Reviewer's report

Title: Replication of the Association of Chromosomal Region 9p21.3 with Generalized Aggressive Periodontitis (gAgP) Using an Independent Case-Control Cohort

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Reviewer: Jamal M Stein

Reviewer's report:

The submitted manuscript describes a confirmative case control study on the association of four SNPs of the chromosomal region 9p21.3, which has been considered as genetic susceptibility locus for coronary heart disease (CHD), in 130 Caucasian patients with generalized aggressive periodontitis (gAgP) compared to 339 Caucasian periodontitis-free control subjects. The authors confirmed significant associations to three of four SNPs (rs1333048, rs496892, rs2891168) in their own study groups. Using a meta-analysis (fixed effects model), the authors’ data and those of a previous study (Schaefer et al. 2009) were combined resulting in a higher statistical significance for the associations of all four SNPs compared to both individual studies. Based on these findings the authors substantiated the hypothesis of a shared genetic susceptibility locus for CHD and gAgP, which might be commonly based on a decreased expression of particular cell-cycle inhibitor encoding genes promoting a pro-inflammatory and pro-proliferative phenotype.

This is a well designed study and a well written paper with valuable data on the genetic background of two disease entities that are supposed to have mutual influence. There are only a few comments.

Major Compulsory Revisions:

1. All study participants have been examined at different centres (different locations in Germany and Northern Ireland). How many examiners were involved? Was there an inter-examiner calibration performed as to periodontal measurements (CAL values) and/or estimation of radiographic bone loss?

2. As explained in the discussion, the predicted risk haplotypes may account for gAgP susceptibility to a certain degree; however, lifestyle factors and other genetic polymorphisms may influence disease manifestation as well. Thereby, smoking is one of the most important dose-dependent confounders for periodontitis. Please provide more detailed data on the definition of smoking status and its incorporation in the multivariable analyses and, if possible, on the amount of smoking.

3. The discussion would benefit from a few sentences regarding the limitations and clinical implications of the findings of this study.
**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.