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A longitudinal study of interleukin-1 gene polymorphisms and periodontal disease in a general adult population

Mary P. Cullinan, Bill Westerman, Stephen M. Hamlet, Janet E. Palmer, Malcolm J. Faddy[1], Niklaus P. Lang[2] and Gregory J. Seymour

The University of Queensland School of Dentistry, Oral Care Research Programme, Brisbane, Australia; [1]School of Mathematics & Statistics, The University of Birmingham, Edgbaston, UK and [2]School of Dental Medicine, University of Berne, Switzerland

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Abstract

Background: Cross-sectional studies have demonstrated that a specific polymorphism (allele 2 of both IL-1A +4845 and IL-1B +3954) in the IL-1 gene cluster has been associated with an increased susceptibility to severe periodontal disease and to an increased bleeding tendency during periodontal maintenance. The aim of the present study was to investigate the relationship between IL-1 genotype and periodontitis in a prospective longitudinal study in an adult population of essentially European heritage.

Methods: From an ongoing study of the Oral Care Research Programme of The University of Queensland, 295 subjects consented to genotyping for IL-1 allele 2 polymorphisms. Probing depths and relative attachment levels were recorded at baseline, 6, 12, 24, 36, 48 and 60 months using the Florida probe. Periodontitis progression at a given site was defined as attachment loss ⩾2 mm at any observation period during the 5 years of the study and the extent of disease progression determined by the number of sites showing attachment loss. *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans* and *Prevotella intermedia* were detected using ELISA.

Results: 38.9% of the subjects were positive for the composite IL-1 genotype. A relationship between the IL-1 positive genotype and increased mean probing pocket depth in non-smokers greater than 50 years of age was found. Further, IL-1 genotype positive smokers and genotype positive subjects with *P. gingivalis* in their plaque had an increase in the number of probing depths ⩾3.5 mm. There was a consistent trend for IL-1 genotype positive subjects to experience attachment loss when compared with IL-1 genotype negative subjects.

Conclusion: The results of this study have shown an interaction of the IL-1 positive genotype with age, smoking and *P. gingivalis* which suggests that IL-1 genotype is a contributory but non-essential risk factor for periodontal disease progression in this population.

Key words: periodontal disease; periodontitis progression; attachment loss; IL-1 gene polymorphism; risk factor; smoking; *P. gingivalis*; adult population

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In recent years, a number of host mechanisms have been identified which, following a bacterial challenge in the gingival sulcus or pocket, will lead to tissue destruction (Page 1991, Seymour 1991). While the essential role of bacteria in initiating the disease process is undisputed, the host response is, nevertheless, of paramount importance for propagation of the disease process (Seymour 1991). Studies in twins have indicated that a great part of the variance in disease progression, may be attributed to genetic factors (Michalowicz 1994, Michalowicz et al. 1991). In a study of Caucasians by Kornman et al. (1997), this genetic variance was, at least in part, attributed to allelic variations in the interleukin-1 (IL-1) gene cluster which results in an increased production of IL-1α and IL-1β pro-in-

flammatory cytokines (Pociot et al. 1992). IL-1 represents the primary activator of early cytokines and is responsible for the induction of adhesion molecules on endothelial cells, thereby facilitating the migration of leukocytes from blood vessels into the tissues. Furthermore, it triggers enzymes leading to the production of PGE2 and is a primary regulator of matrix metalloproteinases and their inhibitors. Also, IL-1 is known to be one of the most active stimulators of osteoclastic activity. Hence, the pivotal role of IL-1 in the early phases of tissue destruction in periodontal disease is evident.

The relationship between IL-1 genotype and periodontal disease has so far been investigated in cross-sectional studies (Armitage et al. 2000, Gore et al. 1998, Kornman et al. 1997, Van Dyke et al. 1999). These studies suggest that IL-1 genotype positive non-smoking patients have a higher probability of experiencing advanced periodontitis at an earlier age. In addition, higher concentrations of IL-1 have been detected in the gingival fluid and tissues of shallow pockets in IL-1 genotype positive patients (Engebretson et al. 1999). More recently, a retrospective analysis of changes in bleeding on probing (BOP) during periodontal maintenance has indicated that this clinical parameter was also significantly affected by genotype status (Lang et al. 2000), with IL-1 genotype positive patients having a significantly higher % of sites with BOP than those who were IL-1 genotype negative. Furthermore, there were significantly more patients with deteriorating (increasing) BOP% and significantly fewer patients with improving (decreasing) BOP% during the last year of supportive periodontal therapy in the IL-1 genotype positive, non-smoking patient group. Further longitudinal studies, are now required to aid our understanding of the impact of this genetic polymorphism on the clinical course of the disease.

The aim of the present study was to investigate the relationship between IL-1 genotype and periodontal disease in a prospective longitudinal study in an adult Australian Caucasian population.

Material and Methods

Subjects

From 504 volunteers participating in a prospective longitudinal study on the progression of periodontal disease in a general adult community, 295 subjects were recruited for this study on the basis of availability and consent to undergo genetic testing. The characterisation of the population tested and the design of the study have been reported previously (Faddy et al. 2000). In brief, the study population consisted of staff of The University of Queensland, Australia, including academic, administrative and blue-collar workers. Institutional ethics review committee approval had been obtained and informed consent was given, in writing, by each subject prior to commencement of the study.

Following a screening examination using the community periodontal index (CPITN), (Ainamo et al. 1982) subjects were examined for the presence or absence of gingival inflammation (BOP), periodontal probing depth and relative attachment level using the Florida Probe® (Florida Probe Co., Gainesville, Fl. USA). Subgingival plaque samples were also collected. Subsequently the subjects were re-examined at 6, 12, 24, 36, 48 and 60 months. Current smoking status was recorded at all examinations.

2 calibrated examiners (MPC and BW) carried out all examinations and to eliminate inter-examiner variability the same examiner carried out all assessments of clinical parameters at all examinations on a given individual. Bleeding on probing (BOP) was assessed in a dichotomous way at 6 sites per tooth as previously described (Lang et al. 1986). A Florida Probe® with a 0.45 mm tip diameter was applied to the bottom of the sulcus/pocket set at a probing pressure of 0.2 N. Percentage BOP was calculated.

Probing depths (PPD) were determined at the same sites using the same probe. To determine relative attachment levels, the Florida Disk Probe® was applied to six sites per tooth. Full mouth recordings, excepting third molars and crowned teeth, were obtained.

Based on the baseline probing depths, the shallowest and deepest site in each sextant of the dentition was selected for subgingival plaque sampling, giving 12 samples per subject. Once determined, these sites were then resampled at subsequent examinations. Following the removal of supragingival plaque, subgingival plaque samples were collected with a sterile curette and placed in 1.5 ml phosphate buffered saline containing 0.01% thimerosal and glass beads and stored at −70°C. Samples were assayed for the presence of *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis* and *Prevotella intermedia* using a previously standardised ELISA (see below).

IL-1 genotyping

At either the 4- or 5-year examinations a peripheral blood sample was collected on DNAase-free blotting paper (Tarlow et al. 1994) taking care not to contaminate the sample with extraneous material. Separate institutional ethics review committee approval was obtained for the genetic testing.

Blood samples were air dried and stored in sealed containers until analysis. IL-1 genotyping was performed by Interleukin Genetics, formerly Medical Science Systems (Flagstaff, Az.), as described previously (Kornman et al. 1997). Laboratory personnel responsible for the genotyping did not know the clinical status or identity of the blood donors.

For a subject to be positive for the composite IL-1 genotype they must have at least one copy of allele 2 at each of two specific polymorphisms, +4845T in the IL-1A gene and +3954T in the IL-1B gene (Kornman et al. 1997).

During the entire period of observation the subjects were given toothbrushes and toothpaste for their personal usage. No other dental services were provided by the Oral Care Research Programme of The University of Queensland. However, the subjects were encouraged to continue with their home and professional dental care as prior to the study. Volunteers who sought periodontal care following a diagnosis of attachment loss, at one or more sites of 2 mm or more from baseline, were exited from the study. Consequently, this population allowed for the study of 'naturally' developing periodontal disease with relatively little interference by the dental profession.

ELISA

Plaque samples were thawed and analysed using an enzyme-linked immunosorbent assay (ELISA) to detect *A. actinomycetemcomitans*, *P. gingivalis* and *P. intermedia.* Briefly, samples were thawed and the plaque dispersed by brief vortexing and sonication for 5 seconds (Sonics & Materials, Connecticut, USA). The suspension was further diluted in an equal volume of 0.1 M car-

bonate buffer pH 9.6, before transferring 100 μl aliquots into wells of a 'Maxisorp' microtiter plate (Nunc, Roskilde, Denmark). To allow quantification of bacterial numbers, 100 μl aliquots of known concentrations of either *A. actinomycetemcomitans* (FDC Y4), *P. gingivalis* (FDC 381) or *P. intermedia* (ATCC 25611), ranging from 150–9×10^4 cells/ml in carbonate buffer were also transferred to the plate. Following overnight incubation at 4°C, plates were washed (×3) in PBS-0.05% Tween-20 (PBS-T). Non-specific binding was blocked by incubating plates for 1 h at room temperature (RT) with PBS-T containing 1% newborn calf serum (Commonwealth Serum Laboratories, Melbourne, Australia). Following washing (×3) in PBS-T, diluted horseradish peroxidase labelled monoclonal antibody (MAb-HRP), specific for the pathogen being detected, was added to the coated wells and incubated for 2 h at RT. After another wash (×3) in PBS-T, colour development was achieved by adding 150 μl of 2.5 mM o-tolidine (Eastman Kodak, Rochester, NY) in 100 mM phosphate citrate buffer pH 3.5 containing 0.025 mM EDTA and activated with 3% H_2O_2. The resulting reaction was stopped after 10 min by adding 50 μl of 1 M HCl. Plates were read in a Bio-Rad microplate reader, model 3550 (Bio-Rad Laboratories, Regents Park, NSW, Australia) at 450 and 655 nm.

Pathogen-specific monoclonal antibodies were generated in mice against *P. gingivalis* FDC 381 (MAb CB5/C5), *A. actinomycetemcomitans* Y4 (MAb 4B5/F2) and *P. intermedia* ATCC 25311 (MAb 3B5/H3) essentially by the method described in Bird and Seymour (1987). Mab's were purified from ascitic fluid and subsequently conjugated to Horseradish Peroxidase (HRP) using a 2-step glutaraldehyde method (Voller et al. 1980).

A subject was classified as being 'positive' for a particular species if at least one site had detectable levels of bacteria. The lower limit of detection for *A. actinomycetemcomitans* was 4.5×10^4 cells/ml, whilst for *P. gingivalis* and *P. intermedia* this limit was 2.5×10^4 cells/ml.

Data management and statistical analysis

In all analyses the individual subject was considered to be the statistical unit. For some analyses, the study population was divided into 3 groups according to age at baseline: (a) subjects aged 18–40 years; (b) subjects older than 40 years of age; (c) subjects older than 50 years of age.

Disease progression at any given site was defined as a loss of attachment (LOA) of 2 mm or more relative to the baseline examination or between any consecutive examinations. Subsequently, the proportions of subjects experiencing attachment loss of $\geqslant$2 mm at either $\geqslant$2, $\geqslant$4, $\geqslant$6 or $\geqslant$8 sites were computed and plotted in relation to the time of observation, for different age groups. The significance of the differences between the proportions of genotype positive and negative subjects was assessed using an approximate normal test for differences between proportions of two independent groups. The level of significance was set at $\alpha=0.05$.

The numbers of proximal sites per subject with PPD $\geqslant$3.5 mm and those with LOA $\geqslant$2 mm were analysed, using a generalised linear model (McCullagh & Nelder 1989) with mean μ and variance $\phi\times\mu\ (1-\mu/N)$ where N was the number of proximal sites in the individual, ϕ is an over-dispersion parameter to allow for lack of independence between sites and $\log[\mu/(1-\mu/N)]=a+\boldsymbol{x}^{\mathrm{T}}\boldsymbol{b}$. Here $\boldsymbol{x}$ is a vector of covariates characterising the individual subjects, and a and vector $\boldsymbol{b}$ are parameters to be estimated from the data with the significance of any effect corresponding to testing the hypothesis that the parameter given by the coefficient of the equivalent covariate is zero. The principal covariate of interest was IL-1 genotype, but other covariates thought to influence the responses were included as possible confounding effects; all these covariates were: (i) age at beginning of study; (ii) gender; (iii) smoking status; (iv) IL-1 genotype; (v) examination number; (vi) response at previous examination (to account for first-order ante-dependence); (vii) presence/absence of *Porphyromonas gingivalis* at previous examination; (viii) presence/absence of *Actinobacillus actinomycetemcomitans* at previous examination; (ix) presence/absence of *Prevotella intermedia* at previous examination; (x) number of days between current and previous examination.

A significance level of 5% was used here for testing the main effect of IL-1 genotype, with a Bonferroni adjustment to 0.56% for interactive effects, since there were nine possible interactive effects with other factors (e.g., age, gender, etc).

Results

The mean age of the 504 subjects at baseline was 39.5 years (standard deviation 10, minimum 18 and maximum 65 years). Of these, 295 gave consent for genotyping. Smoking was documented in 25 subjects. The genotyped population consisted exclusively of Caucasians.

The composite genotype consisting of the less common allelic variants (previously associated with severe periodontitis in non-smokers) was detected in 38.9% of the subjects. In the age subsets, the proportions of IL-1 genotype positive subjects were 42%, 37% and 35% in the $\leq$40, over 40 and over 50 age groups respectively.

While 97% of the 295 subjects analysed presented with some gingivitis at baseline, albeit of rather low severity (mean subject BOP of 13.3% and 14.1% of sites respectively, for IL-1 genotype positive and IL-1 genotype negative subjects), only 10.5% yielded at least one sextant with a CPITN score of 4, i.e. at least one site with probing depth $\geqslant$6 mm. Approximately one third of the subjects showed some increased probing depth resulting in at least one sextant receiving a CPITN score of 3. Most of these initial lesions were found in subjects older than 40 years and in the oldest age group ($>$50 years), there was a slight increase to 38% of subjects with a score of 3. Likewise, for the worst severity of disease (i.e., sextants with a CPITN score of 4), only 3% of subjects $<$40 years had at least one sextant scoring 4 while in the oldest age group ($>$50 years) this increased to 25% of subjects.

Mean probing depths were comparable between the genotypes except in the $>$50 year old non-smoking group where genotype positive subjects maintained significantly higher mean probing depths throughout the 5 years of observation (Fig. 1). Due to the swamping effect of the large number of shallow sites in this population, proximal sites with probing depths $\geqslant$3.5 mm were considered separately.

The generalised linear modelling analysis of the number of proximal sites with pockets $\geqslant$3.5 mm showed no significant main effect of IL-1 genotype, but significant interactive effects between IL-1 genotype and smoking, IL-1 genotype with presence of *P. gingi-*

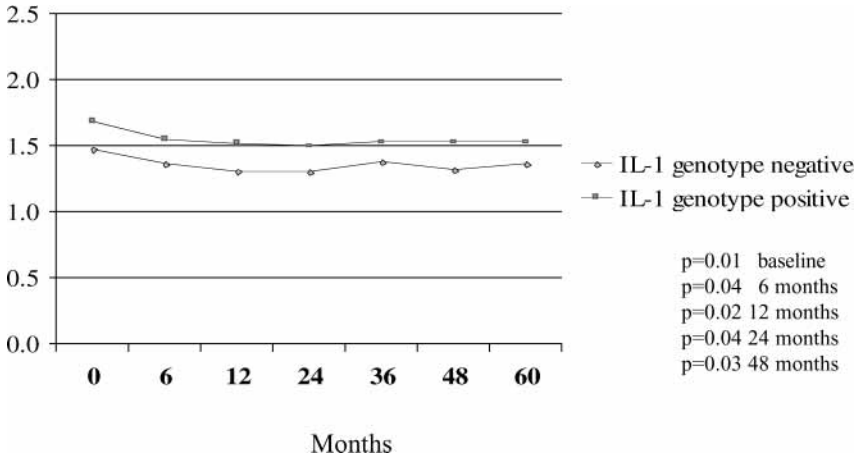

Fig. 1. Mean probing depths in non-smokers >50 years according to genotype status.

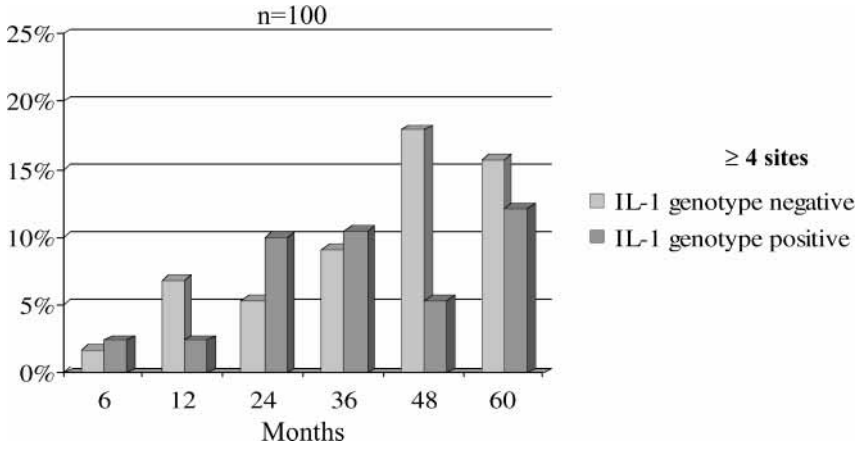

Fig. 2. Non-smokers ≤40: % with attachment loss ≥2 mm from baseline at ≥4 sites for each observation period, according to genotype status.

valis (but not *A. actinomycetemcomitans* or *P. intermedia*) at the previous examination, and IL-1 genotype with the number of pockets ≥3.5 mm at the previous examination. These significant effects were such that IL-1 genotype positive subjects who were smokers would have 70% more pockets on average than IL-1 genotype negative smokers, and those positive for *P. gingivalis* would have 80% more pockets ≥3.5 mm on average than their IL-1 genotype negative counterparts.

The interaction of IL-1 genotype with the number of pockets ≥3.5 mm at the previous visit, showed that these effects of the IL-1 positive genotype were attenuated as more pockets developed. This suggests that in subjects with more deep pockets the influence of IL-1 genotype may be diluted by other factors. Although there were significant interactive effects of IL-1 genotype with age on mean probing depth as reported above, there were no such interactions on the numbers of proximal sites with probing depths ≥3.5 mm.

Disease progression was defined as an episode of measurable loss of probing attachment of ≥2 mm, either from baseline or between consecutive examinations. Overall, 98 and 99% of IL-1 genotype positive and genotype negative subjects respectively, experienced disease progression involving at least one site in the dentition, at some stage during the study. In the subjects >50 years of age, the prevalence of such episodes was 100%, irrespective of the genotype status.

The proportion of subjects experiencing disease progression, including the smokers, decreased when increasing extent of disease from one lesion to ≥4, ≥6 and ≥8 sites per dentition was considered. However, with greater extent, the differences in proportions between IL-1 genotype positive and IL-1 genotype negative subjects became more apparent (Table 1). This was evident, not only for the entire population, but also for the three age groups studied. In the oldest population, 56.5% of IL-1 genotype positive subjects displayed at least four sites with attachment loss as opposed to only 43.5% of IL-1 genotype negative subjects. The greatest extent of attachment loss (≥8 lesions) occurred in 17.4% of the IL-1 genotype positive and in only 8.7% of IL-1 genotype negative subjects. However, none of these differences were statistically significant.

Because of the fact that smoking has been recognised as a strong confounding factor, the 270 non-smokers were considered separately. In the youngest age group, ≤40 years (n=100), the proportion of subjects affected by attachment loss of ≥2 mm from baseline at 4 or more sites for each observation period is depicted in Fig 2. There was no consistent difference between the genotypes in the proportion of subjects affected with this extent of disease. Owing to the small number of subjects affected with attachment loss at ≥6 or ≥8 sites (only occasionally single individuals affected), no further subset analysis was performed in this age group.

For non-smokers older than 40 years (n=170), and >50 years (n=63) there was a trend towards slightly higher percentages of IL-1 genotype positive subjects experiencing disease progression from baseline for the three extent categories (Figs. 3, 4). However none of these differences were statistically significant.

The generalised linear modelling analysis of the numbers of proximal sites with loss of attachment of at least 2 mm showed no significant effects at all of IL-1 genotype.

Discussion

This longitudinal population study has shown a relationship between the IL-1 positive genotype (allele 2) and age, smoking and *P. gingivalis*. The study has demonstrated an increased mean probing pocket depth in non-smokers greater than 50 years of age who are IL-1 genotype positive. Further, it has shown that IL-1 genotype positive smokers and genotype positive subjects with *P. gingivalis* in their plaque have an increase in the number of probing depths ≥3.5 mm. These findings not

only confirm the multifactorial nature of periodontal disease where age, smoking and *P. gingivalis* are widely considered as risk factors (Alpagot et al. 1996, Faddy et al. 2000, Machtei et al. 1997, Norderyd et al. 1999), but also demonstrate the contributory role of this IL-1 composite genotype.

The prevalence of 38.9% of IL-1 genotype positive subjects in the present study was slightly elevated when compared with the prevalence of IL-1 genotype positive subjects in the original report comprising North Americans of northern European heritage (Kornman et al. 1997). This sample from a Caucasian population yielded a prevalence very similar to that reported for Caucasians of central European origin (Lang et al. 2000). However, the prevalence of IL-1 genotype positive subjects in the present study was high when compared with reports of African – Americans (Van Dyke et al. 1999) and of Chinese (Armitage et al. 2000).

Previous cross-sectional studies (Gore et al. 1998, Kornman et al. 1997) have claimed that this allele 2 composite IL-1 polymorphism is a risk factor for severe periodontal disease with genotype positive individuals having greater risk of developing severe periodontitis after the age of 40 compared with genotype-negative subjects (Kornman et al. 1997). This composite IL-1 allele 2 polymorphism has also been linked with the expression of high levels of IL-1 (Engebretson et al. 1999).

In contrast, different IL-1 polymorphisms have been associated with early-onset periodontitis (EOP) (Diehl et al. 1999, Parkhill et al. 2000) and with periodontitis associated with cardiovascular disease (Kornman et al. 1999). While the composite allele 2 polymorphism has been associated with increased IL-1β production by activated peripheral blood neutrophils isolated from patients with advanced disease (Gore et al. 1998), the relationship between IL-1 polymorphisms and disease progression remains to be determined. Indeed, Diehl et al. (1999) have suggested that the composite allele 2 polymorphism which gives rise to high levels of IL-1β may, in fact, be protective for EOP. The present study, however, has shown that the IL-1 (allele 2) genotype is a contributory but not essential factor for periodontal disease development in an adult Caucasian Australian population. The non-essential role of this genotype is highlighted

Table 1. % of subjects (including smokers) with attachment loss ⩾2 mm at ⩾4, ⩾6 and ⩾8 sites at any time throughout the 5 years of observation according to genotype status and for the different age groups

	All subjects n=295		⩽40 years n=113		>40 years n=182		>50 years n=69	
Extent of disease	IL-1− n=181	IL-1+ n=114	IL-1− n=66	IL-1+ n=47	IL-1- n=115	IL-1+ n=67	IL-1− n=46	IL-1+ n=23
⩾4 lesions	43.7	42.1	34.9	31.9	48.7	49.3	43.5	56.5
⩾6 lesions	19.3	24.6	10.6	12.8	24.4	32.8	26.1	30.4
⩾8 lesions	8.8	10.5	1.5	4.3	13.0	14.9	8.7	17.4

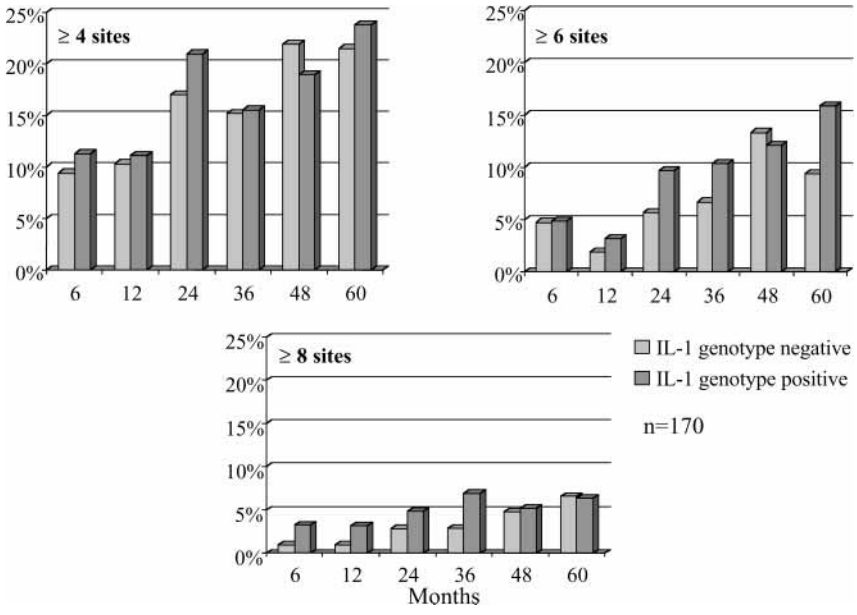

Fig. 3. Non-smokers >40: % with attachment loss ⩾2 mm from baseline at ⩾4, ⩾6, and ⩾8 sites for each observation period, according to genotype status.

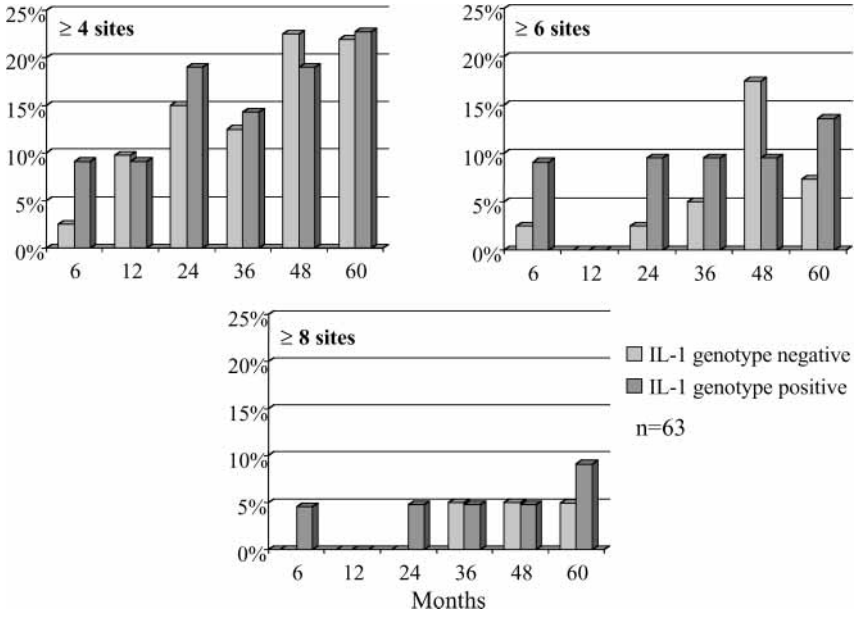

Fig. 4. Non-smokers >50: % with attachment loss ⩾2 mm from baseline at ⩾4, ⩾6 and ⩾8 sites for each observation period, according to genotype status.

in the present study by its apparent dilution in those subjects with more advanced disease.

Despite the fact that different polymorphisms were identified, Diehl et al. (1999) suggested that in EOP, IL-1 genotype was an important but not exclusive risk factor, while Parkhill et al. (2000) suggested a role for IL-1 genotype in combination with an environmental factor such as smoking.

It is clear from these studies that, while a common genetic factor has not been identified for all forms of periodontal disease, at an individual level disease expression is a result of the interplay between innate genetic susceptibility and differing environmental factors. The present study, in considering other risk factors (e.g., *P. gingivalis*) in addition to IL-1 genotype, provides additional insight into the role of this genotype, and explains further the effects observed by Kornman et al. (1997).

The volunteers recruited for the present study were simultaneously enrolled in an ongoing study on the progression of periodontal disease in a general adult population (Faddy et al. 2000). At the start of the study, the majority of subjects presented with only a mild severity and extent of periodontitis, predominantly occurring in older subjects. However, most of the subjects showed generalised gingivitis. In comparison with previous surveys of the adult population of Australia (Barnard 1993, Powell & McEniery 1985, Seymour et al. 1996), this group of subjects was representative of a general adult population ubiquitously encountered in most industrialised countries (Pilot 1998). This, in turn, means that the progression of periodontal disease in the total population sample was most likely fairly slow and quite localised. Consequently, as in other longitudinal studies of periodontal disease (Lindhe et al. 1989a, b), only a few incidences of the defined attachment loss of $\geqslant$2 mm, in the order of magnitude of single percents, were to be expected. Hence, the study population chosen for the present analysis is ideal for the evaluation of the influence of genetic risk factors.

Smoking is widely regarded as an important risk/modifying factor for periodontal disease (Bergström & Preber 1994, Haber 1994). Despite this, however, the actual mechanism by which smoking affects periodontal disease is unclear. There are a number of reports which suggest that smoking may alter the immune response by suppressing the secretion of IL-1β from gingival mononuclear cells (Bernzweig et al. 1998, Soliman & Twigg 1992). Recently, Faddy et al. (2000), using an ante-dependence model for disease progression, have shown that the major effect of smoking may be in its inhibition of healing rather than in promoting increased disease progression, again highlighting the complex multifactorial aetiology of periodontal disease.

In the present study, no relationship was found between IL-1 (allele 2) genotype, *A. actinomycetemcomitans, P. intermedia* and disease. This suggests that in this Australian population these organisms are of lesser importance. In recent years, a number of studies (Muller et al. 1996, Papapanou et al. 1993, Wolff et al. 1993) have shown that *A. actinomycetemcomitans,* while associated with early-onset forms of periodontal disease, is often found in healthy subjects. Similarly, *P. intermedia* is now considered to be of lesser significance and receiving less attention. In an interesting study, Socransky et al. (2000) have recently reported that IL-1 (allele 2) genotype influences the levels of specific bacterial complexes with an increase in those containing periodontal pathogens. In the current study, we have shown an interaction between IL-1 genotype, *P. gingivalis,* and disease. The relationship between IL-1 genotype and specific bacteria is unknown. While it is conceivable that cytokine polymorphisms may result in a non-protective immune response, thus allowing specific pathogens to persist, the results of the present study do demonstrate that the two factors, IL-1 genotype and *P. gingivalis*, are acting together in some way.

There is little doubt that there is increasing severity of periodontal disease with increasing age (Alpagot et al. 1996, Beck et al. 1990, Locker & Leake 1993). It is generally assumed, however, that this is a result of the cumulative effect of disease over time. Recently, however, Faddy et al. (2000) have suggested that with increasing age the reduced capacity to heal contributes to the more extensive disease expression seen with age. In the present study, proportionally more older subjects (over 50 years) who were IL-1 genotype positive had more extensive disease in terms of the number of sites showing loss of attachment of 2 mm or more over time than those who were IL-1 genotype negative. Over all age groups, however, IL-1 genotype positive individuals did not show greater loss of attachment compared with genotype negative individuals. This further supports the concept that IL-1 genotype acts in concert with risk factors and that by itself may have only a minor effect. This concept may also explain apparent conflicting results (Ehmke et al. 1999, Lang et al. 2000) where IL-1 genotype was shown to be of limited value in predicting disease progression following non-surgical periodontal therapy (Ehmke et al. 1999) but at the same time was associated with an increased number of sites showing bleeding on probing during supportive periodontal therapy (Lang et al. 2000).

It is clear from the present study that genetic risk factors for periodontal disease do not act in isolation and that future genetic studies cannot ignore bacterial and environmental factors.

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Zusammenfassung

Langzeitstudie über Interleukin-1-Genpolymorphismus und Parodontalerkrankung in einer Population von Erwachsenen

Grundlagen: Querschnittstudien haben gezeigt, dass ein spezifischer Polymorphismus (Allel 2 von IL-1A +4845 und IL-1B +3954) im IL-1-Gencluster mit einer erhöhten Anfälligkeit für eine schwere Parodontalerkrankung sowie einer erhöhten Blutungsneigung während der Erhaltungstherapie assoziiert ist. Das Ziel der vorliegenden Studie war es, in einer prospektiven Lanzeitstudie an einer Population von Erwachsenen die Beziehung zwischen IL-1-Genotyp und Parodontitis zu untersuchen.

Methoden: Aus einer laufenden Studie des Oral Care Research Programms der Universität von Queensland, willigten 295 Personen ein, dass eine Genotypisieren hinsichtlich IL-2-Allel-2-Polymorphismus durchgeführt wird. Die Sondierungstiefe und das relative Attachmentniveau wurden bei der Eingangsuntersuchung, sowie nach 6, 12, 24, 36, 48 und 60 Monaten mittels Florida Probe erhoben. Die Progression der Parodontitis in einer bestimmten Tasche wurde definiert als Attachementverlust von $\geqslant$2 mm während einer Beobachtungsperiode innerhalb der 5 Jahre der studie und das Ausmaß der Progression der Erkrankung wurde bestimmt

über die Anzahl der Taschen mit Attachementverlust. *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans* und *Prevotella intermedia* wurden mittels ELISA nachgewiesen.
Ergebnisse: 38.9% der Personen waren positiv bezüglich des Composit-IL-1-Genotyps. Bei Nichtrauchern, die älter als 50 Jahre waren wurde eine Beziehung zwischen positivem IL-1-Genotyp und erhöhter durchschnittlicher Sondierungstiefe festgestllt. Des weiteren hatten IL-1-Genotyp-positive Raucher und Genotyp-positive mit *P. gingivalis* in ihrer Plaque eine höhere Anzahl an Sondierungstiefen ⩾3.5 mm. Im Vergleich zu den Genotyp-negativen Personen gab es bei den IL-1-Genotyp-positiven einen beständigen Trend Attachementverlust zu bekommen.
Schlussfolgerung: Die Ergebnisse dieser Studie haben gezeigt, dass es eine Interaktion zwischen positivem IL-1-Genotyp und Alter, Rauchen sowie *P. gingivalis* gibt, welche annehmen lässt, dass der IL-1-Genotyp in dieser Population ein beitragender, aber nicht eine essentieller Risikofaktor für die Progression einer Parodontalerkrankung ist.

Résumé

Une étude longitudinale des polymorphismes du gène de l'interleukine 1 et la maladie parodontale dans une population globale adulte
Origine: Des étude croisées ont démontré qu'un polymorphisme spécifique (allèle 2 pour les deux IL1-A +4845 et IL1-B +3954) du groupe de gène IL1, a été associé avec une susceptibilité accrue à une maladie parodontale sévère et à une tendance au saignement augmentée pendant la maintenance parodontale. Le but de cette étude est de rechercher les relations entre le génotype IL-1 et la parodontite dans une étude prospective longitudinale dans une population adulte esentiellement d'origine européenne.
Méthodes: 256 sujets, issus d'une étude en cours du programme de recherche de soins buccaux, acceptèrent un génotypage pour les polymorphismes de l'allèle 2 de l'IL-1. Les profondeurs au sondage et les niveaux relatifs d'attache furent enregistrés avec une sonde de Florida, initialement, puis, à 6, 12, 24, 48, et 60 mois. La progression de la parodontite, sur un site donné fut définie par une perte d'attache ⩾2 mm, à n'importe quel moment pendant les 5 ans de l'étude, et l'étendu de la progression de la maladie fut définie par le nombre de sites présentant des pertes d'attache. *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans,* et *Prevotella intermedia ont* été détecté par ELISA.
Résultats: 38.9% des sujets étaient positifs pour le génotype composite de l'IL-1. Il existe une relation entre les génotypes positifs et un accroissement des profondeurs de poches moyennes chez les non-fumeurs de plus de 50 ans. De plus, les fumeurs au génotype positif et les sujets au génotype positif porteurs de *P. gingivalis* dans la plaque présentaient un nombre accru de profondeurs de sondage ⩾3.5 mm. Il y avait une tendance constante à la perte d'attache chez les sujets positifs par rapport aux sujets négatifs.
Conclusions: Les résultats de cette étude ont montré une interaction du génotype IL-1 positif avec l'âge, le tabagisme et *P. gingivalis*, ce qui suggère que le génotype IL-1 est un facteur de risque contributif mais pas essential de progression de la maladie parodontale dans cette population.

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Address:

Mary P. Cullinan
The University of Queensland
Oral Biology and Pathology
Brisbane, Queensland 4072
Australia

Fax: + 61 7 3365 1109
e-mail: m.cullinan@mailbox.uq.edu.au