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GENE-GENE INTERACTION AMONG CYTOKINE POLYMORPHISMS INFLUENCE SUSCEPTIBILITY TO AGGRESSIVE PERIODONTITIS

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Aggressive periodontitis (AgP) is a complex multifactorial disease: bacterial infection is the primary etiologic agent, but also other host factors are involved, in particular the immune system seems to play an important role in the pathogenesis.

Gene-gene interaction is a general ubiquitous component of the genetic architecture of complex diseases and it is quite reasonable to expect that gene-gene interaction may play a crucial role in periodontitis too. The purpose of this paper was to apply, on a dataset of candidate gene polymorphisms for AgP, different multivariate analysis tools, with the aim to infer biological structures from genetic markers by means of an epistatic analysis.

Our sample is composed by 122 generalized AgP patients and 246 systemically healthy controls, recruited among subjects seeking care for periodontal treatment at three different Italian centers. We focused our attention on 28 polymorphisms, all lying in genes involved in inflammation and/or immunity response. Genotyping was performed using MassArray high-throughput DNA analysis with MALDI-TOF mass spectrometry (Sequenom, Inc., San Diego, CA).

We made a case-control association analysis with PLINK. Subsequently we analyzed combined genotypes using both parametric algorithms, such as General Discriminant Analysis (GDA) and Generalized Linear Model Analysis (GLZ), and the non parametric Multifactor Dimensionality Reduction (MDR) approach.

Our results confirm an important role of IL-6 in susceptibility to AgP: IL-6(-572) variant shows a strong independent effect ($p<0.001$) whereas IL-6(-6106) and IL-6(-1480) contribute to the disease interacting with IL-18 ($p<0.001$), IL-4 ($p<0.001$) and, less significantly, with IL-2 ($p=0.04$). We highlight also a significant contribute to AgP susceptibility of Fc gamma receptor gene variants both independently and as combined genotype: FCGR2A*C-FCGR3B*C shows an increased effect on susceptibility to AgP ($p=0.003$) and this is not attributable to LD between the two polymorphisms, since the two markers are in complete equilibrium.

Two other interesting results emerge: an involvement of Selenoprotein S gene SEPS1 in the determination of AgP, both as independent factor ($p=0.005$), and in association with IL-2 ($p<0.001$); and a relation between Tumor Necrosis Factor Surface Receptor 1 gene and AgP in association with IL-2 ($p<0.001$). At the best of our knowledge, this is the first evidence reported in literature showing a potential association of these latter genes and AgP susceptibility.

As a last consideration, none of the analyses performed revealed an involvement of Interleukin-1 cluster genes, the most studied factor in periodontitis, in determining the pathological phenotype. This is consistent with our previous findings in a similar Caucasian sample.