

Studies have demonstrated that genotype expression did not affect guided tissue regeneration treatment response at 1 year, but had a great impact on long-term stability (year 4).

In a 3-year period, patients with a positive interleukin-1 genotype lost about 50% of the clinical attachment level gained in the first year and were about 10 times more likely to experience $\geq$2 mm clinical attachment loss when compared to oral hygiene-matched genotype-negative patients.

IL-1 and Microbiology



Socransky et al. investigated the presence of periodontal pathogens in genotype-positive patients.

Higher levels of the ‘‘red’’ and ‘‘orange’’ complexes were detected in genotype-positive subjects more frequently than genotype-negative patients.

Il-1 Polymorphism & Agp

STUDIES examined interleukin-1a and interleukin- 1b genetic polymorphisms in unrelated European white Caucasian patients with generalized early onset periodontitis and found no significant differences between patients and controls.

It was concluded a lack of association between the interleukin-1 polymorphisms and aggressive periodontitis.

2.)VDR gene polymorphism in AgP

- Polymorphisms present in the vitamin D receptor (VDR) gene, which have been correlated with both bone mineral density and bone turnover rate, were reported to be associated with localized aggressive periodontitis (but not generalized aggressive periodontitis)

3.)Fc RECEPTOR POLYMORPHISMS

The Fc portion of an antibody is responsible for binding to receptors present on natural killer cells, macrophages, T lymphocytes, monocytes, and mast cells.

The interaction between FC γ Rs and IgG triggers a variety of biological responses, including phagocytosis, endocytosis, antibody-dependent cellular cytotoxicity, release of inflammatory mediators, and enhancement of antigen presentation.

The genes for **FCγR** are found on long arm of chromosome 1 and encode for **FCγRI , FCγRII, FCγRIII.**

- Polymorphisms in the genes encoding the low affinity receptors Fc γ RIIa, Fc γ RIIb, Fc γ RIIIa, and Fc γ RIIIb may result in variations in antibody binding and phagocytosis and hence susceptibility to periodontitis .

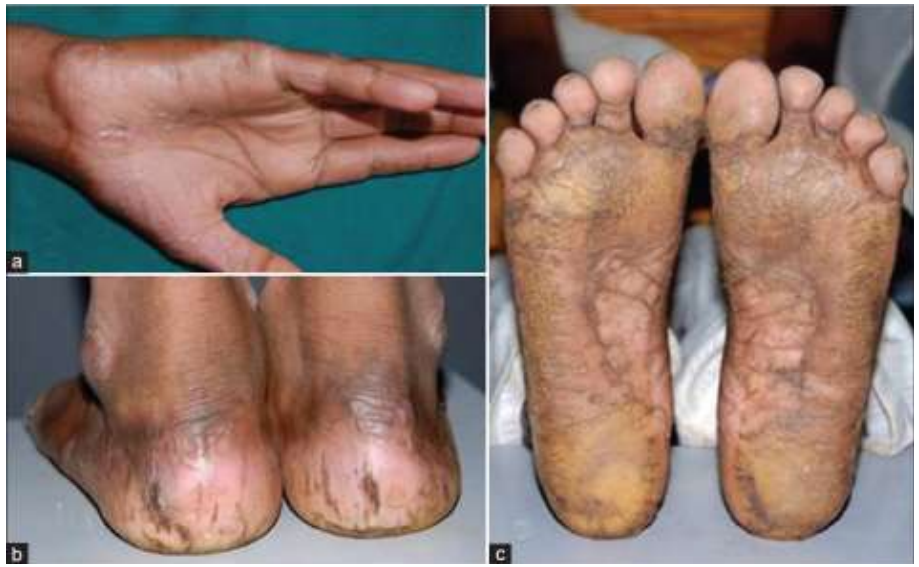
PERIODONTITIS IN GENETIC SYNDROMES AND OTHER DISEASES

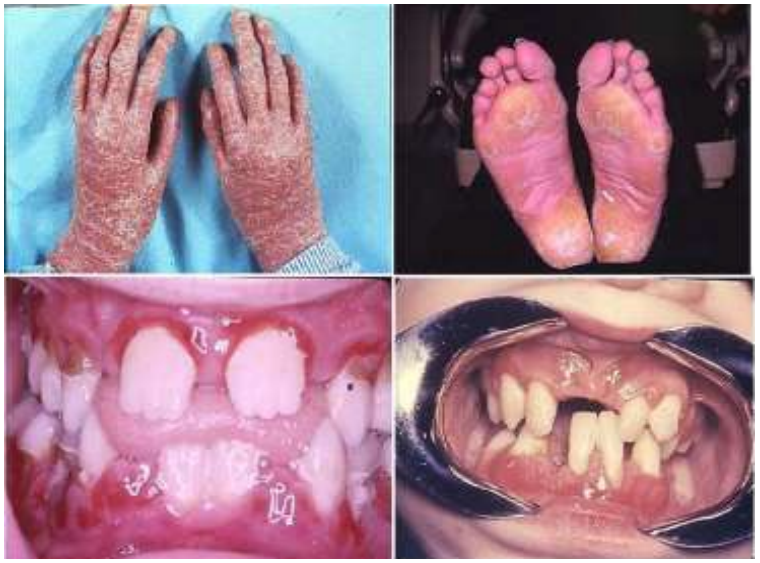
PAPILLON-LEFEVRE SYNDROME

- Rare autosomal recessive congenital differentiation disorder of chromosome **11**p14-q21.
- Occurs in children from consanguineous marriages.
- Gene responsible: Cathepsin C, lysosomal protease (Toomes et al.1999).
- Cathepsin C is suggested to be implicated in a wide variety of immune and inflammatory processes (Toomes et al. 1999).
- Prevalence : 1-4 per million, equal in males and females. (Hattab et al. 1995)

Two essential features of Papillon-Lefèvre syndrome:

- Generalized rapid destruction of the periodontal attachment apparatus resulting in premature loss of both primary and permanent teeth (Deas et al. 2003).
- reduced osteoblastic activity and reduced thickness of cementum have been described (Ghaffer et al. 1999; Hattab et al. 1995).





External signs are hyperkeratosis of the palms and soles (either diffuse or localized) (Kressin et al. 1995).

Virulent gram-negative anaerobic microbiota has been considered to be an important initiator of the destructive periodontitis observed in these patients.

•Aggregatibacter actinomycetemcomitans has been reported to be the major periodontal pathogen.

•Capnocytophaga gingivalis, Eikenella corrodens, black-pigmented Bacteroides, and Fusobacterium spp : subgingival periodontal lesions in Papillon-Lefèvre syndrome patient (Ishikawa et al. 1994; Lundgren et al. 1998; Rudiger and Berglundh 1999; Velazco et al. 1999).

Papillon-Lefèvre syndrome has been associated with

- decreased neutrophil chemotaxis
- reduced random neutrophil migration
- impaired neutrophil phagocytosis
- reduced myeloperoxidase activity

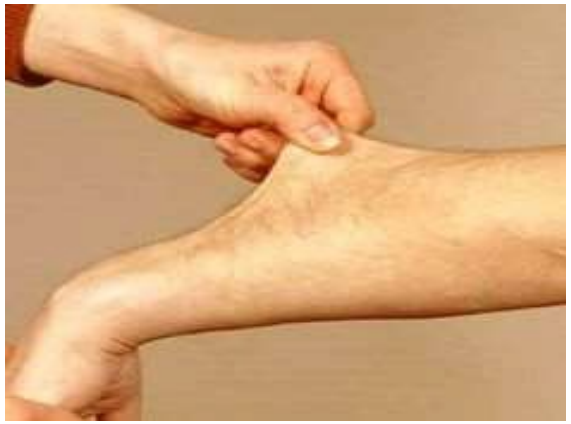
increased superoxide radial neutrophil production, associated with a decreased lymphocyte response to pathogens

EHLER DANLOS SYNDROME

- Also known as dystrophia mesodermalis and fibrodysplasia elastica generalisatica.

- Heterogenous group of inherited disorders of connective tissue, which may affect the skin, ligaments, joints, eyes, and vascular system (Reichert et al. 1999).

- EDS is divided into 11 types in accordance with clinical, genetic, and biochemical features (Majorana and Facchetti 1992).



The primary cause may be a

- Type I or type II collagen deficiency, a lysyl hydroxylase deficiency

- Deletion of *N-telopeptide,* or

- Disorders of copper homeostasis and fibronectin defects (Reichert et al.

- The **temporomandibular joint** often demonstrates **profound laxity** in conjunction with **generalized joint mobility and dislocation** (Fridrich et al. 1990).

- Periodontal conditions have been reported with EDS types I, VII, and VIII.

➢ ***Defective dentinogenesis***, resulting in aplasia or hypoplasia of root development affecting the mandibular incisors, and predisposition for localized periodontal disease was reported in EDS type I.

➢ Radiographic appearance of a ***bulbous enlargement of the roots together with pulp stones at other teeth were reported.*** ***EDS type VII*** is an autosomal dominant/ recessive disease.

- Poor healing after extractions
- Prevelance of dental caries

CYCLIC NEUTROPENIA

- Rare condition, characterized by cyclical depletion of polymorphonuclear leukocyte numbers, typically in 3-week cycles, although this can be between 2 and 5 weeks.

- Episode of neutropenia is usually short, but the patient polymorphonuclear leukocyte count never returns to normal levels, and the differential blood-cell count for polymorphonuclear leukocytes is at least 40% less than normal levels.

Periodontal manifestations include

- Inflamed gingiva
- Gingival ulceration
- Periodontal attachment, and bone loss (Kinane 1999; Rezaei et al. 2004).

FAMILIAL NEYTROPENIA

- Inherited as an **autosomal dominant trait**, and in these patients, **neutrophils are not released properly from the marrow.**

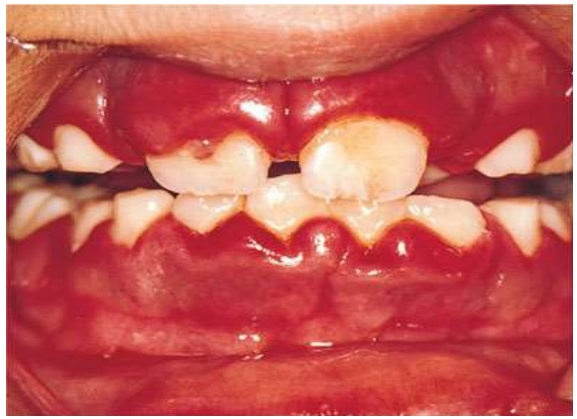
- A **slight monocytosis** occurs, possibly as compensation, together with the moderate neutropenia.

- The condition is often diagnosed in patients with a history of recurrent infections.

Susceptibility to these infections tends to vary with neutrophil count.

The ***periodontal manifestations*** include Fiery red edematous gingivitis, which is often hyperplastic and

Accompanied by periodontal bone loss (Kinane 1999).



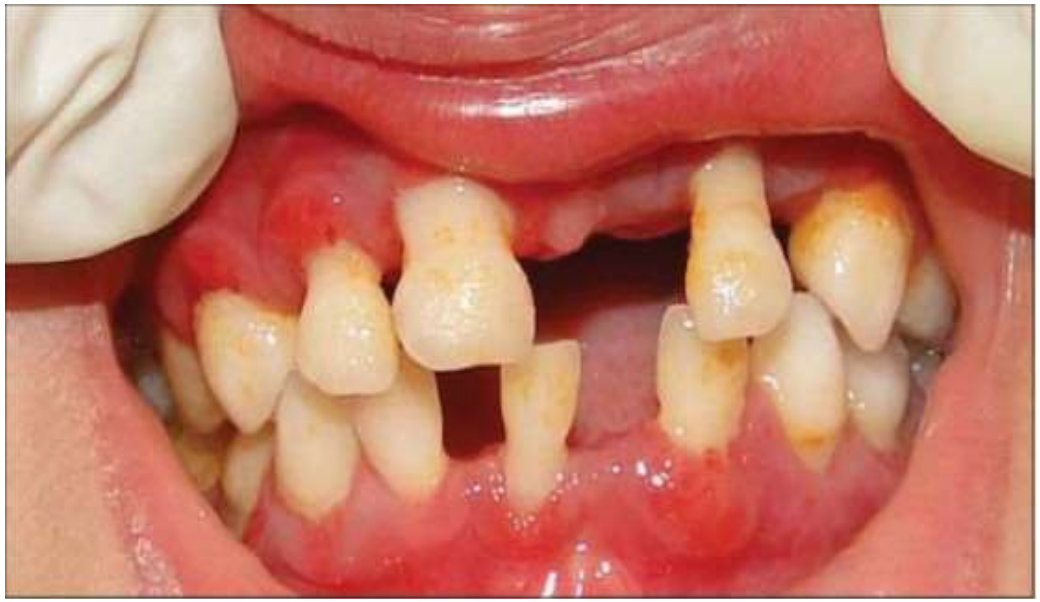
CHEDIAK HIGACHI SYNDROME

- It is a rare autosomal recessive disease associated with impaired function of cytoplasmic microtubules or microtubule assembly in PMNs (Oh et al. 2002).

- The susceptibility to infections, although humoral and cellular immunity are normal, leads to early death (often before 5 years of age).

The disease reveals itself periodontally by Severe gingivitis and

Rapid loss of attachment, leading to exfoliation of the teeth.



LEUKOCYTE ADHESION DEFICIENCY

•Two LADs have been described in humans: LAD I and LAD II.

•Both diseases block a sequence of leukocyte– endothelial-cell interactions, which is generally referred to as the *multistep adhesion cascade.*

•LAD is a rare but well-defined autosomal recessive disease that results in the formation of nonfunctional intracellular adhesion molecule (ICAM receptor).

The disease results from mutations in the region on the CD18 gene encoded on chromosome 21q22.3, which codes for the b2 integrin subunit of the leukocyte adhesion molecule.

The defective or absent expression of these molecules on the surface of leukocytes decreases their ability to adhere to endothelial cells and to migrate to sites of infection.

- ***Clinical features*** usually present in infancy or early childhood and consist of recurrent, indolent bacterial infections of the skin, mouth, and the respiratory tract. Delayed separation of the umbilical cord.

- ***Skin infections*** may progress to large chronic ulcers that may become polymicrobial in character.

- In addition, ***lack of swelling, redness, heat, or pus is noted in the area of the infection***

- Severe gingivitis with an early loss of primary teeth, followed by the early loss of secondary teeth, is seen.

GENE THERAPY

WHAT IS GENE THERAPY ?

• Experimental technique for correcting defective genes.

APPROACHES:

1) Normal gene inserted to compensate for non-functional gene.

2) Abnormal gene replaced for a normal gene.

3) Abnormal gene repaired through selective reverse mutation.

4) Change the regulation of the gene.

HOW IT WORKS ???

• The therapeutic gene is delivered either directly or through a vector into a patient's target cell.
• Functional proteins are created from the therapeutic gene causing the cell to return to normal state.

SUCCESS CASES OF GENE THERAPHY:

PARKINSON'S DISEASE; COLOR BLINDNESS

GENETIC ENGINEERING

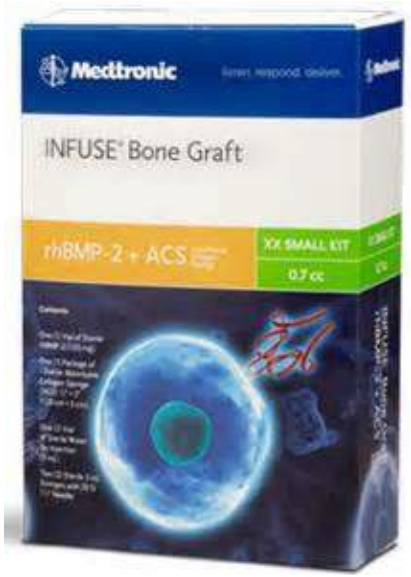
- Cutting the DNA from one organism and joining it with the DNA of other organism.

It is possible because …..

- DNA molecules of all organisms share the chemical structure.
- Differ only in the sequence of nucleotides.
- Host DNA linked with foreign DNA that can drive DNA replication.
- When introduced, this foreign DNA replicates with host DNA.

RECOMBINANT BONE GRAFTS

rh BMP - INFUSE



rh PDGF – GEM 21S

PERIODONTAL VACCINE

• Cysteine proteases have the greatest potential as a vaccine antigen.
• *Porphpain –2* purified from P. gingivalis is effective in inducing protection (Page et al, 2000)

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