GENETIC FACTORS IN PERIODONTAL DISEASE

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- Ref: Carranza's Clinical Periodontology 13th Edition
- Chapter 11

Introduction and definitions

In 1986 in a classic study of natural history of periodontitis (in Sri Lankan tea laborers), Loe found that:

- When the oral hygiene is poor and no access to dental care

-some people developed periodontal disease at a rapid rate

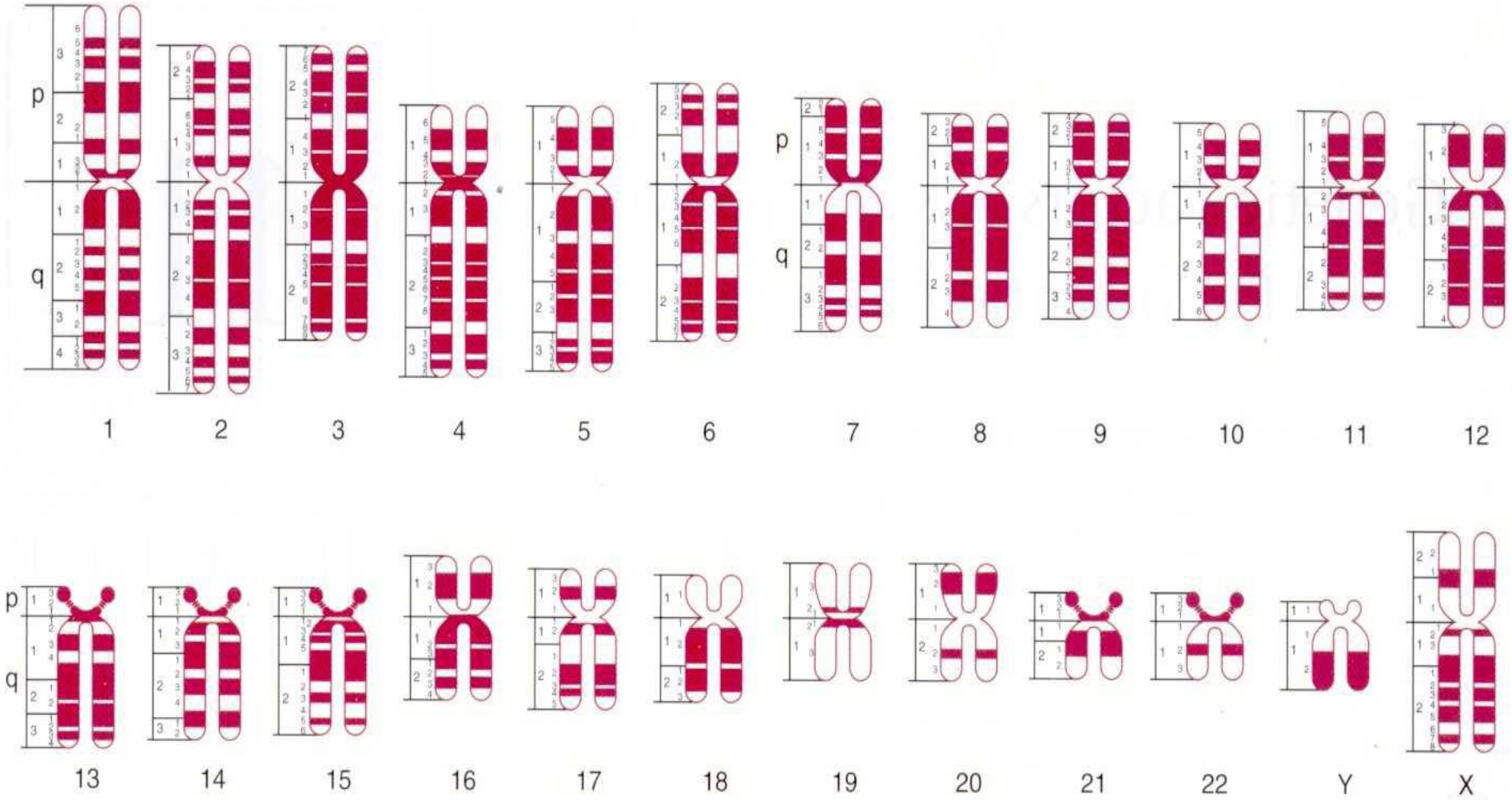
- others developed little or no periodontal disease

This may be explained by:

- Unrecognized environmental factors or
- Individual differences in susceptibility to disease (genetic variations)

Introduction and definitions

- A person's unique genetic code is contained in the sequences of nucleotide bases (adenine, thymine, cytosine and guanine), which make up deoxyribonucleic acid (DNA).
- The human genome consists of more than 3 billion pairs of bases contained in 22 pairs of chromosomes, (autosomes) and two sex chromosomes
- Each cell in human body contains about 25000-35000 genes that carry information that determines someone's traits(characteristics) for example green eyes, curly hair etc



Each chromosome contains a short arm (p, or petite) and long arm (q).
In this schematic, termed an *ideogram, the chromosomes are depicted as they appear after* Giemsa staining (thus the term *G banding patterns). Genes are located based on their* positions within these bands. For example, 11q23 denotes a position in the third band of the second region on the long arm of chromosome 11. Sub-bands are designated by decimal points (e.g., 11q23.2).

Introduction and definitions

- Each gene has a special job to do. It carries the instructions for making proteins. Each gene may make as many as 10 different proteins.

- The genetic composition of an organism is called genotype and collection of traits is called phenotype. The phenotype is determined by the interactions of genes and the environment.

Introduction and definitions

- If traits and diseases are caused by a single gene they are termed monogenic, by several genes oligogenic, by many genes polygenic.
- If diseases have genetic and environmental factors in their etiology they are termed multifactorial.

- Specific locations on chromosomes are called loci and the variations in the sequence of nucleotide at a locus are termed alleles.

Introduction and definitions

- If the alleles are identical on homologous chromosomes at a given locus, an individual is considered homozygous,

  if the alleles are different is considered heterozygous.

- The role of genes is different in monogenic disorders and in complex multifactorial diseases like periodontal disease.

- In monogenic diseases genes are causative because everyone with the mutation develop the disease

Introduction and definitions

- Genes involved in multifactorial diseases are referred to as susceptibility genes(susceptibility alleles) .People who inherit these genes will not develop disease unless they are exposed to deleterious environment.
- For periodontal disease environmental risk factors are gram (–) anaerobic microorganisms, cigarette smoking and poor oral hygiene
- Variations in any number of genes that control,

  1. the development of periodontal tissues

  2. function of immune systems could effect the individuals risk for periodontal disease

- Once the genetic bases for a disease has been established it is important to determine;

1. Which alleles have a measurable effect on the phenotype

2. Can prevention, diagnosis or treatment of the disease be improved?

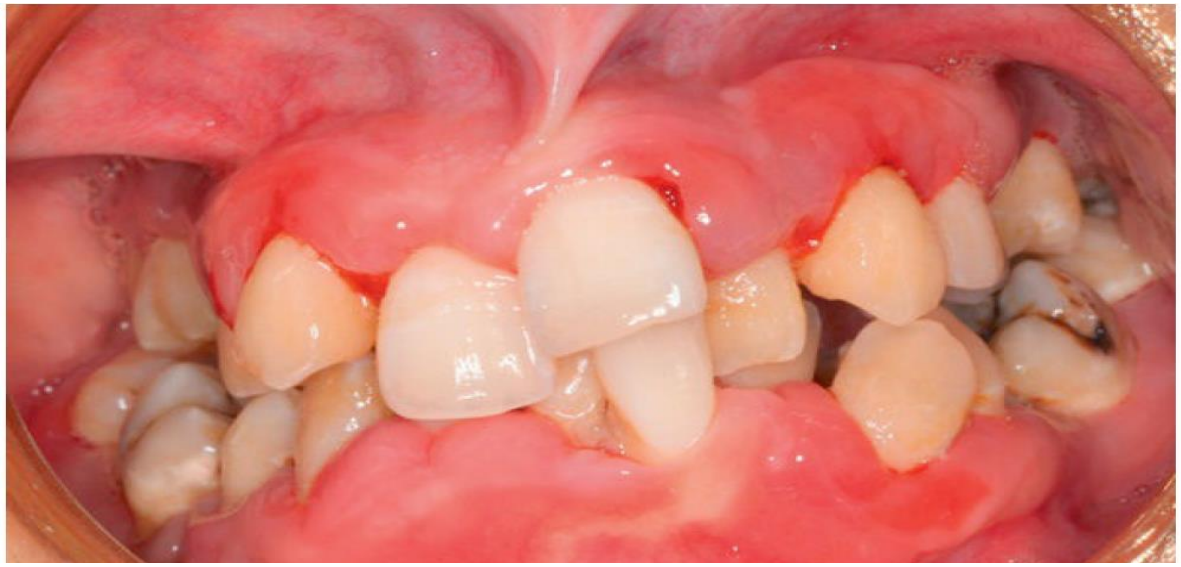
Periodontal diseases

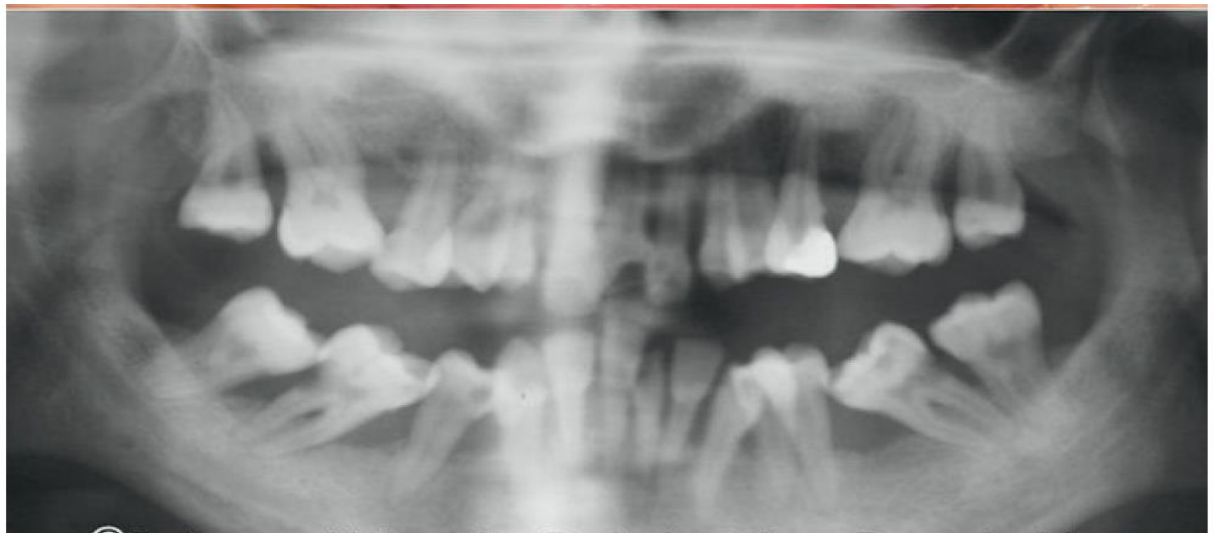
- The search for periodontitis susceptibility alleles is complicated because of:
- 1. Etiologic heterogeneity: Multiple causes(genetic and nongenetic) for the same disease
- 2. Genetic Heterogeneity: Different genetic mechanism may lead to the same clinical endpoint

Associations of periodontitis with genetic and inherited conditions

- In several inherited or genetic disorders severe and rapidly progressing periodontitis is a consistent feature
- Gene mutations can affect the risk for periodontal disease in variety of ways.
- The mutant alleles may affect:
  - the function of phagocytic immune cells
  - the structure of epithelia, connective tissue or the teeth

Neutropenia

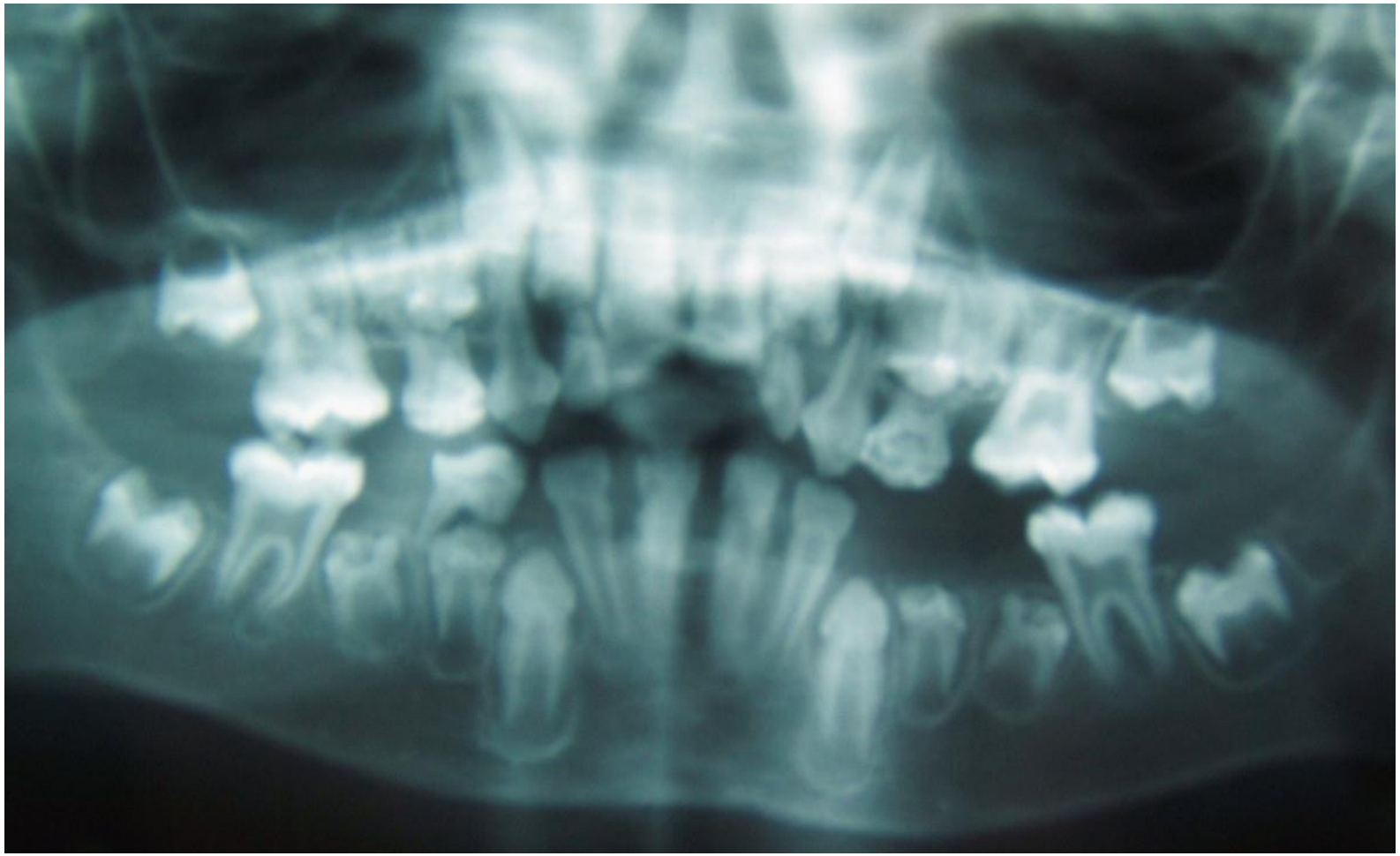




Associations of periodontitis with genetic and inherited conditions

- Hypophosphatasia (autosomal dominant or recessive):

  Mutation in the tissue nonspecific alkaline phosphatase gene(1p36.1-p34) ⟹ deficiency in alkaline phosphatase enzyme activity ⟹ abnormal bone mineralization, skeletal anomalies, cementum hypoplasia ⟹ premature loss of primary and permanent teeth



Hypophosphatasia

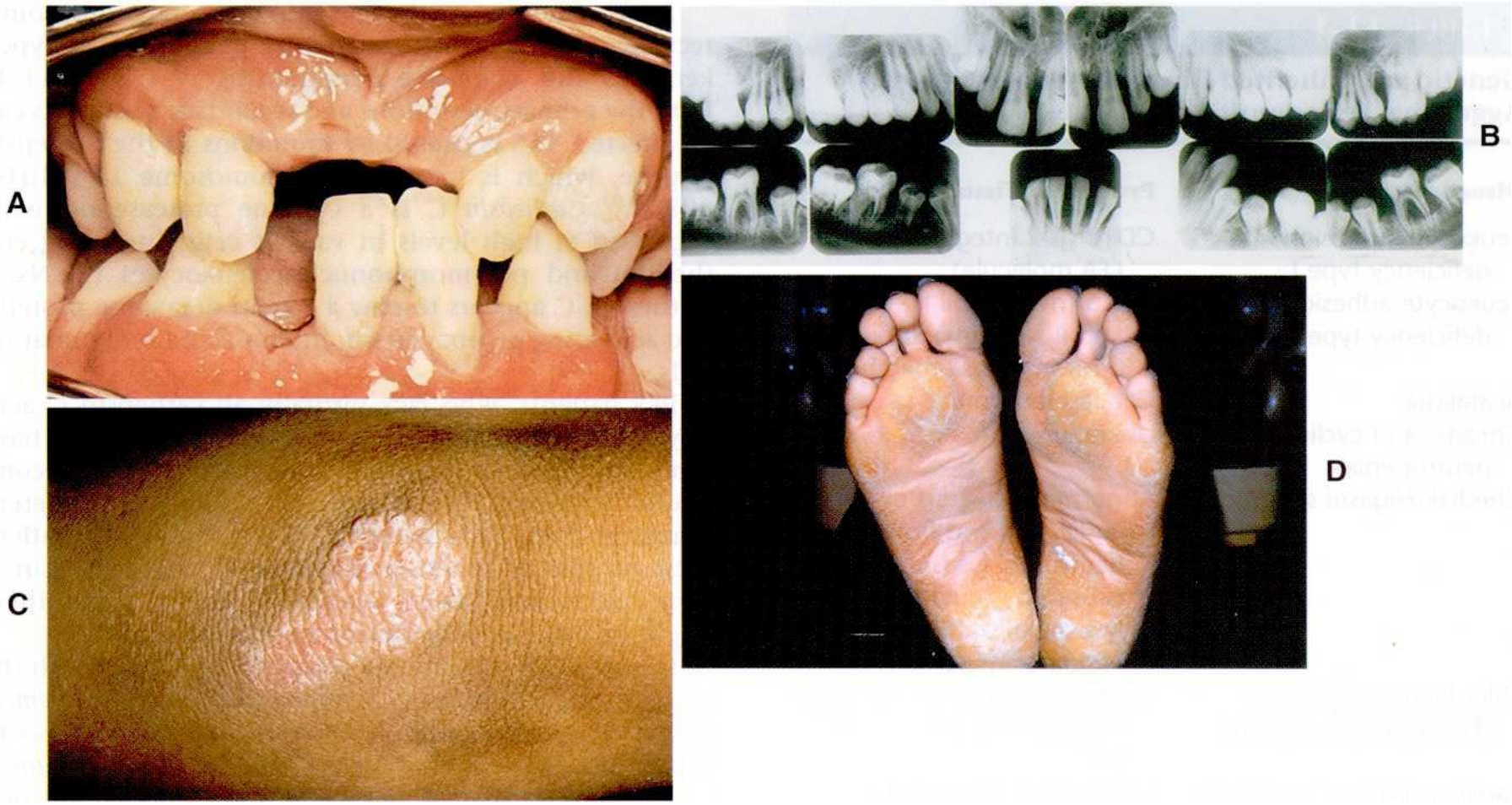
Associations of periodontitis with genetic and inherited conditions

- Papillon-Lefevre syndrome (PLS) (autosomal recessive):
- Characterized by palmoplantar hyperkeratosis and periodontitis
- Both the primary and secondary dentitions affected.
- PLS is caused by mutations in the cathepsin C gene located on chromosome 11 (11q14 -q21)(increased activity of enzyme)

- Cathepsin C is a cysteine protease expressed at high levels in various cells, including epithelial cells and polymorphonuclear leukocytes (PMNs).
- Cathepsin C has a role in degrading proteins and activating proenzymes in immune and inflammatory cells.

Associations of periodontitis with genetic and inherited conditions

- In some PLS patients periodontitis is associated with virulent microorganism Aa. Periodontal destruction can be arrested by eliminating Aa. In these patients AP is not a direct result of gene mutation but rather consequence of specific bacterial infection in highly susceptible host.



Oral (A), radiographic (B), and dermatologic (C and D) findings in the Papillon-Lefevre syndrome (PLS). Pocketing and bone loss usually affect the primary and secondary teeth shortly after eruption. The hyperkeratotic lesions of PLS can affect the elbows (C) and knees and the palms and plantar surfaces of the feet (D). (Courtesy Dr. Robert J. Gorlin, Minneapolis.)

- **Chédiak–Higashi Syndrome**
- Chédiak–Higashi syndrome affects the production of organelles found in almost every cell; mostly the melanocytes, platelets, and phagocytes. It causes partial albinism, mild bleeding disorders, and recurrent bacterial infections.
- Neutrophils contain abnormal, giant lysosomes that can fuse with the phagosome, but their ability to release their contents is impaired.
- Periodontitis has been described in these patients. This autosomal recessive condition occurs due to a mutation of the LYST gene that encodes for a lysosomal trafficking regulator protein.

Associations of periodontitis with genetic and inherited conditions

Leukocyte adhesion deficiency:

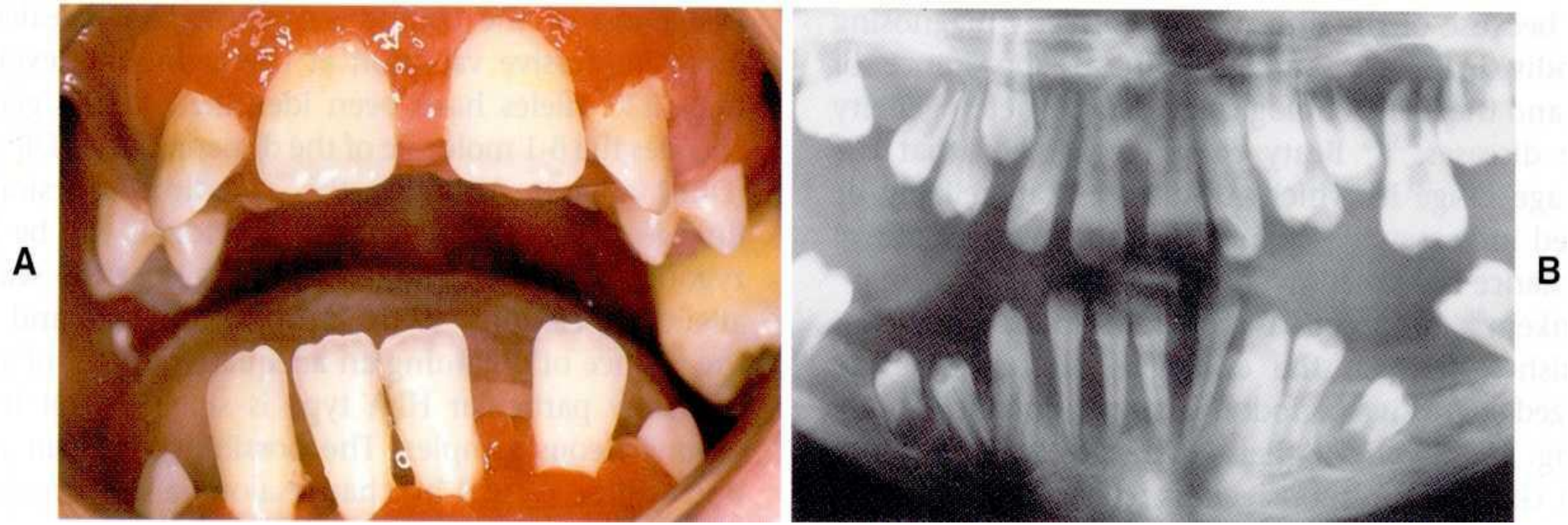
- Many patients with prepubertal periodontitis have some inherited or congenital defect in phagocytic cell function.
- Patients generally have systemic infections in addition to periodontitis.
- Phagocytes must adhere and then traverse the blood vessel wall to reach the periodontal tissues.

Associations of periodontitis with genetic and inherited conditions

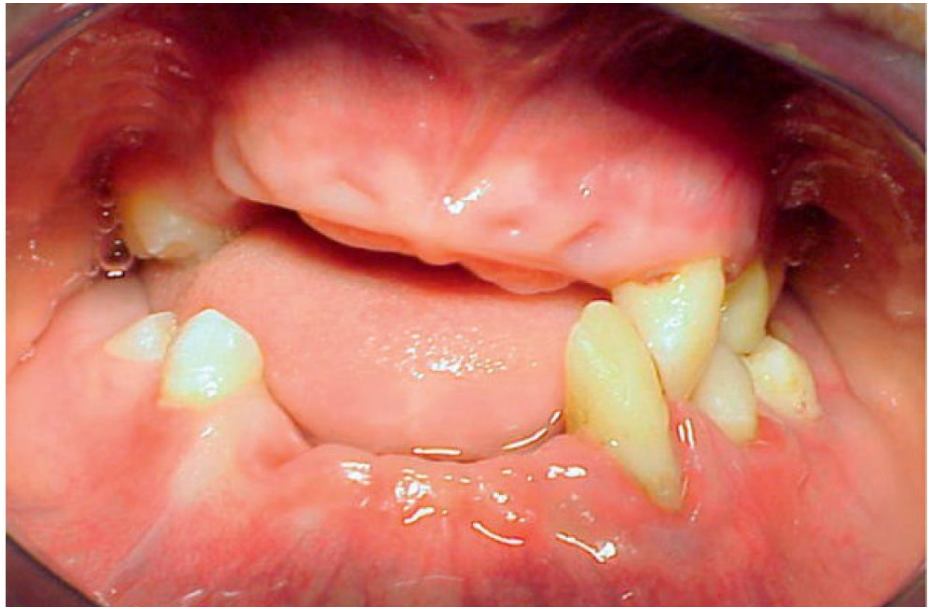
- Adhesion is mediated by the surface molecules present on both the phagocyte and the endothelium. When these molecules numbers are not sufficient, cells cannot adhere to endothelium and cannot pass to the tissues from blood vessels.
- Patients with inherited deficiencies in leukocyte adhesion molecules are at high risk for periodontitis.
- There are two inherited forms of LAD.

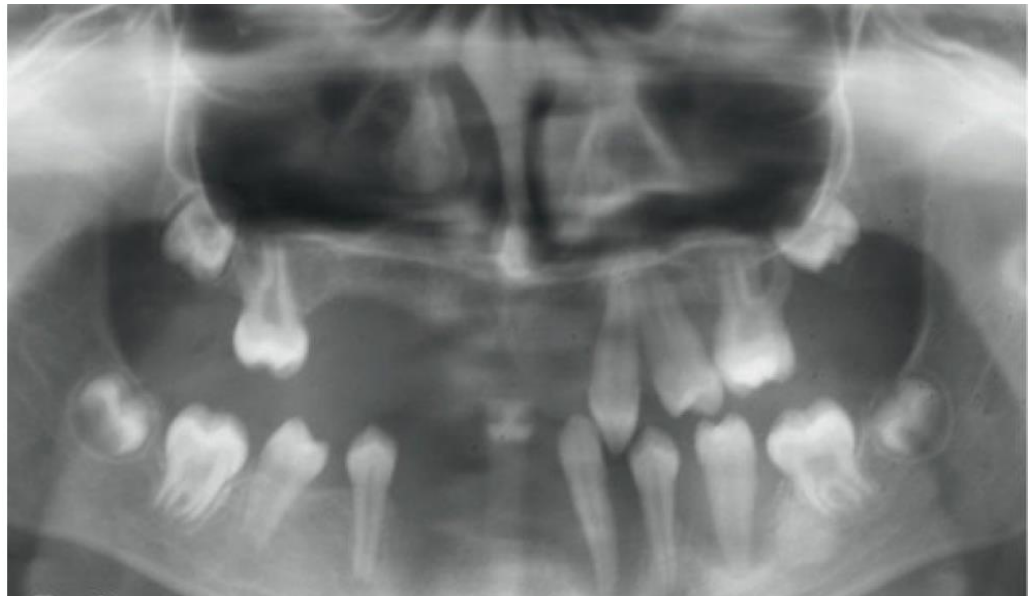
  -Homozygote (carry two copies of mutant alleles)

  -Heterozygote (carry one copy of mutant allele)



Oral (A) and radiographic (B) appearance of a patient with leukocyte adhesion deficiency (LAD). *The patient suffered from recurrent infections* of the middle ear, tongue, as well as the periodontium. (From Majorana A, Notarangelo LD, Savoldi E, et al: Leukocyte adhesion deficiency in a child with severe oral involvement, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:691, 1999.)*





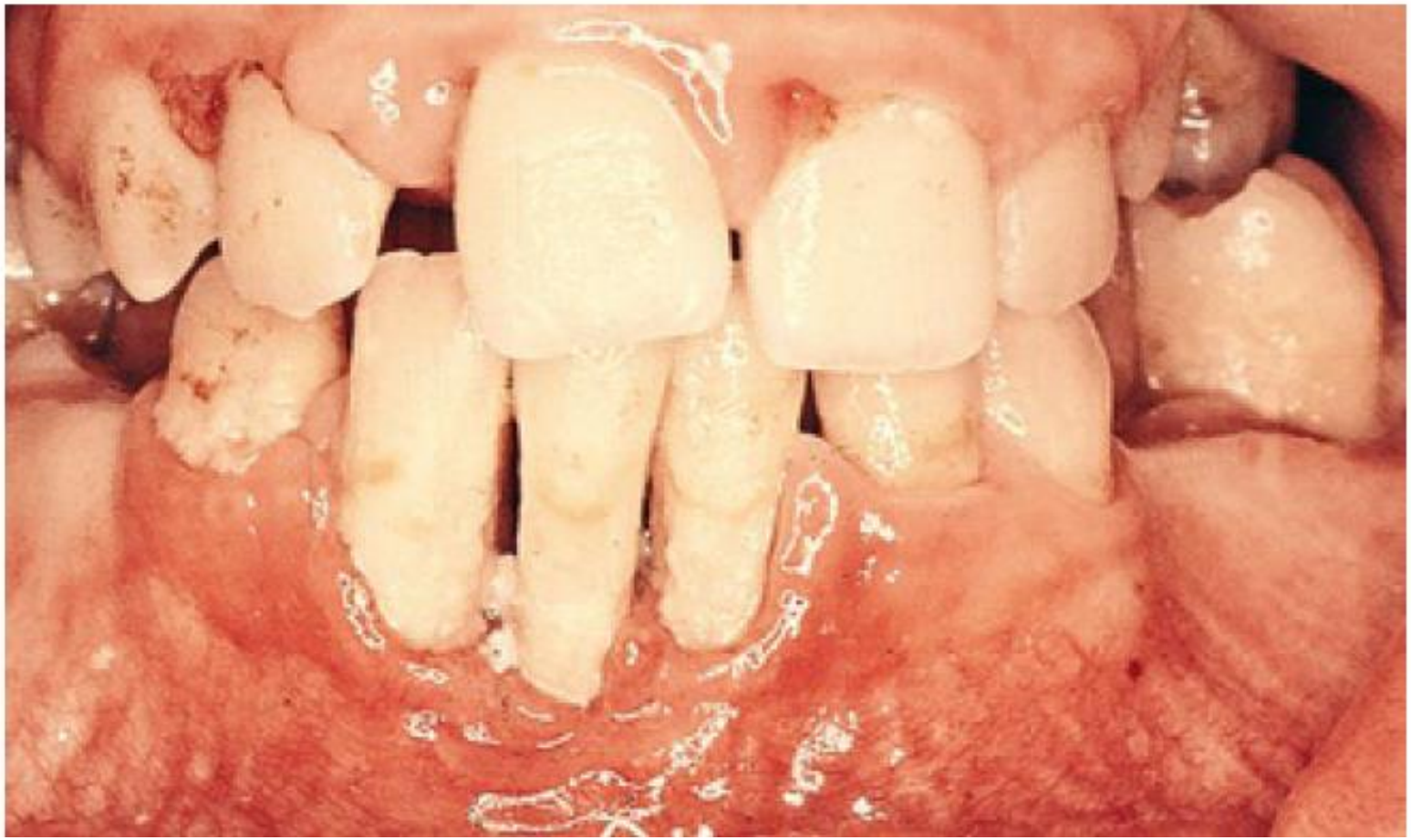
An 11 year old girl with leukocyte adhesion deficiency: She has recurrent skin, ear lung infections. Severe periodontal breakdown with loss of many teeth

Associations of periodontitis with genetic and inherited conditions

Interleukin 1:

- It is produced by activated monocytes.
- Plays an important role in the initiation and progression of periodontal lesion.
- IL -1stimulates bone resorption, inhibits collagen synthesis and regulates MMP activity and prostaglandin synthesis.
- An IL-1 antagonist blocks the activity of IL-1 by competitively binding to its receptors.
- Genes encoding IL-1 and its receptor antagonist are located on the long arm of chromosome 2.
- Mutations in IL-1 and its receptor antagonist genes have been associated with Periodontitis (in African Americans)

- **Down Syndrome**
- Down syndrome (mongolism, trisomy 21) is a congenital disease caused by a chromosomal abnormality and is characterized by mental deficiency and growth retardation.
- The prevalence of periodontal disease in patients with Down syndrome is high, occurring in almost 100% of patients.
- The high prevalence and increased severity of periodontal destruction associated with Down syndrome is most likely explained by poor PMN chemotaxis, phagocytosis



Down syndrome

Associations of periodontitis with genetic and inherited conditions

- Periodontitis in Caucasians is more likely to occur in patients who have a genotype that effects IL-1 expression that can result in a fourfold increase in IL-1 production.

Clinical implications of genetic studies

- Genetic tests may identify patients most likely to develop disease, suffer from recurrent disease and tooth loss.
- With knowledge of specific genetic risk factors, clinicians can direct prevention and treatments to individuals who are most susceptible to disease.

Clinical implications of genetic studies

- Genetic information may be useful in predicting treatment outcome (for example IL-1 genotype increases risk of tooth loss 2.7 times.IL-1 genotype + heavy smoking increase risk of tooth loss 8 times)
- New treatment strategies may be developed to directly counter the deleterious effects of certain risk alleles. (selective anti-inflammatory drugs in patients who are genetically programmed to be hyper responders to bacterial antigens)

Problems in research

- Whatever be the cause of the disease, symptoms are the same.
- In majority of the cases, periodontitis is influenced by environmental risk factors, rather than solely by genetic factors.
- Genetic studies in relation to periodontitis are hampered by population heterogeneity and differences in patient selection and diagnostic criteria.
- Valid comparison between different studies is not possible because of the different definitions that have been used for cases periodontitis.

Thank You