Author’s response to reviews

Title: Immunomodulatory factors gene polymorphisms in chronic periodontitis: An Overview

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Author’s response to reviews:

Dear Editor

Thank you for your attention and for revising our article. All revisions to the manuscript are clearly highlighted so that they are easily identified within the text of the manuscript.

Reviewer reports:

Stefan Reichert (Reviewer 1): The authors conducted a literature search to evaluate genetic risk factors for chronic periodontitis. From my point of view, the work has methodological deficits and the linguistic quality is not good.

Thank you for your kind comment. The present study is a simple review and is not a systematic review or meta-analysis. Therefore, contrary to structured studies and meta-analysis, only studies that played a prominent role in the results of the periodontal studies were selected in recent years. We did not limit ourselves to a specific time frame and did not limit ourselves to a specific time frame.

Abstract

The abstract in the present form is not well structured. I would divide the abstract as follows: Background, aim, methods, results conclusions.
Thank you for your kind comment. It was done.

Introduction

Polymorphisms in genes can influence not only the amount of cytokine produced, but also its composition. This depends, among other things, on the position of the polymorphism on the gene, for instance promoter, coding region, introns etc..

Thank you for your kind comment. According to the studies, Polymorphisms seem to affect both the amount of production and the structure of the cytokine and we confirm this. In this study, the relationship between polymorphisms and the levels of biomarkers has been investigated; because, as we found out, there was no study on the function of polymorphisms in the structure and composition of cytokines and its relation with periodontitis.

Main text

How did the authors carried out the literature search? For instance, which databases (e.g. medline) were used, which keywords were used, according to which quality criteria the cited studies were selected.

Thank you for your kind comment. As mentioned above, the present study is a simple review and is not a systematic review or meta-analysis. Only studies that played a prominent role in the results of the periodontal studies were selected in recent years using medline, scopus, science and

The text should refer to Table 1.

Thank you for your kind comment. It was done in introduction, page 4.

The authors should try to give the rs numbers for the listed SNPs.

Thank you for your kind comment. Using the rs numbers may confuse the reader because over 99% of the articles and reports about polymorphisms do not use rs numbers. As we found, the best way to name SNPs is to use the replacement type and its address in genome because this method is very familiar, and is easy to see the type and position of the sequence change.

Page 10 line 246: What means "Stereological analysis of interdental gingiva…?"

Thank you for your kind comment. Stereology is the three-dimensional interpretation of two-dimensional cross sections of materials or tissues. It provides practical techniques for extracting quantitative information about a three-dimensional material from measurements made on two-
dimensional planar sections of the material. Stereology is a method that utilizes random, systematic sampling to provide unbiased and quantitative data. It is an important and efficient tool in many applications of microscopy such as biosciences including histology, bone and neuroanatomy. In addition to two-dimensional plane sections, stereology also applies to three-dimensional slabs, one-dimensional probes, projected images, and other kinds of 'sampling'. It is especially useful when the sample has a lower spatial dimension than the original material. Hence, stereology is often defined as the science of estimating higher-dimensional information from lower-dimensional samples.

Page 13 line 315: The first bacterial name should be capitalized, for instance "Prevotella intermedia". In many journals, bacterial names must be written in italics.

Thank you for your kind comment. It was done in entire text.

Summary and conclusions

What could be the reasons for the inconsistent results regarding the investigated SNPs? Here I am thinking of ethical differences, differences in the selection of patients and control subjects, differences in the number of subjects examined, etc.. The results of genome-wide association studies should also be taken into account. In the authors' opinion, when would an SNP be suitable for the clinical diagnosis of CP and what therapeutic consequences would result from a genetic risk assessment?

In general, the entire text should be revised by a native speaker, as some sentences are incomprehensible and also spelling errors occur.

Thank you for your kind comment. As you mentioned, important reasons for the inconsistent results regarding the investigated SNPs are ethical differences, differences in the selection of patients and control subjects, differences in the number of subjects examined, etc. As we found, significantly, the studies demonstrate that the ethnicity more than other factors may affect the carriage rate of SNPs among different population. Therefore, possible positive associations between a SNP and disease within one population may not necessarily be extrapolated to other populations. To confirm this, larger populations should be investigated. And meta-analysis studies are also influential. In regard to the genome-wide association studies, there is not suitable study about mentioned SNPs which could be matched to current study.

SNP in sort polymorphism data can be used as molecular marker and based on you can make a diagnostic kit for pharmacogenomics and prediction of disease. But polymorphism may be
unique. If you want to use SNP marker as a Diagnostic tool, it should be present in genic region which will influence the phenotype (in other words it should be an FNP). So when you want to use a SNP as a diagnostic marker, first thing one should do is performing sequence alignment between two differently expressed phenotypes from the same region of sequence. Once if you can identify an SNP in any of the two sequences due to amino acid codon is changed or a stop codon is introduced then you can use it as diagnostic marker. This just identification, to validate this you can design an allele specific marker or design a pair of primers perform genotyping experiment using real time PCR or go SSCP. Successful GWA studies are the most visible and exciting outcome of HapMap which has also been invaluable in developing genotyping and analytic methods to realize advances in the prevention and treatment of common diseases. The tool of sequencing enables scientists to pinpoint functional variants from association studies and improve the knowledge available to researchers interested in evolutionary biology, and hence may lay the foundation for predicting disease susceptibility and drug response. Linguistic quality of the text improved by a native speaker.

Vetriselvi Venkatesan (Reviewer 2): Authors have complied the published works on various cytokine gene polymorphisms and CP, the paper has good data on various studies from different countries. Though the manuscript is well written it requires some minor corrections.

1. The title of the manuscript is cytokine gene polymorphism and the authors have included vitamin D receptor in the review, authors have to justify on what basis Vitamin D polymorphisms in included.

   Thank you for your kind comment. We corrected the title.

2. Line 31 - The sentences -" Polymorphisms have sophisticated relationships with each other" makes no meaning it can be deleted

   Thank you for your kind comment. It was deleted.

3. Line 96 - "+2018" explain?

   Thank you for your kind comment. It means IL1RN+2018 SNP.
4. Line 98 - authors have mentioned .......d is in linkage disequilibrium with IL-1α+4845G/T polymorphism in exon 5 (more than 99%), there is no reference for more than 99%.

Thank you for your kind comment. It was deleted.

5. Throughout the manuscript the authors have used the word carriage rate, does it mean frequency?

Thank you for your kind comment. Yes it means frequency.

6. Line 147 - have an important effect on immunization nd must be considered can be deleted.

Thank you for your kind comment. It was deleted.

7. Line 160 - Explain - 174R allele

Thank you for your kind comment. It was corrected.

8. How the SNPs can change the signaling pathways of Wnt/b-catenin, p53 and JAK/STAT and induce CP, has to explained in detail. (Line 374)

The Wnt/b-catenin, p53 and JAK/STAT are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors. For example, signaling by the Wnt family of secreted glycolipoproteins is one of the fundamental mechanisms that direct cell proliferation, cell polarity and cell fate determination during cell development and tissue homeostasis. As a result, mutations and SNPs in the Wnt pathway are often linked to human birth defects, cancer and immune diseases. A critical and most studied Wnt pathway is canonical Wnt signaling, which functions by regulating the amount of the transcriptional co-activator β-catenin that controls key developmental gene expression programs. In regard to the JAK-STAT signalling pathway, it is a chain of interactions between proteins in a cell, and is involved in processes such as immunity, cell division, cell death and tumour formation. The pathway communicates information from chemical signals outside of a cell to the cell nucleus, resulting in the activation of genes through a process called transcription. There are three key parts of JAK-STAT signalling: Janus kinases (JAKs), Signal Transducer and Activator of Transcription proteins (STATs), and receptors (which bind the chemical signals). Disrupted
JAK-STAT signalling may lead to a variety of diseases, such as skin conditions, cancers, and disorders affecting the immune system such as CP.