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Periodontal status of patients with Crohn's Disease

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect any segment of the gastrointestinal tract including oral cavity and has extra-intestinal manifestations as well (1, 2). There exist several similar features in the pathophysiology of CD and periodontitis (Fig. 1).

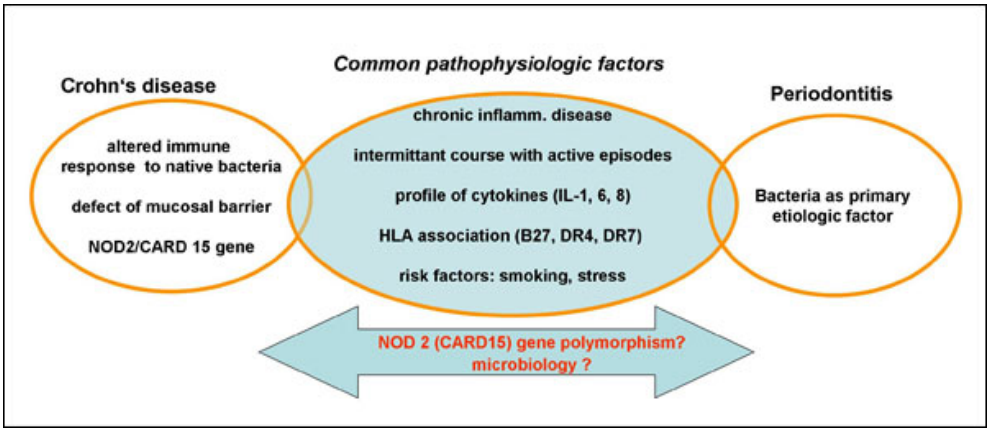


Fig 1: Possible relationship between Crohn's disease and periodontitis

CD has been reported to have periodontal manifestations. However, most of the knowledge is based on case reports (3, 4) and one cohort study with a limited number of patients (5). Data on periodontal parameters and microbiology is rare (6). Besides, recent studies showed an association of single nucleotide polymorphisms (SNPs) in the NOD2(CARD15) gene with CD (7, 8). These SNPs (SNP8,12,13) are involved in recognition towards peptidoglycans of bacterial lipopolysaccharides (9) and might therefore affect interactions between CD and periodontitis.

Objectives

The aim of our study was to investigate the clinical periodontal status of patients with CD taking into account periodontal pathogens and the NOD2(CARD15) SNPs 8, 12 and 13.

Material and Methods

The periodontal status of 147 Caucasian patients with CD (age range: 18-59) was assessed. Plaque index (PI, Silness & Löe [10]), gingiva index (GI, Löe & Silness [11]), periodontal probing depth (PD) and clinical attachment loss (CAL) were measured in each patient. Smoking status and intake of immunosuppressive medicaments has been recorded.
Subgingival plaque samples were obtained from all individuals. Paper-point samples were taken from the deepest subgingival site in each quadrant of the dentition (12, 13). Detection of periodontopathic bacteria Actinobacillus actinomycetemcomitans (A.a.), Tannerella forsythia (T.f.), Porphyromonas gingivalis (P.g.), Prevotella intermedia (P.i.) and Campylobacter rectus (C.r.) were established by dot blot hybridization with 16S rRNA directed DNA-probes. Patients were considered positive for a bacterium, if its number was > 103.
NOD2(CARD15) genotyping was done with allele specific multiplex PCR using the Taqman assay (7). 3 SNPs were differentiated: SNP8 (rs2066844 C2023T); SNP12 (rs2066845 G2641C); SNP13 (rs2066847 2936insC). For each SNP 2 alleles could be discriminated (allele 1 = mutant, allele 2 = wild type).
The unpaired t-test was used for comparison of the values of continuous variables between the mutant and the wild type subgroup. Investigation of associations between allele type (mutant or wild type) and various categorical variables was done with Fishers Exact Text. Statistical comparison of the 3 NOD2(CARD15) SNP subgroups with the wild type regarding bacterial scores was done with Chi2 Test with Yates correction or Fishers Exact Test if appropriate. Moreover, multivariate statistical analyses were used in order to determine the effect of the variables sex, age, smoking, immunosuppression, PI, GI, bacterial scores and the NOD2(CARD15) SNP subtypes on different PD and CAL variables. Multiple logistic regression analyses were used for binary PD/CAL scores, while covariance analyses were conducted in cases of continuous PD/CAL variables. All p values were corrected according to Bonferroni adjustment.

Results

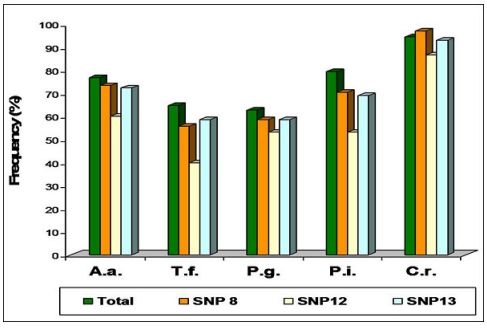
1. Clinical and demographic parameters

	Total	**SNP 8**	**SNP 12**	**SNP 13**	**Mutant (SNP 8, 12, 13)**	**Wild Type**	**Mutant vs. Wild Type Significance**
	N = 147	N = 34	N = 15	N = 29	N = 66	N = 81	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p
age (years)	36.6 (9.9)	34.9 (11.0)	32.7 (10.5)	36.2 (8.8)	35.5 (9.8)	37.5 (9.8)	0.304 (n.s.)
females %	52.4	47.1	60.0	62.1	50.0	54.3	0.869 (n.s.)
smokers %	37.4	44.1	26.7	44.8	43.9	32.1	0.168
immuno-suppression %	47.6	38.2	46.7	44.8	42.4	51.9	0.411 (n.s.)
PI (0-3)	1.2 (0.6)	1.1 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	0.553 (n.s.)
GI (0-3)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)	1.2 (0.7)	1.3 (0.6)	1.1 (0.5)	0.140 (n.s.)
PD (mm)	3.6 (0.8)	3.4 (0.7)	3.3 (1.0)	3.4 (0.8)	3.5 (0.7)	3.6 (1.0)	1.000 (n.s.)
% teeth with							
PD > 3.5	53.1	55.9	53.3	55.2	59.1	48.1	0.189 (n.s.)
PD > 5.5	2.7	0.0	0.0	0.0	0.0	4.9	0.133 (n.s.)
CAL (mm)	3.8 (1.0)	3.6 (0.9)	3.6 (1.1)	3.6 (1.0)	3.7 (0.8)	3.8 (1.2)	0.987 (n.s.)
% teeth with							
CAL > 3.5	59.9	61.8	60.0	58.6	65.2	55.6	0.242 (n.s.)
CAL > 5.5	4.8	2.9	6.7	3.4	3.0	6.2	0.699 (n.s.)
missing teeth	6.1 (3.7)	4.6 (2.7)	6.4 (4.3)	6.2 (2.7)	5.8 (3.4)	6.3 (3.9)	0.752 (n.s.)

Tab 1: Clinical and demographic characterization of different NOD2(CARD15) subgroups. mutant = at least one allele 1 (mutant allele) for SNP 8, 12 or 13 present. Wild Type = only wild type allele 2 present.

Among all 147 patients with CD, 34 (23.13%) were carriers of the mutant allele 1 of NOD2(CARD15) SNP8, 15 (10.20%) had allele 1 for SNP12 and 29 (19.73%) had allele 1 for SNP13. 66 patients (44.9%) had at least one allele 1 for SNP8, 12 or 13 ("mutant" group). In 81 patients (55.1%) there was none of the allele 1 ("wild type" group). Table 1 shows all demographic values in the total group of all SNP subgroups. In all groups, there was a similar distribution of the gender, number of smo-kers and intake of immunosuppressive medicaments. There were no clinical differences between the "mutant group" and the "wild type" group regarding PI, GI, PD and CAL.

2. Microbiologic results



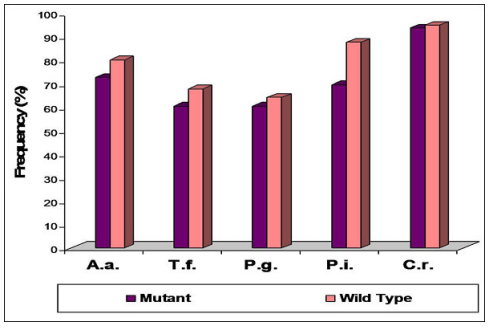


Fig 2a: Distribution of periodontopathic bacteria in all SNP subgroups

Fig 2b: Presence of periodontopathic bacteria in patients with "mutant" and "wild type" NOD2(CARD15).

Figures 2a and 2b show the distribution of the periodontopathic bacteria in all NOD2(CARD15) SNP subgroups. All investigated species were detected in more than 60% of all patients. C.r. had the highest frequency (94.56%). Comparing the "mutant" group with the "wild type" group there was a trend for a lower frequency of all bacteria and, in particular, a significantly decreased frequency of P.i. in the "mutant" group (46/66, 69.7% vs.71/81, 78.65%; p = 0.007, pBf = 0.035).
When the results of the present study were compared to cohorts with and without periodontitis published by other authors, CD associated bacteria reached a similar (or even higher) frequency as (than) patients with chronic or aggressive periodontitis (Table 2).

	CD *(present study, N = 147)*	**Healthy Patients without periodontitis** *(Boutaga et al. 2006, N = 111)*	**Chronic periodontitis** *(Boutaga et al. 2006, N = 259)*	**Aggressive Periodontitis** *(Darby et al. 2000, N = 96)*
Presence of A.a. (%)	76.9	18.0	27.4	20.8
Presence of P.g. (%)	62.6	9.9	45.5	62.5
Presence of P.i. (%)	79.6	23.2	83.0	79.2
Presence of T.f. (%)	64.6	33.2	89.2	91.7
	CD *(present study, N = 147)*	**Healthy Patients without periodontitis** *(Saygun et al. 2004, N = 16)*	**Chronic periodontitis** *(Colombo et al. 2006*, N = 49)*	**Aggressive Periodontitis** *(Albandar et al. 1997, N = 148)*
Presence of C.r. (%)	94.6	18.8	35.0	71.0

Tab 2: Frequency of periodontopathic bacteria among patients with CD with different study populations published in the literature. (* = detection of C.r. in crevicular epithelial cells)

3. Multivariate analyses
Multivariate analyses were done to determine different variables on PD and CAL as well as on periodontopathic bacteria (Table 3a, b). Logistic regression and covariance analyses resulted in a significant impact of age (> 35 years) and gingiva index on PD and CAL values more than 3.5 mm. Since C.r. was the most frequent bacterium in all CP patients, we tested the influence of different detection levels (10^3, 10^4 and 10^5). High levels of C.r. (10^5) were associated with increased PD and a higher frequency of sites with CAL > 5.5 mm. Regarding the presence of the investigated bacteria, only age and GI were risk factors for the presence of P.g. (age) and T.f. (GI).

parameter	**intercept**	**immuno-suppression**	**age (> 35)**	**GI**	**smoking**	**C.r. ≥ 10^3**	**C.r. ≥ 10^5**	**NOD2(CARD15) mutation**
PD > 3.5	0.0025	---	**0.0019**	0.6413	0.2637	0.7669	0.0109	0.0529
PD > 5.5	0.0180	---	0.0196	---	0.8639	0.9140	**0.0005**	0.3478
CAL > 3.5	0.0292	---	**<0.0001**	0.0035	0.0150	0.6419	---	0.0899
CAL > 5.5	0.9304	---	0.9005	0.4214	0.2655	0.9853	0.0229	---
% sites PD > 3.5	---	---	**<0.0001**	**0.0005**	0.5725	0.7173	0.0947	---
% sites PD > 5.5	---	---	0.0070	0.0784	0.7643	0.8741	0.0029	0.0977
% sites CAL > 3.5	---	---	**<0.0001**	**<0.0001**	0.0436	0.6868	0.0125	---
% sites CAL > 5.5	---	---	0.0643	0.0272	0.4626	0.7048	**<0.0001**	0.0603

Tab 3a: Logistic regression and covariance analyses for PD and CAL values. Significant p-values according to Bonferroni correction (p < 0.0024) are marked.

parameter	**intercept**	**gender (female)**	**age (> 35)**	**GI**	**smoking**	**immuno-suppression**	**NOD2(CARD15) mutation**
A.a. ≥ 10^3	0.2028	---	0.2158	0.3102	---	---	---
P.g. ≥ 10^3	0.9292	---	**0.0010**	0.2339	---	---	---
P.i. ≥ 10^3	0.4204	---	0.0095	---	---	---	0.9855
T.f. ≥ 10^3	0.0930	---	0.1213	**0.0023**	0.0146	---	---
C.r. ≥ 10^3	0.0009	---	0.2825	---	---	---	---

Tab 3b: Logistic regression and covariance analyses for periodontopathic bacteria. Significant p-values according to Bonferroni correction (p < 0.0024) are marked.

Conclusions

The results of our study suggest that patients with Crohn's disease have an increased prevalence but only moderate severity of periodontal disease. Our data do not support a role of NOD2(CARD15) on periodontal status in CD. However, in all patients there was a high frequency of periodontopathic bacteria A. actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia and C. rectus with highest scores in the NOD2(CARD15) wild type. C. rectus, which has already been reported to impair neutrophils in patients with CD (6), might be of particular value for the periodontal manifestation of CD. Trigger effects for autoimmune responses or cross tolerance referred to this bacterium might be possible mechanisms. Further studies are necessary to confirm the role of periodontopathic bacteria and its possible value for diagnostics and therapy of CD.

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Abbreviations

CD: Crohn\'s diseases
NOD: Nukleotide-Oligodimerisation-Domain
CARD: Caspase Recruitment Domain
A.a.: Actinobacillus actinomycetemcomitans
P.g.: Porphyromonas gingivalis
P.i.: Prevotella intermedia
T.f.: Tannerella forsythia
C.r.: Campylobacter rectus
PI: Plaque Index (Silness & Loe)
GI: Gingiva Index (Loe & Silness)
PD: Probing depth
CAL: Clinical attachment level

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Poster Faksimile:

Periodontal status of patients with Crohn's Disease

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect any segment of the gastrointestinal tract including oral cavity and has extra-intestinal manifestations as well (*Podolsky 1991, Glickman 1998*). There exist several similar features in the pathophysiology of CD and periodontitis (Fig. 1).

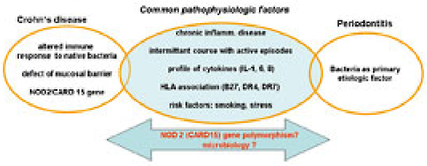
Common pathophysiologic factors
Crohn's disease
altered immune response to native bacteria
defect of mucosal barrier
NOD2/CARD 15 gene
chronic inflamm. disease
intermittant course with active episodes
profile of cytokines (IL-1, 6, 8)
HLA association (B27, DR4, DR7)
risk factors: smoking, stress
Periodontitis
Bacteria as primary etiologic factor
NOD 2 (CARD15) gene polymorphism?
microbiology ?

Figure 1: Possible relationship between Crohn's disease and periodontitis

CD has been reported to have periodontal manifestations. However, most of the knowledge is based on case reports (*Engel et al 1988, Rhodes et al. 1982*) and one cohort study with a limited number of patients (*Flemmig et al. 1991*). Data on periodontal parameters and microbiology is rare (*Van Dyke et al. 1986*). Besides, recent studies showed an association of single nucleotide polymorphisms (SNPs) in the NOD2(CARD15) gene with CD (*Hampe et al. 2002, Hugot et al. 2001*). These SNPs (SNP8,12,13] are involved in recognition towards peptidoglycans of bacterial lipopolysaccharides (*Girardin et al. 2003*) and might therefore affect interactions between CD and periodontitis.

The aim of our study was to investigate the clinical periodontal status of patients with CD taking into account periodontal pathogens and the NOD2(CARD15) SNPs 8, 12 and 13.

MATERIAL AND METHODS

The periodontal status of 147 Caucasian patients with CD (age range: 18-59) was assessed. Plaque index (PI, Silness & Löe), gingiva index (GI, Löe & Silness), periodontal probing depth (PD) and clinical attachment loss (CAL) were measured in each patient. Smoking status and intake of immunosuppressive medicaments has been recorded.

Subgingival plaque samples were obtained from all individuals. Paper-point samples were taken from the deepest subgingival site in each quadrant of the dentition (*Mombelli et al. 1991, 1994*). Detection of periodontopathic bacteria *Actinobacillus actinomycetemcomitans (A.a.), Tannerella forsythia (T.f.), Porphyromonas gingivalis (P.g.), Prevotella intermedia (P.i.) and Campylobacter rectus (C.r.)* were established by dot blot hybridization with 16S rRNA directed DNA-probes. Patients were considered positive for a bacterium, if its number was > 10^3.

NOD2(CARD15) genotyping was done with allele specific multiplex PCR using the Taqman assay (*Hampe et al. 2001*). 3 SNPs were differentiated: SNP8 (rs2066844 C2023T), SNP12 (rs2066845 G2641C); SNP13 (rs2066847 2936insC). For each SNP 2 alleles could be discriminated (allele 1 = mutant, allele 2 = wild type).

The unpaired t-test was used for comparison of the values of continuous variables between the mutant and the wild type subgroup. Investigation of associations between allele type (mutant or wild type) and various categorical variables was done with Fishers Exact Text. Statistical comparison of the 3 NOD2(CARD15) SNP subgroups with the wild type regarding bacterial scores was done with Chi^2 Test with Yates correction or Fishers Exact Test if appropriate. Moreover, multivariate statistical analyses were used in order to determine the effect of the variables sex, age, smoking, immunosuppression, PI, GI, bacterial scores and the NOD2(CARD15) SNP subtypes on different PD and CAL variables. Multiple logistic regression analyses were used for binary PD/CAL scores, while covariance analyses were conducted in cases of continuous PD/CAL variables. All p values were corrected according to Bonferroni adjustment (p_{Bf}).

RESULTS

1. Clinical and demographic data

Table 1: Clinical and demographic characterization of different NOD2(CARD15) subgroups. mutant = at least one allele 1 (mutant allele) for SNP 8, 12 or 13 present. Wild Type = only wild type allele 2 present.

	Total	SNP 8	SNP 12	SNP 13	Mutant (SNP 8,12,13)	Wild Type	Mutant vs. Wild Type Significance
	N = 147	N = 34	N = 15	N = 29	N = 66	N = 81	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p
age (years)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
females %	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
smokers %	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
immunosuppression %	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PI (0-3)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GI (0-3)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PD (mm)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
% teeth with							
PD > 3.5 mm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PD > 5.5 mm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CAL (mm)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
% teeth with							
CAL > 3.5 mm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CAL > 5.5 mm	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
missing teeth	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Among all 147 patients with CD, 34 (23.13%) were carriers of the mutant allele 1 of NOD2(CARD15) SNP8, 15 (10.20%) had allele 1 for SNP12 and 29 (19.73%) had allele 1 for SNP13. 66 patients (44.9%) had at least one allele 1 for SNP8, 12 or 13 ("mutant" group). In 81 patients (55.1%) there was none of the allele 1 ("wild type" group). Table 1 shows all demographic values in the total group of all SNP subgroups. In all groups, there was a similar distribution of the gender, number of smokers and intake of immunosuppressive medicaments. There were no clinical differences between the "mutant group" and the "wild type" group regarding PI, GI, PD and CAL.

2. Microbiologic results

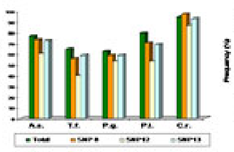

Figure 2a: Distribution of periodontopathic bacteria in all SNP subgroups

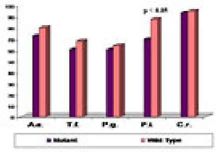

Figure 2b: Presence of periodontopathic bacteria in patients with „mutant" and „wild type" NOD2(CARD15).

Figures 2a and 2b show the distribution of the periodontopathic bacteria in all NOD2(CARD15) SNP subgroups. All investigated species were detected in more than 60% of all patients. C.r. had the highest frequency (94.56%). Comparing the "mutant" group with the "wild type" group there was a trend for a lower frequency of all bacteria and, in particular, a significantly decreased frequency of P.i. in the "mutant" group (40/66, 69.7% vs 71/81, 78.65%; p = 0.007, p_{Bf} = 0.035).

When the results of the present study were compared to cohorts with and without periodontitis published by other authors, CD associated bacteria reached a similar (or even higher) frequency as (than) patients with chronic or aggressive periodontitis (Table 2).

Table 2: Frequency of periodontopathic bacteria among patients with CD with different study populations published in the literature. (* = detection of C.r. in crevicular epithelial cells)

	CD (present study N = 147)	Healthy Patients without periodontitis ([illegible])	Chronic periodontitis ([illegible])	Aggressive Periodontitis ([illegible])
Presence of A.a. (%)	[illegible]	[illegible]	[illegible]	[illegible]
Presence of P.g. (%)	[illegible]	[illegible]	[illegible]	[illegible]
Presence of P.i. (%)	[illegible]	[illegible]	[illegible]	[illegible]
Presence of T.f. (%)	[illegible]	[illegible]	[illegible]	[illegible]
	CD (present study N = 147)	Healthy Patients without periodontitis ([illegible])	Chronic Periodontitis ([illegible])	Aggressive Periodontitis ([illegible])
Presence of C.r. (%)	[illegible]	[illegible]	[illegible]	[illegible]

3. Multivariate analyses

Multivariate analyses were done to determine different variables on PD and CAL as well as on periodontopathic bacteria (Table 3a + b).

Logistic regression and covariance analyses resulted in a significant impact of age (> 35 years) and gingiva index on PD and CAL values more than 3.5 mm. Since C.r. was the most frequent bacterium in all CP patients, we tested the influence of different detection levels (10^3, 10^4 and 10^5). High levels of C.r. (10^5) were associated with increased PD and a higher frequency of sites with CAL > 5.5 mm. Regarding the presence of the investigated bacteria, only age and GI were risk factors for the presence of P.g. (age) and T.f. (GI).

Table 3a: Logistic regression and covariance analyses for PD and CAL values. Significant p-values according to Bonferroni correction (p < 0.0024) are marked.

parameter	intercept	immuno-suppression	age (> 35)	GI	smoking	[illegible]	[illegible]	NOD2(CARD15) mutation
[illegible]	[illegible]	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	———	[illegible]	———	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	———	[illegible]	[illegible]	[illegible]	[illegible]	———	[illegible]
[illegible]	[illegible]	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	———
[illegible]	———	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	———
[illegible]	———	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	———	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	———
[illegible]	———	———	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 3b: Logistic regression and covariance analyses for periodontopathic bacteria. Significant p-values according to Bonferroni correction (p < 0.0024) are marked.

parameter	intercept	gender (female)	age (> 35)	GI	smoking	immuno-suppression	NOD2(CARD15) mutation
[illegible]	[illegible]	—	[illegible]	[illegible]	—	—	—
[illegible]	[illegible]	—	[illegible]	[illegible]	—	—	—
[illegible]	[illegible]	—	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	—	—
[illegible]	[illegible]	—	[illegible]	—	—	—	—

DISCUSSION AND CONCLUSION

The results of our study suggest that patients with Crohn's disease have an increased prevalence but only moderate severity of periodontal disease. Our data do not support a role of NOD2(CARD15) on periodontal status in CD. However, in all patients there was a high frequency of periodontopathic bacteria *A. actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia* and *C. rectus* with highest scores in the NOD2(CARD15) wild type. *C. rectus*, which has already been reported to impair neutrophils in patients with CD (*Van Dyke 1986*), might be of particular value for the periodontal manifestation of CD. Trigger effects for autoimmune responses or cross tolerance referred to this bacterium might be possible mechanisms. Further studies are necessary to confirm the role of periodontopathic bacteria and its possible value for diagnostics and therapy of CD.

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