original research article

GENETIC SUSCEPTIBILITY AND PERIODONTAL DISEASE: A RETROSPECTIVE STUDY ON A LARGE ITALIAN SAMPLE

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SUMMARY
Background. Periodontal disease (PD) is a multifactorial illness in which environment and host interact. The genetic component plays a key role in the onset of PD. In fact the genetic compound can modulate the inflammation of the mucous membranes and the loss of alveolar bone. The genetics of PD is not well understood. Previous studies suggest a strong association between PD occurrence and individual genetic profile. The role of genetic susceptibility could impact on the clinical manifestations of PD, and consequently on prevention and therapy.
Materials and methods. Genetic polymorphisms of VRD, IL6 and IL10 were investigated in Italian adults affected by PD. 571 cases classified according the criteria of the American Academy of Periodontology were included. All patients were Italian coming from three areas according to italian institute of statistics (ISTAT) (www.istat.it/it/archivio/regioni). The sample comprised 379 patients from North (66%), 152 from Central (26%) and 40 of South (8%).
Results. No significant differences were found among allele distribution.
Conclusion. Chronic PD is a complex disease caused by a combination of genetic susceptibility, patients habits (oral hygiene, smoking, alcohol consumption) and oral pathogens. In our report no differences were detected among three Italian regions in allele distribution.

Key words: periodontal disease, genetic susceptibility, periodontitis, oral disease, population.

Introduction

Periodontal disease (PD) is a multifactorial illness in which environment and host interact. The genetic component plays a key role in the onset of PD, in fact the genetic compound can modulate the inflammation of the mucous membranes and the loss of alveolar bone. The role of genetic susceptibility could impact on the clinical manifestations of PD, and consequently on prevention and therapy of this disease.
PD is a chronic and multifactorial disease caused by pathogens, aggregated in biofilm along gingival margin and sulcus. Periodontopathogenic bacteria and in particular the "red complex" species (i.e. *Porphyromonas Gingivalis, Tanerella Forsythia* and *Treponema Denticola)* may cause gingival inflammation, which may lead to the destruction of the periodontal ligament and the adjacent supporting bone, resulting in tooth loss (1-7).
Despite PD is very prevalent in all populations, only 10 to 20% of patients develop severe forms of PD, leading to teeth loss. The manifestations of different forms of PD are consistent with the different genetic susceptibility of each individual (8-11).
PD is characterized by the destruction of the supporting tissues of teeth starting by a change

of biofilm bacteria composition (from aerobic to anaerobic) and triggering the immune response. The virulence of pathogens of the bacterial species involved influences the intensity of the host's response to infection. Some species were found to be more prevalent in some types of PD. However, the same periodontal bacteria may or may not cause the occurrence of PD. So, it's clear that genetic factors could play a crucial role in modulating different forms of PD. Genetic factors of PD have been previously studied. Some genes were investigated to be responsible for susceptibility to PD. PD is a multifactorial disease, so genetic factors and environment factors (oral hygiene, smoking, stress diet, etc.) interact each other to develop this disease (6, 12-19).

Investigations about genetics and PD started about 30 years ago. The host immune response to the periodontal bacteria is mediated by genetic factors. The relationship between genetic and pathogens may be considered fundamental element in pathogenesis and progression of PD. The aim of the present study was to investigate the distribution of host genetic alleles in three geographic areas of Italy: North, Center and South. Specifically, polymorphisms of IL6, IL10 and VRD genes are investigated.

Materials and methods

The present study was conducted at different Italian private practices between February 2013 and 2017. The sample comprised of 571 patients all diagnosed with PD. The inclusion criteria were as follows, age >18 yrs., probing depth of 3 mm or more. The diagnosis of chronic periodontitis was based on the criteria established by the American Academy of Periodontology, which states that the patient must have at least one site with a probing depth and clinical attachment loss ≥ 4 mm. The exclusion criteria were medically compromised patients, patients who have been administered antibiotic or antimicrobial in the past 6 months, pregnant and lactating mother. The three areas included Italian regions according to italian institute of statistics (ISTAT) (www.istat.it/it/archivio/regioni). The sample comprised 379 patients from North (66%), 152 from Central (26%) and 40 of South (8%) of Italy.

Table 1 - Single nucleotide polymorphism (SNP) assay.

Gene	SNP ID	Alleles A/a
IL6	rs1800795	G/C
IL10	rs1800872	C/A
VDR	rs731236	T/C

Sub-gingival plaque samples of the four sites of greatest probing depth in each patient were used to obtain genetic testing. Sterilized n. 60 paper tips were inserted to the depth of the pocket, left in place for 30 seconds, transferred to a sterile tube and sent for subsequent DNA extraction and polymerase chain reaction (PCR) analysis.

Single nucleotide polymorphism (SNP) assays were selected using the Applied Biosystems SNPbrowser Software (Applied Biosystems, Foster City, CA, USA) (Table 1). Genotyping were performed using an ABI PRISM 7500 Sequence Detection System and TaqMan chemistry according to the manufacturers' protocols (Applied Biosystems) (11, 12).

SPSS program was used to perform statistical analyses. A 5% level of significance and 95% confidence interval were used for all statistical tests.

DNA extraction

After collection, two paper probes were processed for bacterial DNA extraction, by using the GenEluteTM Bacterial Genomic DNA Kit (Sigma-Aldrich, St., St. Louis, MO, USA) and following the manufacturing procedures. Briefly, to isolate DNA, samples were incubated with lysozyme in a specific lysis buffer and, sub-

sequently with proteinase K. Later, extracted DNA was purified by spin-column method.

Real-Time Polymerase Chain Reaction

PCR processing was performed as previously described (12-15).

Results

Periodontal specimens from 571 patients were analyzed to genotype of IL6, IL10, VDR genes in the three different areas (North, Centre, South). As reported in Figures 1, 2, 3, no differences in prevalence and distribution of IL6, IL10, VDR alleles were found among PD patient in the three different areas by mean of t-test.

Discussion

Chronic PD is a multifactorial disease related to patient's habits (oral hygiene, smoking, alcohol consumption) and oral pathogens that interact with genetic susceptibility. Here we considered the allelic distribution of IL6, IL10 and VRD in three geographic areas of Italy.

Previously some studies established a strong association between PD recurrence and individual genetic susceptibility (20, 21), but in some cases the sample was not very wide so that an investigation on a large sample size can help in understanding disease pathogenesis. Since the immune system plays an important role in the pathogenesis of PD, the identification of specif-

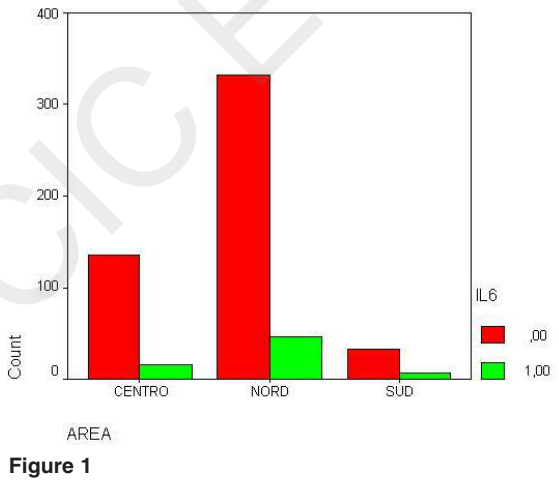

Figure 1
T-test results comparing IL6 variant allele carriers between three Italian geographic areas (Centre, North, South Italy).

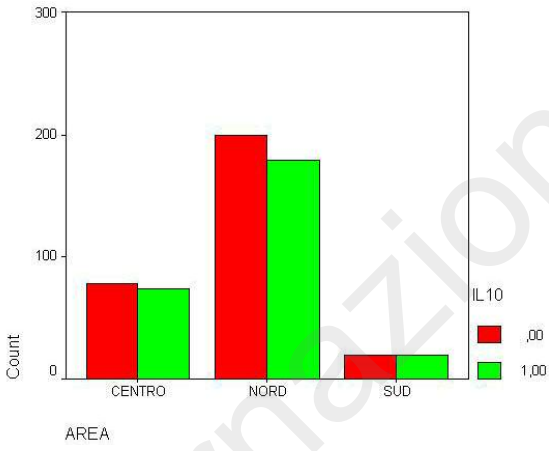

Figure 2
T-test results comparing IL10 variant allele carriers between three Italian geographic areas (Centre, North, South Italy).

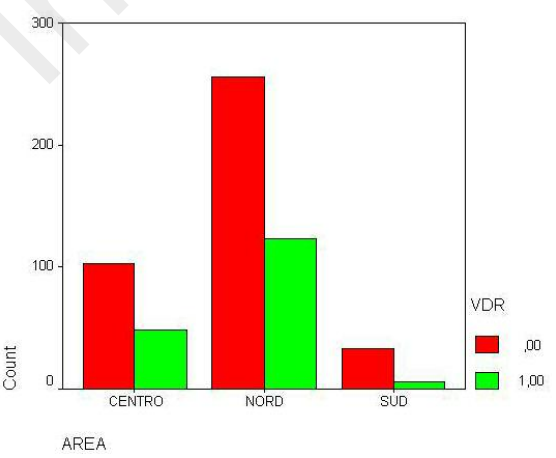

Figure 3
T-test results comparing VDR variant allele carriers between three Italian geographic areas (Centre, North, South Italy).

ic alleles can help in prevention and treatments. In addition bacterial loading and types are of paramount importance in the onset of the disease. Infection can happen with high frequencies in bone regeneration (22-25) also after cancer resection (26-30). In some pediatric conditions can be useful to have a low bacterial loading especially in syndromic conditions (31-39).

Our research studied the geographic distribution of variant alleles of IL6, IL10 and VRD genes in a wide Italian population sample. The lack of statistical differences demonstrated an uniform distribution of alleles in Italy.

Previous studies discussed the association between IL-6, IL-10 and VDR and periodontitis. In a recent study on a Brazilian sample (40), was investigate the association between single nucleotide polymorphisms (SNPs) in the IL10 gene and chronic periodontitis (CP) and aggressive periodontitis (AgP). Analysis of SNPs and haplotypes in the IL10 gene did not present any significant association with AgP or CP.

As regard VDR a previous studies focus on the association in Jordanian population (41) especially it investigates if VDR gene polymorphisms are associated with chronic periodontitis (CP) and aggressive periodontitis (AgP) in a Jordanian population. A total of 99 patients with CP, 63 patients with AgP, and 126 controls were genotyped using PCR-restriction fragment length polymorphism (RFLP) for BsmI, ApaI, and TaqI single nucleotide polymorphisms (SNPs). The analysis revealed that inheritance of the BsmI bb genotype or the ApaI aa genotype was associated with increased risk of developing CP but with reduced risk of developing AgP. This study supports an association of VDR gene polymorphisms with CP in a Jordanian population.

As regards IL-6 a recent study conducted in Japan (42) evaluates whether the alteration of interleukin-6 (IL-6) gene promoter methylation in the gingival tissue (GT) and peripheral blood (PB) is unique to chronic periodontitis (CP). Authors concluded that the increased expression of IL-6 gene transcription may be related to IL-6 promoter hypomethylation in the GT from CP patients.

It should be remembered that allelic frequencies vary in different population so that replicative studies on different samples are needed before can be clearly stated.

In addition further studies should be performed to establish the relationship between periodontal patogens and peri-implantis. Tooth replacement with implants is a well-known technique used worldwide in the last 40 years (43-80). There are some variables which can be shared between PD and peri-implantitis. In fact, the bacteria of periodontal disease may worsen the implants survival rate (61, 62, 64, 81-92, 93).

In conclusion, studies on crevicular biomarkers are a promise tool to discover new diagnostic markers. Genetic background plays a role in the onset of PD. No differences in allelic distribution of IL-&, IL-10 and VDR are detected among three geographic areas of Italy.

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