An Increased Prevalence of Periodontal Disease, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in anti-CCP positive individuals At-Risk of Inflammatory Arthritis

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Background

The prevalence of periodontal disease is increased in RA, and periodontitis is associated with the bacterium *Porphyromonas gingivalis (Pg),* which can citrullinate arginine residues. These observations suggest periodontitis may be a key initiator of RA-related autoimmunity. Importantly, clinical periodontal disease, and the relative abundance of periodontal bacteria have not been described in seropositive individuals at risk of developing RA who do not have synovitis.

Objectives

To investigate the prevalence of periodontal disease and the relative abundance of key periodontal bacteria in anti-CCP positive at-risk individuals without synovitis.

Methods

Anti-CCP positive individuals with no clinical synovitis (CCP+), early RA (RA) patients and healthy controls (HC) were recruited. CCP+ underwent a 38 joint ultrasound (US) assessment. Periodontal examination was performed by a dentist; six sites per tooth were assessed for clinical attachment level (CAL), pocket depth (PD) and bleeding on probing (BOP). Periodontal disease sites (PDD) were defined as CAL ≥2mm and PD ≥4mm. A clinical consensus was agreed for each case. DNA, isolated from subgingival plaque from diseased and healthy periodontal sites, was pair-end sequenced (Illumina HiSeq3000). Taxonomic and functional profiles were obtained from MG-Rast and differences between groups studied using DESeq2. Mann-Whitney U tests were used to compare groups and Spearman Rho used for correlations. For metagenomic data, Wald test was used to compare relative abundance.

Results

48 CCP+, 26 RA and 32 HC were recruited. Groups were balanced for age, sex and smoking. All but 2 (96%) CCP+ had no US synovitis (greyscale ≥1 and power Doppler ≥1). Dentists classified 73% CCP+, 38% HC ($p=0.02$) and 54% RA as having clinical periodontitis. The percentage of periodontal sites with CAL ≥2mm, PD ≥4mm, BOP, PDD and active PDD (PDD + BOP) were all greater in CCP+ compared to HC ($p<0.05$) and similar to RA. Metagenomic data indicated CCP+ had increased relative abundance of both *Pg* and *Aggregatibacter actinomycetemcomitans* (*Aa*) compared to HC ($p<0.001$) and RA ($p<0.01$). However, clinical periodontitis was only associated with increased relative abundance of *Pg* ($p<0.001$) but not *Aa.* Furthermore, the relative abundance of *Pg* was associated with the percentage of sites with active PDD in CCP+ ($p=0.05$) and HC ($p=0.04$) but this was not seen for Aa (figure).

Conclusions

We report an increased prevalence of periodontal disease, *Pg* and *Aa* in anti-CCP positive at-risk individuals without synovitis. Interestingly, relative abundance of Pg, but not Aa, was associated with periodontitis, suggesting potential mechanistic differences that require further exploration. These data support the concept that periodontal inflammation and periodontopathic bacteria may both be important in the initiation of RA-related autoimmunity.

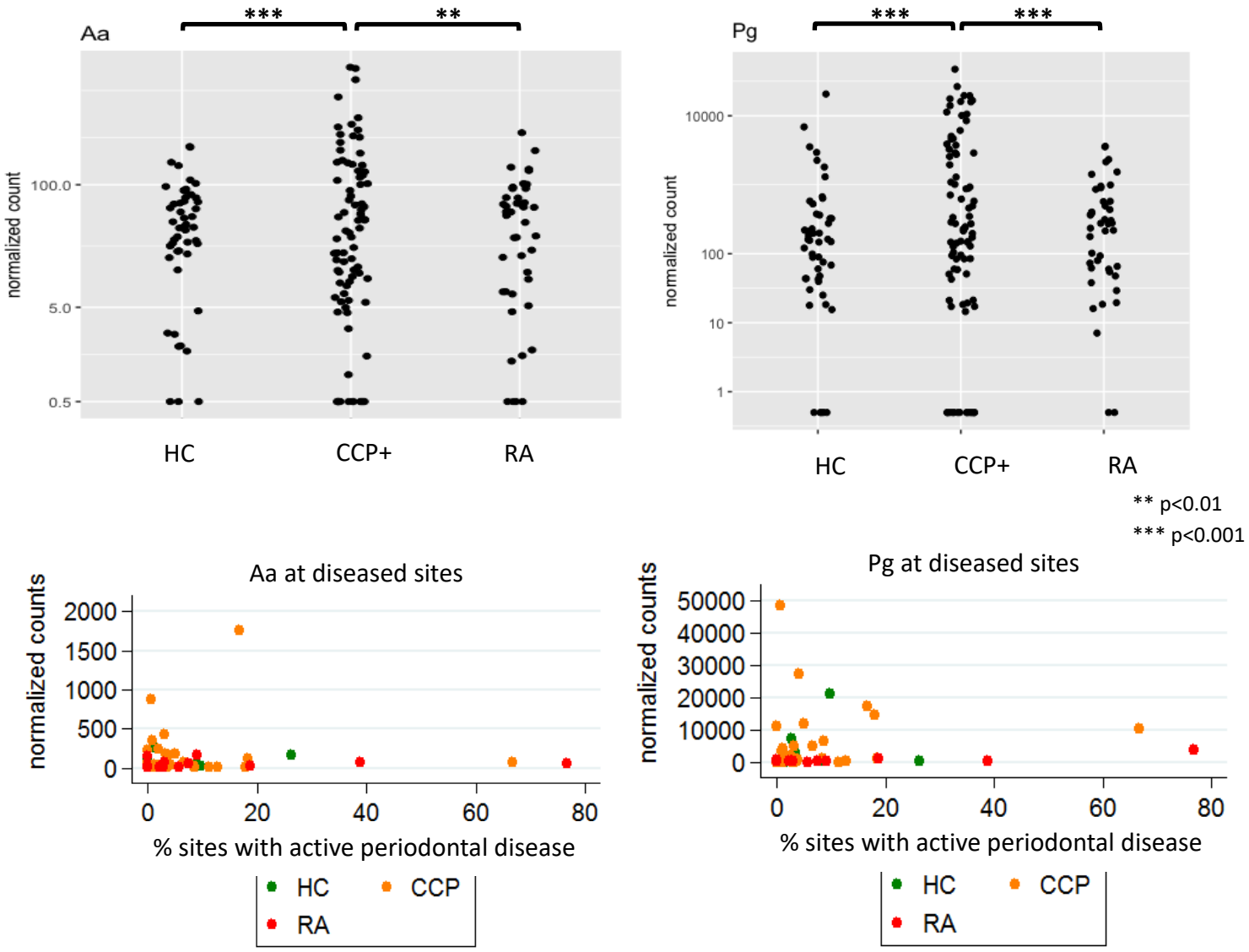

Figure 1. Relative abundance of *Aggregatibacter actinomycetemcomitans* (*Aa*) and *Porphyromonas gingivalis (Pg)* according to RA status and extent of periodontal disease