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: Paula Trevilatto

Reviewer's report:

The manuscript is well justified as presents its background. It replicates findings of an association between the chromosomal region 9p21.3, containing three cell-cycle inhibitor encoding genes, and generalized aggressive periodontitis (gAgP). Replication studies in the context of genome-wide association (GWA) approaches are mandatory and may add relevant pieces of information on real significant associations. Also, the authors claim that gAgP shares underlying genetic background controlling common physiopathologic mechanisms together with environmental and behavioral risk factors with coronary heart disease, based on the association of this chronic disease with the same mentioned chromosome region in several GWA studies.

The paper is also well-designed and counts on a reasonable number of individuals well characterized in terms of phenotypes. The statistical analyses are appropriate and make use of adequate software and tools. The authors propose the multiplicative genetic model as the most plausible one for such an association.

Discretionary Revision:

1) Obesity is not considered a known risk factor for gAgP as it is for heart diseases. In this context, shouldn’t the authors consider removing this condition from examples of common risk factors between both gAgP and coronary heart disease in the Introduction section on the 4th page, second paragraph, line 7?

2) The authors ascertain that the four analyzed SNPs were found to be in Hardy-Weinberg equilibrium (HWE) (Results, page 8, first paragraph), but in table 2 p values of SNP rs496892 for all and unaffected subjects are smaller than 0.05. Are the p values correct? If yes, this marker is not in HWE. I suggest you include a brief comment on that in the Discussion section and also this information in the appropriate part of the Results. Thus, this alteration should be simple once this SNP was not associated with gAgP and does not belong to the LD block associated with it.

3) Are the authors sure that the SNP ascertained rs496892 for the studies of Greifswald and Schaefer et al. cohorts (Table 1), whose alleles were termed A/G and C/T, is the same one? If yes, I suggest you consider the A/G alleles, with their frequencies: 49 and 51% frequencies are very close and, in my opinion, are not “opposite” as the authors mention in the Results, first paragraph.
4) Using adjusted SNP data, shouldn’t analyses be adjusted by the covariate sex as well, once the frequencies of males and females invert in the case and control subjects (Results, page 8, last paragraph)?

5) There is a parenthesis which should be removed after the last word of the first paragraph on page 10 (after respectively).

6) In the Discussion section where is figure 1 referenced? Shouldn’t it be placed in the first paragraph, on page 11?

7) The authors could include some information about ANRIL gene in the Discussion section, once most of the SNPs, including the putative functional ones, are inside and nearby this gene. Why didn’t the authors perform the genotyping of rs10757278 and rs1333045 SNPs? Haplotype analysis could be done with their own results instead of using data from the Hapmap.

8) In the Conclusions section: …an association between the chromosomal region 9p21.3 AND gAgP…

**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'