Reviewer's report

Title: Polymorphisms of interleukin-21 and interleukin-21-receptor genes confer risk for autoimmune thyroid diseases

Version: 1 Date: 3 January 2013

Reviewer: Matt Simmonds

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Comments to Authors

I found that the manuscript by Zhang et al following up previously detected association at the IL-21 gene and its receptor IL-21R in a Chinese autoimmune thyroid disease (AITD) population was of interest and is definitely worthy of publication. However I do have some important points which require clarification before accepting this manuscript as detailed below:

Major comments:

Abstract and throughout the manuscript, the authors have put IL-21 and IL-21R in italic to represent they are genes and then written the word gene after them. If you put a gene name in italics you then do not need to write the word gene after. Can the authors please correct this throughout the entire manuscript.

Abstract and throughout the manuscript, Can the authors please present all OR and 95% CI to only two decimal places. Also through the manuscript the authors swap between having OR = XX and OR=XX and as such can the authors please choose one style and stick to it.

Abstract, Results, line 1, can the following be added the start of the sentence ‘For IL-21’ to help put the results in context.

Abstract, Conclusion, Can the authors please state the names of the Il-21 and Il-21R SNPs they found associated with AITD.

Introduction, paragraph 2, can the authors please provide some more detail on what they mean when they say ‘In autoimmune diseases, such as systemic lupus erythematosus (SLE) [3], rheumatoid arthritis (RA) [4] and Sjogren’s syndrome (SS) [5], animal and clinical researches disclosed the disregulations of IL-21 and IL-21R.’ such as how are they dysregulated?

Introduction, paragraph 3, the authors’ state ‘In HapMap-CEU population, IL-21 included in a large block (480kb) of linkage disequilibrium which showed genetic associations with type 1 diabetes mellitus (T1DM) [7,8], RA [8], juvenile idiopathic arthritis (JIA) [9], psoriasis and psoriatic arthritis(PA) [10].’ Can the authors please explain a little more what they mean by this point, such as have other genes in the region been associated with these diseases and if so can the authors give an idea of how many genes are encompassed within this 480kb
block.

Introduction, paragraph 4, the authors state 'Vincent Plagnol [17] reported that the SNPs in chromosome 4q27 were associated with the GD susceptibility.' Can the authors please state which SNPs were associated with GD and also state that this was a Caucasian dataset.

Materials and Methods, 2.2 Genotyping, paragraph 2, Why did the authors select 4 SNPs in IL-21 and 2 SNPs in IL_21R to screen? Did these SNPs represent Tag SNPs which captured all common variation in these gene regions? If so can the authors please state this and if not can the authors please perform Tag SNP screening of all common variation in these genes.

Results, 3.1 Association of the IL-21 gene polymorphisms with GD and HT, paragraph 1, can the authors need to also report HWE for their GD and HT cases as well as for their controls.

Results, 3.2 Association of the IL-21R gene polymorphisms with GD and HT, paragraph 1 currently reads 'As shown in Table 2, the minor allele frequencies of rs3093301 and rs2285452 in IL-21R gene were 47.1% and 11.5%, respectively, in controls, 48.0% and 11.0% in GD patients and 42.3% and 7.9% in HT patients. None of the alleles exhibited any association with the genetic susceptibility to GD or HT (rs3093301: PGD = 0.752, PHT = 0.138; rs2285452: PGD = 0.797 PHT = 0.068).’ as the results are negative can this paragraph be altered to ‘As shown in Table 2, the rs3093301 and rs2285452 SNPs in IL-21R showed no association with GD or HT (P = 0.797-0.068).’.

Results, 3.4 Gene-gene interaction analysis in HT, due to the small number of HT samples screened I am not sure that the authors would have had power to undertake such an analysis and think it would be better to remove this whole paragraph and any associated discussion of these results from the manuscript.

Discussion, paragraph 3, can the authors please also comment on who your study supports or does not support the findings by Plagnol et al.

Discussion, paragraph 3, The authors talk about the power of their datasets by saying they have 0.8. This value alone is meaningless can the authors please state at what OR this is and for what SNP minor allele frequency this is applicable. As such it would be helpful for the authors to assay what effect size their study could exclude for IL-21R to provide greater clarity for the reader.

Discussion, paragraph 4, the authors need to add a few lines saying that replication of these associations is required in larger independent datasets to verify these results.

Throughout the manuscript, although the English is of a high standard within the manuscript can the authors please just double check the manuscript for consistency of abbreviation and typos

Minor comments:
Introduction, paragraph 4, can ‘Vincent Plagnol [17] reported’ can it be changed to ‘Plagnol et al [17] reported’.

Introduction, paragraph 4, the authors state ‘Vincent Plagnol [17] reported that the SNPs in chromosome 4q27 were associated with the GD susceptibility.’. can ‘chromosome’ be changed to ‘chromosome’.

Results, 3.1 Association of the IL-21 gene polymorphisms with GD and HT, paragraph 1 and 2, these two paragraphs need to be combined as one larger paragraph.

Discussion, paragraph 1, line 2, please change ‘IL-21 receptor’ to ‘IL-21R’ to make it consistent with the rest of the manuscript.

Discussion, paragraph 1, the authors state ‘The dysregulation of IL-21 and IL-21R plays a role in multiple immune-mediated diseases, including SLE, psoriasis, RA and other chronic inflammatory diseases. Like other autoimmune diseases, GD and HT are chronic conditions initiated by the loss of immunological tolerance to self-antigens. Researchers have showed many immune-related genes may participate in the development of AITD.’ Can references be added to the end of each line and can ‘researchers’ be changed to ‘researchers’

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