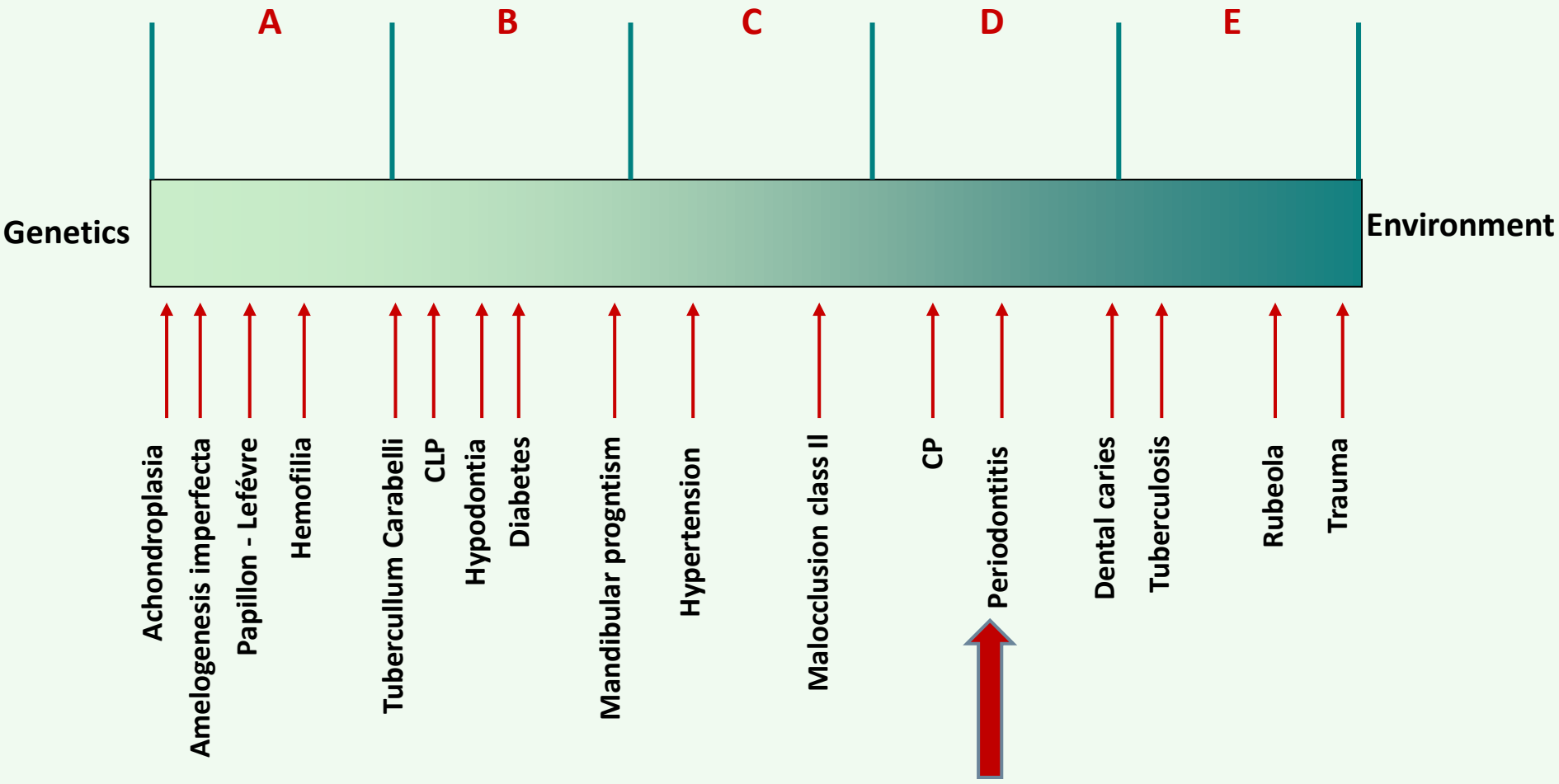
HEREDITY OF PERIODONTAL DISEASE

M.Švábová

Genetics versus environment



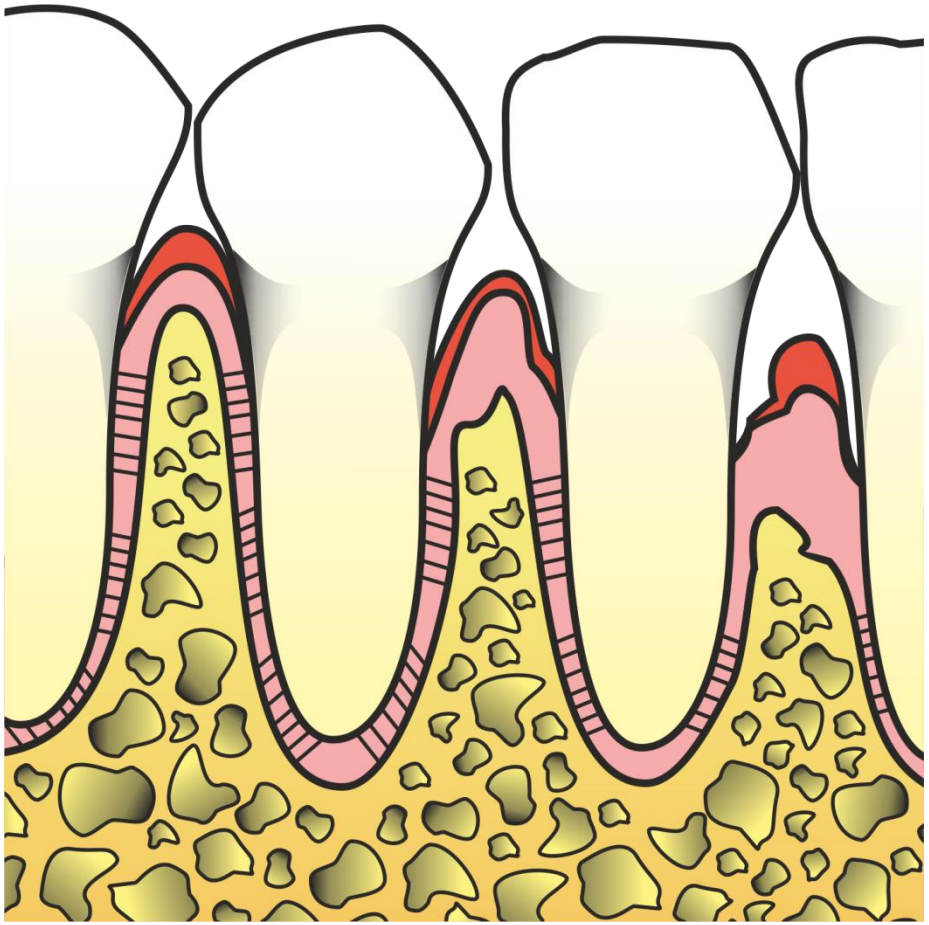
Our knowlege of the exact role that genetics plays in the resistance or susceptibility to dental caries is somewhat limited, the genetic aspects of periodontal disease are even less clear.

It is similar to dental caries : is widespread, shows extensive variability and is influenced by evirommnmental conditions, such as diet, oral hygiene and occlusion.

Stewart , Prescott: Oral facial genetics , 1976

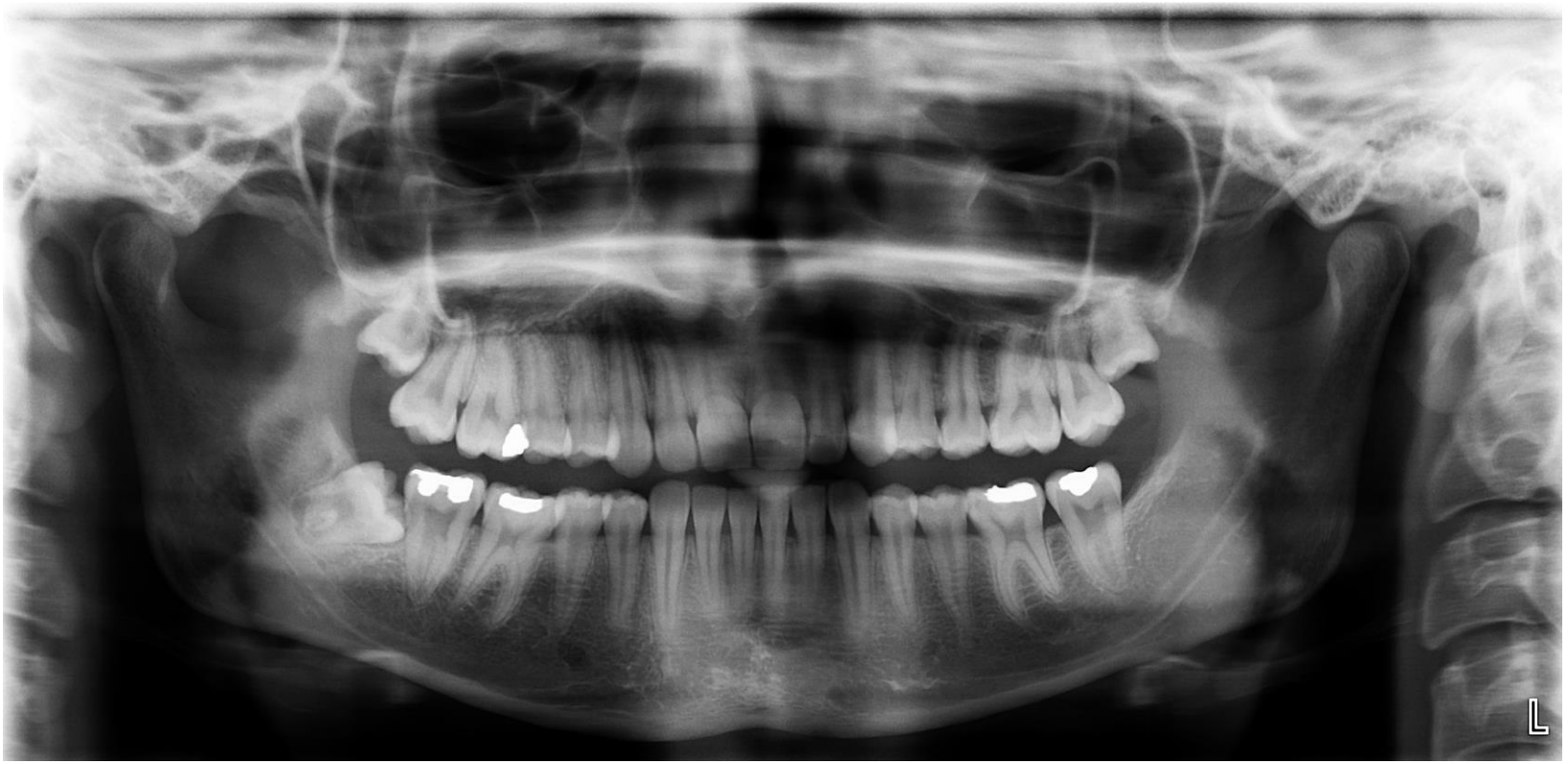
Periodontitis

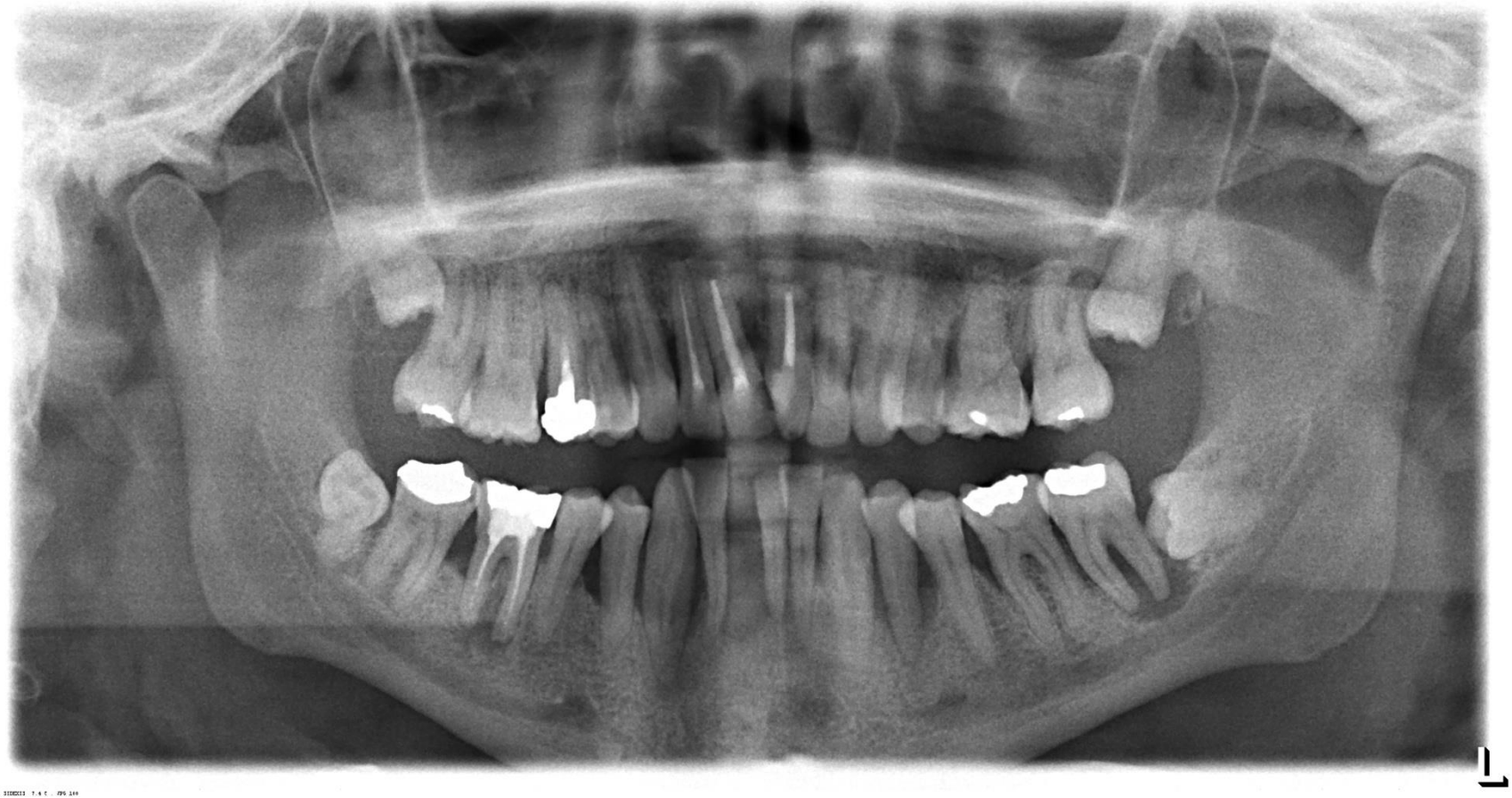
- Two major forms – agressive and chronic periodontitis
- It is a multifactorial polymicrobial infection iniciated by bacterial infection in gingival region
- Periodontopathogenic bacteria cause gingival inflammation, which leads to the destruction of periodontal ligaments and the adjanced supporting bone, resulting in tooth loss
- It is very prevalent , but only 10-15 % develop the severe, destructive forms



- The disease started by a bacterial atack, which triggers the host specific immune response
- Environmental factors (subgingival biofilm) and genetic factors could influence the modulation of the disease activity.
- Disease-modifying genes are responsible for susceptibility to periodontitis.

The interplay of genetic and environmental factors, and not the genes alone, determines the outcome.


L



Chronical periodontitis

- In US **20%** of adult population
- It manifests with **gingival pocket** formation and clinical **attachement lost** and results in gradual **destruction** of **periodontal tissues** and tooth supporting **alveolar bones**
- CP is considered the **main cause of tooth loss** among adults and is associated with severe quality of life impact

Chronical periodontitis incresed risk of systemic conditions

- Corronary heart diseases
- Pregnancy outcomes
- Poor diabetes mellitus control

Risk factors for chronical periodontitis

- **Smoking**
- **Diabetes mellitus**
- Age
- Race
- Obesity

Pubmed 4049 citations(2014)

4320	(2015)
4691	(2016)
7300	(2020)

Single gene effect

Table 4-1. Diseases commonly accompanied by periodontal pathology

Disease	*Mode of inheritance**
Inherited systemic or metabolic disorders	
Acatalasemia	AR
Hypophosphatasia	AR
Agammaglobulinemia	XL and AR
Connective tissue diseases	
Ehlers-Danlos syndrome	AD
Mucopolysaccharide disorders	
Hurler's syndrome	AR
Hunter's syndrome	XL
Scleroderma	?
Hereditary amyloidosis	AD
Hereditary gingival fibromatosis	AD
Chromosomal disorder	
Trisomy 21	
Hematologic or vascular diseases	
Cyclic neutropenia	?AD
Thalassemia	AR
Sickle cell disease	AR
Hereditary telangiectasia	AR
Sturge-Weber syndrome	?AD
Angio-osteohypertrophy	?AD
Diffuse angiokeratosis (Fabry's disease)	XL
Dermatological diseases	
White sponge nevus	AD
Pachyonychia congenita	AD
Hereditary benign intraepithelial dyskeratosis	
Darier's disease	AD
Epidermolysis bullosa	
Dystrophica	AD and AR
Letalis	AR

Single gene effect

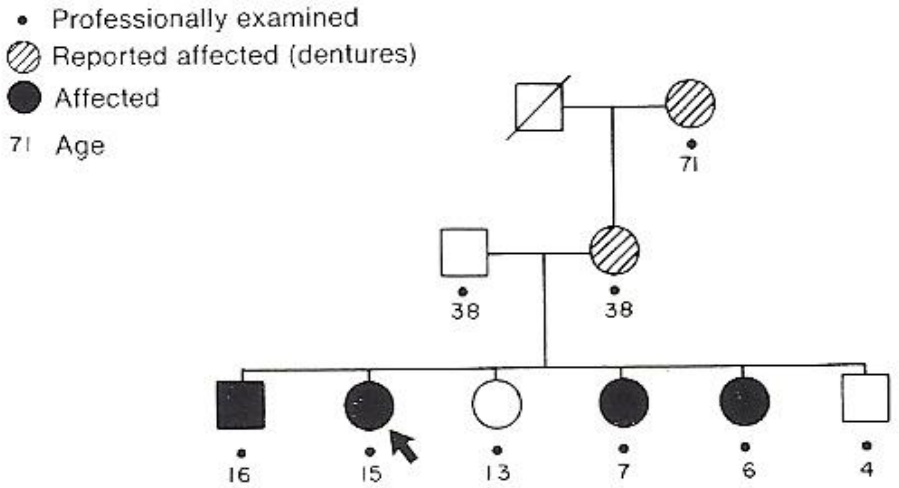
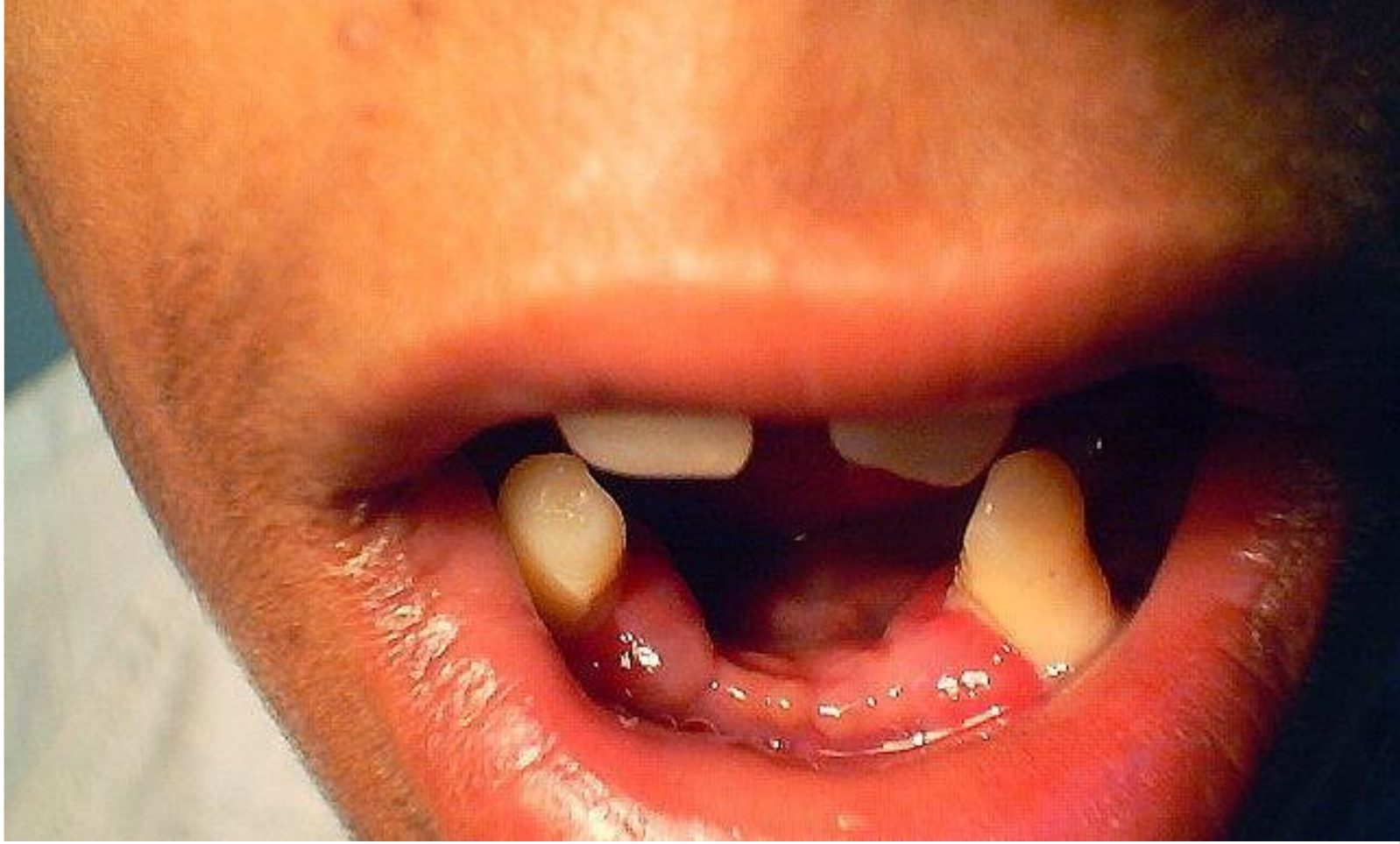


Fig. 4-4. Pedigree of family exhibiting autosomal dominant pattern of inheritance for juvenile periodontosis. (Modified from Bixler, D.: Genetic aspects of dental anomalies in children. In McDonald, R. E.: Dentistry for the child and adolescent, ed. 2, St. Louis, 1974, The C. V. Mosby Co.)

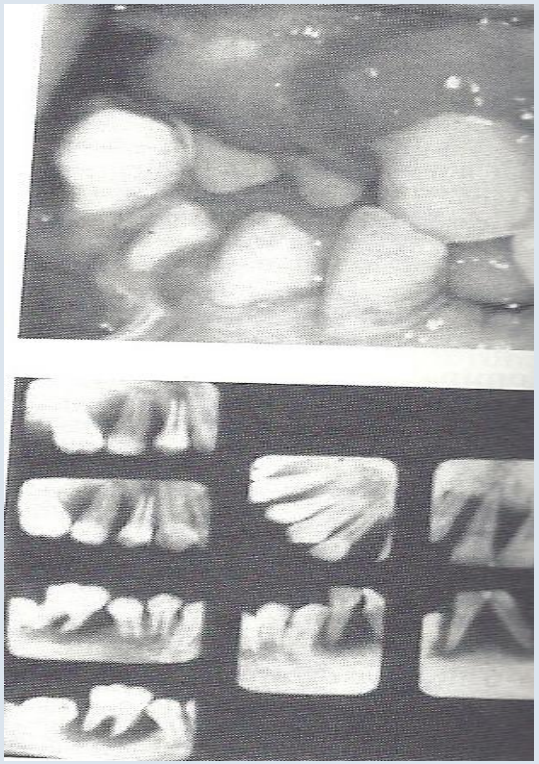
Monogenic transmission

- Periodontal diseas is known as a part of several syndromes:
- Mutation of the cathepsin C gene (CTSC) is responsible for periodontal diseae in Papillon –Lefévre syndrome
- Mutation in CHS gene is resposible for periodontal disease in Chediak –Higashi syndrome



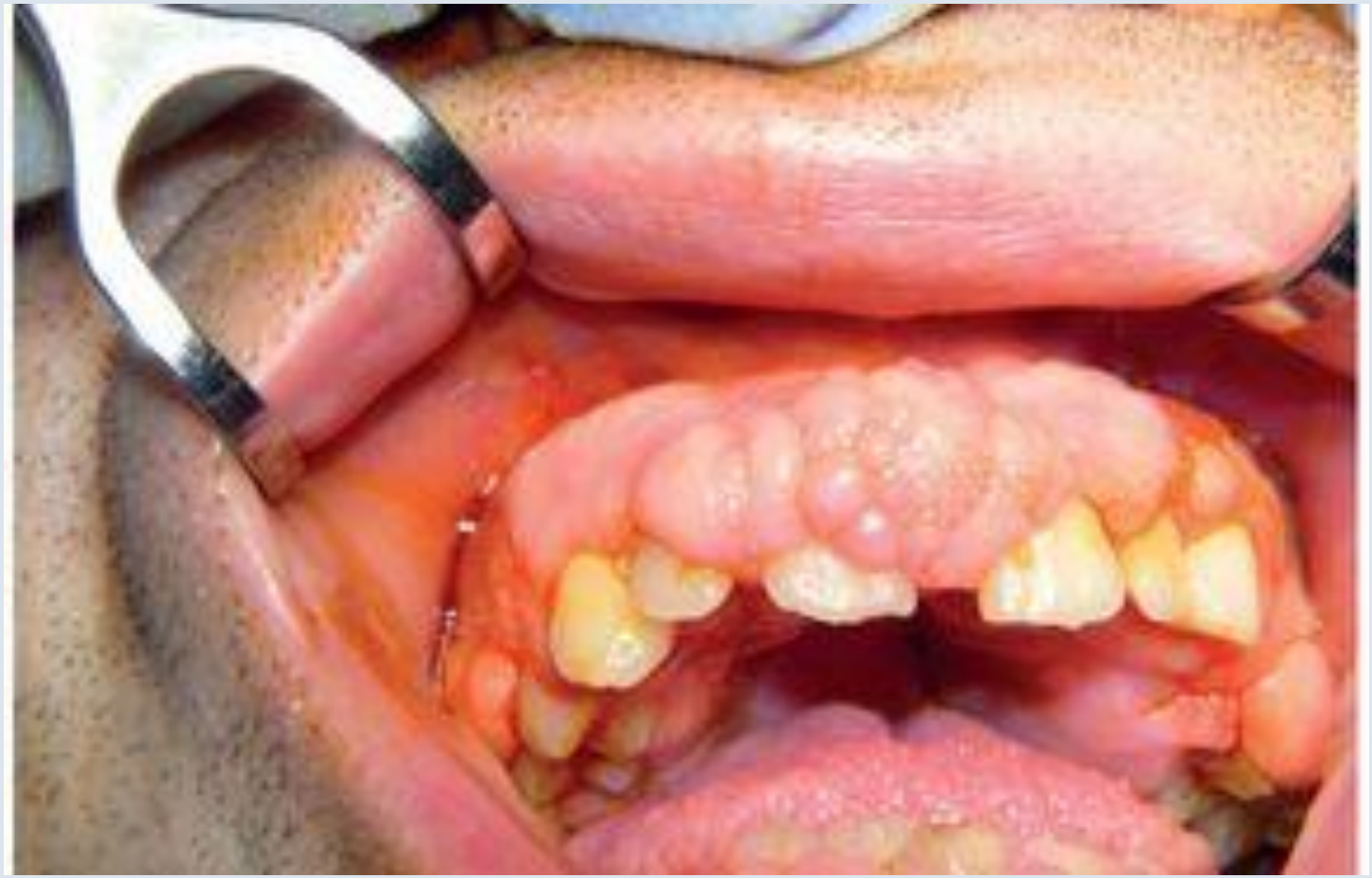
Papillon-Lefévre syndrom

Hyperkeratosis palmoplantaris and periodontoclasia in childhood- by the age of 4 years nearly all primary teeth are lost



Papillon - Lefévre

AR. Over 250 cases have subsequently been described



Hyperplastic fibrosis

Hereditary form AD

Multifactorial

The major genetic factors in complex disease models are not single mutations that dramatically change a gene or its product, but rather, those that involve more **subtle genetic changes** that may slightly alter the expression or function of a gene product.

Human family studies

- The significant increase in the frequency of gingivitis among Japanese children of consanguineous marriages – a recessive gene?

  Schull and Neel : The effect of inbreeding in Japanese children (1965)

- Brandywine isolate

  Wikop et al (1966)

Human family studies

- Hawaii´s schoolchildren, support the the polygenic determination

Chung et al (1970) :

Twin studies

Gorlin et al : Genetic and periodontal disease. J Periodontol, 1967

Twin studies- Minnesota study

Twins treated apart.

In a study based on 110 pairs of adult twins, a significant genetic component was identified. Authors suggest that 38–82% of the population variance for probing depth (PD), attachment loss (AL) and dental plaque may be attributed to genetic factors

Michalowicz et al. Periodontal findings in adult twins. JPeriodontol. 1991 May;62(5):293-9.

Twin studies - Minnesota

Michalowicz BS, Aeppli DP, Kuba RK, Bereuter JE, ConryJP, Segal NL, et al. A twin study of genetic variation in proportional radiographic alveolar bone height. J Dent Res. 1991 Nov;70(11):1431-5.

A subsequent study on 117 pairs of adult twins (64 MZ and 53 DZ pairs) revealed that approximately half of the variance in disease in the population is attributed to genetic variance. For all clinical measures, MZ twins were more similar than DZ twins

.Michalowicz BS. Genetic and heritable risk factors in periodontal disease. J Periodontol, 1994, 65(5 Suppl): 479-488.

The authors have proved, that **aggressive form,** which could appear very early (before puberty) is genetically determined, heritability is **70%.**
In the **chronic form,** which affects adults, heritability is **50 %**

Genomic population studies

The frequencies of polymorphisms of candidate genes, whose protein products play a role in the inflammatory or immune response, can be compared between cases and controls.

A significant difference in the frequency of a specific polymorphism, between a diseased group and a control group, is evidence that the candidate gene plays some role in determining susceptibility to the disease.

Genomic studies

- The simplest type of polymorphism results from a single base mutation which substitutes one nucleotide for another, and has recently been termed as a single nucleotide polymorphism (SNP)
- Other types of polymorphism are restriction fragment length polymorphism (RFLP)
- simple tandem repeats (STRs)

Genomic studies

Kinane DF, Hart TC. Genes and Gene Polymorphisms Associated with Periodontal Disease. Crit Rev Oral Biol Med, 2003, 14(6): 430-449.

They supposed that determination of chronic form will be probably influenced by several major genes

Marazita ML, Burmeister JA, Gunsolley JC, Koertge TE, Lake K, Schenkein HA. Evidence for autosomal dominant inheritance and race-specific heterogeneity in early-onset periodontitis. J Periodontol, 1994, 65(6): 623-630.

Genomic studies

- Candidate gene studies have focused on genes related to host immunity and inflammatory response such as cytokines, cell surface receptors, chemokines, enzymes and antigen recognition

Genomic studies

- Interleukin *IL-1, IL-6*
- Fc gama receptor *(FCGR2A)*
- Tumor necrosis factor alfa *(TNF)*
- Human vitamin D receptor *(VDR)*
- Cluster of diferentiation *(CD)-14*
- Matrix metalloproteinase -1
- Toll-like receptor*(TLR)*
- Cyclo-oxygenase- 2 *(COX2)*

Interleukin 6 gene

- overexpression of this cytokine in inflamed tissues
- key cytokine involved in bone resorption and has been detected in high levels in individuals with severe periodontitis

Genomic studies

- It is likely that the additive effect of multiple genes is a determinant of disease susceptibility in complex diseases such as chronic periodontitis.

Genomic studies

Divaris et al: Exploring the genetic basis of chronic periodontits : a genome wide association study. Human Molecular Genetics ,2013

4504 European-Americans , several candidate genes, no strong proof

Gene therapy

In the near future, periodontal gene therapy will be a reality for clinicians. An improved understanding of periodontal biology, coupled with current advances in scaffolding matrices, has introduced novel treatments that use cell and gene therapy to enhance periodontal tissue reconstruction and its biomechanical integration.

Therapy and prediction

Single genes may contribute to susceptibility, but since we have many interactions at the gene-gene and the gene-environmental levels, the real contribution to disease outcome might not be decisive.