Reviewer's report

Title: Association Analysis Identifies ZNF750 Regulatory Variants in Psoriasis

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Reviewer: Judith Bergboer

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The study investigates variants in the ZNF750 gene region and their possible association with psoriasis by resequencing a large number of cases and controls. Forty-seven variants were found but none of the discovered variants by itself showed association with psoriasis. Haplotype analysis showed that for the common variants 2 haplotypes were associated with disease (P=0.0024 and P=0.0311). For the rare variants this was the case for the 5’ regulatory variants (P=0.041). Also data about mRNA and effects of the 5’UTR variants on promoter activity are presented. The clinical characterization of 7 (out of 10) patients with a 5’UTR variant was assessed, five of seven patients showed some similarities in disease phenotype. Lastly, the segregation over the families was discussed; for most variants no clear segregation patterns were present.

General remarks
The study is much more elaborate than the previous studies of this gene.
The manuscript is clearly written.
The authors are aware of the limitations of this study.

Major Compulsory revisions
1. Resequencing of candidate genes to find variants associated with complex diseases is a promising approach to identify functional mechanisms that would contribute to disease causation. In case the allele frequencies of these variants are low, large numbers of cases and controls are required. In this study a large number of variants were found but after correction for multiple testing none of the individual variants was found to be significantly associated. In an attempt to investigate if haplotypes of rare variants were associated with disease, six of these were examined and only the 5’-regulatory variants reached borderline significance. Was the p-value corrected for multiple testing?

Similarly, how were the empirical p-values of the common haplotypes obtained?

2. In the Results section the segregation analysis is quite extensively shown. The study set up was a case-control study. I don’t see the added value of the segregation analysis, because in complex diseases like psoriasis there are often no clear segregation patterns, and this is also the case in the presented analysis. The data on the (non)segregation of the 2233C>T variant with disease are anecdotal and do not contribute to our understanding of disease mechanisms. I would skip the last 4 lines of the Results section.
3. In the Methods, section statistical methods, HWE was calculated and the threshold was set at p=0.001. Why?

4. What do you mean with a biological triplicate? Did you actually use 3 different keratinocyte donors. Or did you perform 3 independent experiments with one donor cell line?

5. In Figure 2, could you please clarify the large differences in SD in the 5’UTR variant vectors and WT luciferace activity?

Discretionary Revisions
1. In the Results section the 2 isoforms of ZNF750 mRNA were introduced. The authors checked the presence of isoform A and B in several cell lines, but do not show the data. It would be illuminating to present this data. Moreover, it would also be informative in the PMA stimulations of primary keratinocytes to show which isoform is upregulated by PMA and to consider these two isoforms in the discussion section.

Minor Essential Revisions
1. Results, section association testing of identified variants last sentence states p<0.05, this should be p>0.05.

2. Table 2, please check cells Novel_15 and Novel_24 for F_case values.

Level of interest: An article whose findings are important to those with closely related research interests

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