Genetic Risk Factors for Periodontitis

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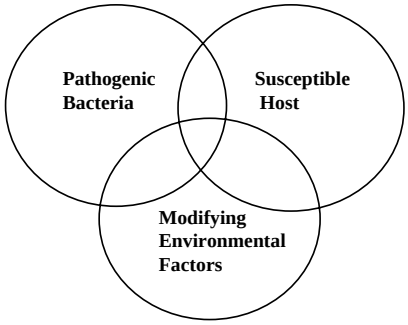


Clinical Implications

- Focus prevention on those most at risk
- Better determine prognosis

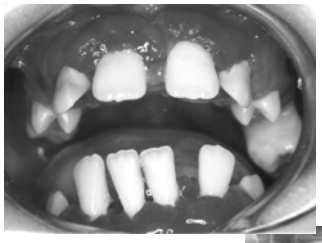
Approaches to Evaluate Genetic Risk

- Animal Models
- Associations with Syndromes
- Segregation Studies
- Twin Studies
- Linkage (Family) Studies
- Association (Case-Control) Studies

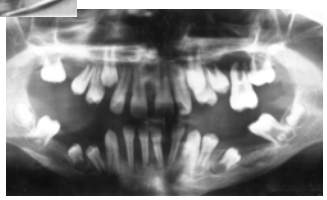
Aggressive Periodontitis

- Pre-pubertal periodontitis
- Juvenile periodontitis
- Early onset periodontitis
- Rapidly progressive periodontitis

Disorder	Protein or Tissue Defect
Leukocyte Adhesion Deficiency Type I	CD18 (β-2 integrin chain of the LFA molecule)
Leukocyte Adhesion Deficiency Type II	CD15 (neutrophil ligand for E and P selectins); inborn error in fucose metabolism
Acatalasia	Catalase enzyme
Chronic and Cyclic Neutropenias	Unknown
Chediak-Higashi Syndrome	Abnormal transport of vesicles to and from neutrophil lysosomes caused by mutations in the lysosomal trafficking regulator gene
Ehler-Danlos Syndrome [types IV & VIII]	Type III collagen for EDS type IV, unknown for EDS type VIII
Papillion-Lefevre Syndrome	Cathepsin C (dipeptidyl aminopeptidase I)
Hypophosphatasia	Tissue non-specific alkaline phosphatase
Trisomy 21	Multiple; critical trisomic region is at least 5 Mb long



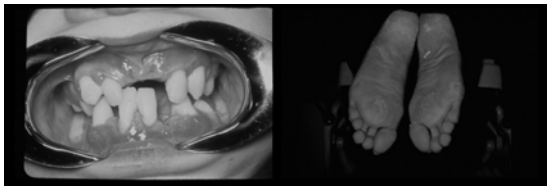
LAD Deficiency

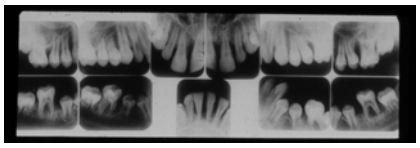


Papillon-Lefèvre Syndrome

- several point mutations in the cathepsin C gene are associated with the phenotype
- mutations may be missense, nonsense, insertions or deletions
- almost total loss of enzyme activity in PLS patients (i.e., homozygotes or compound heterozygotes)
- reduced enzyme activity in obligate carriers

Papillon-Lefèvre Syndrome





Cathepsin C

- lysosomal protease present in neutrophils and macrophages
- dipeptidyl aminopeptidase I (removes dipeptides from amino terminus of protein)
- chromosomal location: 11q14.1-q14.3
- gene spans over 46 kb region and contains 7 exons
- Over 60 nonsense mutations identified to date

CONCLUSIONS

- Several inherited or genetic disorders are consistently associated with aggressive periodontitis.
- Defects in phagocytes, particularly neutrophils, confer a large risk for periodontitis.

Segregation Analyses of Non-Syndromic AgP

- AR, AD, and X-linked modes of inheritance have all been proposed
- Largest collection of families to date favors AD inheritance
- Frequency of disease allele greater in blacks than whites
- Highlights genetic heterogeneity

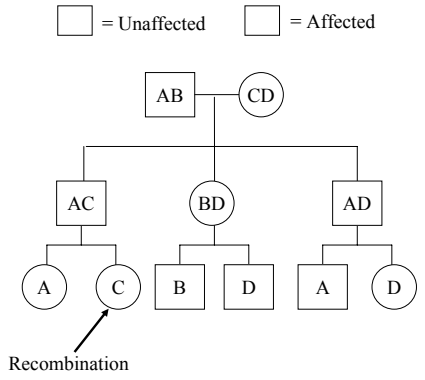
Linkage Studies

- Results typically summarized using a LOD (log odds ratio) score

$$\text{Log}_{10}\left\{\frac{\text{P disease allele and marker are linked}}{\text{P disease allele and marker are not linked}}\right\}$$

Microsatellite Marker Sets

- Primarily trinucleotide and tetranucleotide repeats
- CIDR marker set consists of 392 primer pairs with average spacing of 8.9 cM
- No gaps in the map larger than 18 cM
- Average marker heterozygosity = 0.76

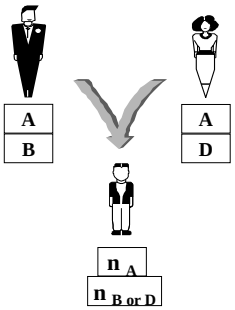


Linkage studies of AgP

- No consistent findings to date (that is, "linked" markers have not be confirmed in independent samples)

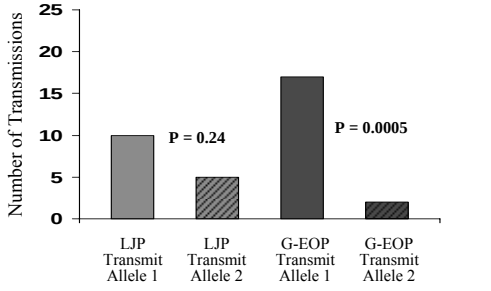
  Examples:
  - tri-racial isolate (chromosome 4), large collection in Virginia rejected linkage to this location
  - subset of families (4 of 20) in the Boston area showed linkage to chromosome 1 (1q25)

Transmission Disequilibrium Test (TDT)



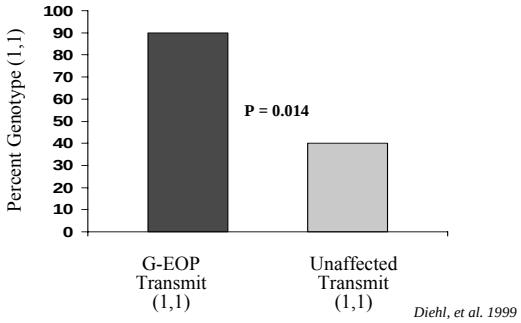
Count number of transmissions of specific alleles from heterozygous parents to affected offspring.

IL-1β +3953 Alleles



Diehl, et al., 1999

IL-1β +3953 (1,1)Genotypes



Diehl, et al. 1999

CONCLUSIONS

- AgP is **familial**
- There is a significant environmental component (**multi-factorial**)
- Segregation analyses suggest transmission as an AD disorder, although it is likely a **complex inheritance pattern**
- AgP is genetically **heterogeneous**

Chronic (Adult) Periodontitis

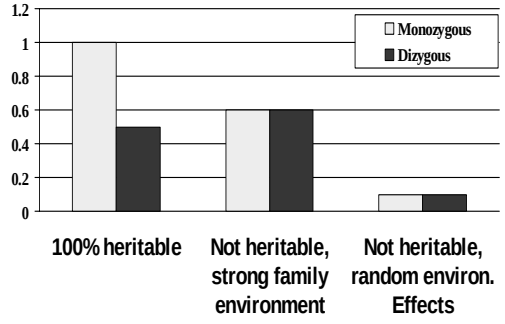
Twins Study Design

- Differences between MZ twins of a pair are due to differences in environment.
- Differences between DZ twins of a pair are due to differences in environment plus unshared genes.

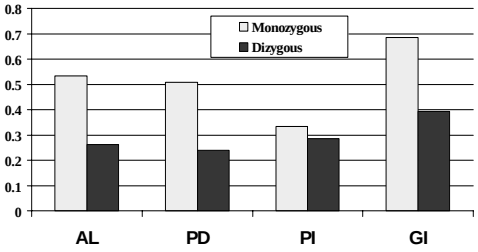
Twin Study Design

- Differences (in correlations) between MZ and DZ twins is due to the effects of one-half the genetic variance (the difference in gene sharing between MZ and DZ twins) plus .
- Twice this difference is heritability (h^2)

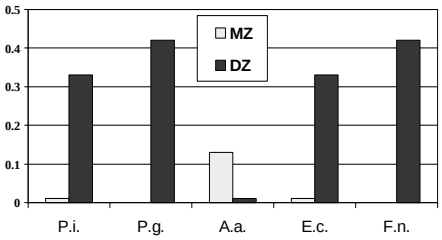
Interpretations of Twin Correlations



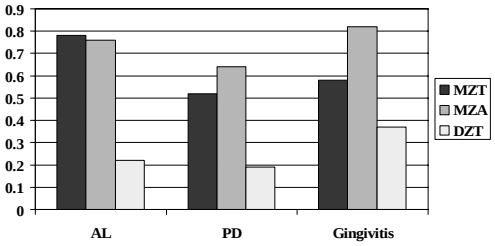
Twin Intraclass Correlations for Clinical Measures



Twin Correlations for Presence of Periodontal Pathogens



Comparing Reared Together and Apart Twins



Michalowicz et al., 1991, 1994

Conclusions

- Approximately 50% of the population variance for attachment loss and probing depth is attributed to genetic variance
- Genetic factors do not significantly influence levels of plaque or calculus, or the presence of specific bacteria in subgingival plaque
- The family environment does not significantly influence measures of disease in adults

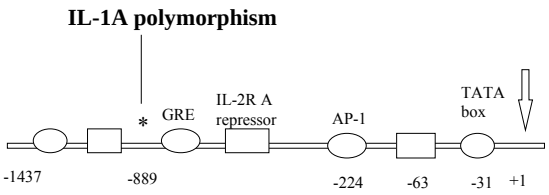
Conclusions

- Any influence that the early family environment has on the composition of one's subgingival plaque is not apparent in adulthood

Association Studies

- Case-control study design
- Exploit phenomenon that alleles at nearby loci co-segregate
- Focus on candidate genes or, more recently, conduct genome-wide searches
- Focus on common genetic variations, e.g., single nucleotide polymorphisms (SNPs) with minor allele frequencies > 5%

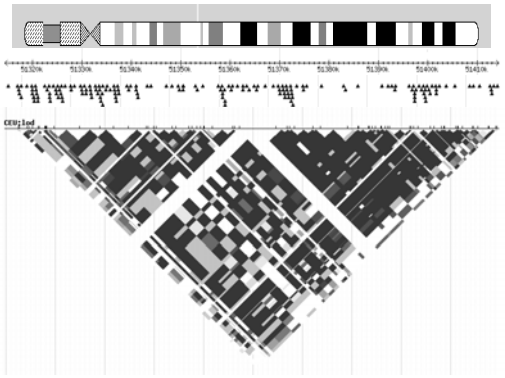
IL-1A polymorphism



* Cytosine for Thymine substitution

McDowell et al., Arthritis & Rheumatism, 1995

100 K basepairs from Chr13



Candidate Genes for Periodontal Disease

- Cytokines, including interleukin-1
- Vitamin D receptor
- N-formyl peptide receptor
- Class II HLA antigens (DR, DQ, DP)
- Cathepsins
- Toll-like receptors
- MMPs

IL-10 G-1082A

Genotype	CASE	CONTROL
11	24%	16%
12	60	47
22	17	37

χ^2 P value = 0.031

Effect Likelihood-Ratio Tests

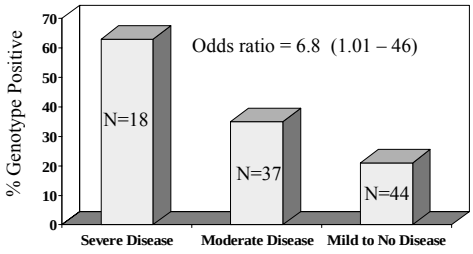
Source	DF	L-R χ^2 P value
sex	1	0.617
age	1	0.000
smoking status	2	0.036
IL-10 G-1082A	2	0.025

Ethnicity of subjects	Patients			Associated with periodontitis	Associated with severity of periodontitis
	Diagnosis of cases	*n*	Genotype positive (%)		
Caucasian	AP	99*	36	n.t.	+
Caucasian	AP	32	34	–	–
Caucasian	CP	42	38	n.t.	+
Caucasian	CP	33	48	n.t.	–
Caucasian	CP	44	41	+	n.t.
Caucasian	CP	90	34	n.t.	+
Caucasian	G-EOP	56	46	–	n.t.
Caucasian	AP	105	46	–	n.t.
Caucasian	EOP	132	45	–	+
Caucasian	CP	60	38	n.t.	–
Caucasian	CP	61	28	–	n.t.
Caucasian	CP	295	39	– (+†)	n.t.
Caucasian	CP	154	44	n.t.	– (+*)
Caucasian	CP	45	44	–	n.t.
Caucasian	EOP and AP	69	29	–	n.t.
Caucasian	CP	402	38	– (+†)	n.t.
Caucasian	AgP	28	36	–	n.t.
Caucasian	CP	1085	36	n.t.	– (+*)
Chinese	CP	300	2	–	–
African-American	LJP	37	8	–	n.t.
Thai	Mixed status	123	2	–	n.t.
Hispanic	AP	16	25	–	n.t.
Chilian	AgP	36	25	–	n.t.

PST® Test

- IL-1β/α genotype determined from a fingerstick blood or saliva sample
- Genotype "positive": possess at least one allele 2 at each of the two IL-1 loci
- Genotype status, along with smoking status, can predict risk for severe adult periodontitis in Caucasians

Interleukin-1 Genotype Association with Periodontitis in Non-Smokers



Kornman et al, J Clin Periodont 1997

Association Between Severe Periodontal Disease and Il-1 Genotype*

- Odds Ratio = 6.8
- Sensitivity = 67%
- Specificity = 77%
- Positive Predictive Value = 10%
- Negative Predictive Value = 98%
- Relative Risk = 6.2

*extrapolating figures in Kornman paper to the general population

CONCLUSIONS

- Genes seem to play an important part in determining risk for periodontitis
- For more common forms, the number of genes involved is unknown
- To date, no useful clinical applications have been developed for non-syndromic forms of periodontitis