Author's response to reviews

Title: Familial autoimmunity: a meta-analysis

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Author's response to reviews: see over
The authors report on a systematic review and meta-analysis on familial aggregation of autoimmunity in five major autoimmune disease groups (rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease (AITD), multiple sclerosis and type 1 diabetes mellitus). They included 47 studies and found significant familial aggregation regarding the specific disease but also regarding autoimmune disease in general with odds ratios between 1.77 to 1.96.

The authors conclude that familial autoimmunity is a consistent condition observed in the major ADs.

This is an interesting topic and the authors have put in a lot of work here.

Major compulsory revisions:

1. Did you consider unpublished data? And if so, please label them accordingly.

R/ We did not include unpublished data in the search strategy. This issue is clarified in the “Methods” section: “Articles were included if they fulfilled the following conditions: …articles were published as full articles and, as mentioned earlier…” A new sentence was added: “unpublished data were excluded”

2. The conclusion needs to be adjusted "Its study will help to decipher the common mechanisms of ADs.". It is not clear what the authors mean. The conclusion should be based on the results found in this paper. Did the authors mean that THIS study will help to decipher the common mechanisms of AD? I don’t think that this is the case.

R/ This point is now clarified in the revised manuscript (see abstract)

3. The abstract results should clearly show the likelihood (odds ratios) for the familial aggregation of the specific disease (for example, how much more likely is it to have MS if another family member has MS) and the odds ratios for the familial aggregation of autoimmune disease in general (how much more likely is it to have an autoimmune disease if another family member has an autoimmune disease). These 2 aspects should be the backbone of this paper, and also be mentioned in the results section of the abstract (briefly).

R/ This article deals with the second question raised by the reviewer. This point is now clarified in the revised manuscript.

4. Statistics: The transformation of effect sizes is explained in a rather lengthy but still not sufficiently clear way. Was the aim to finally have all effect sizes as odds ratios? Please state how you transformed risk ratios to odds ratios, etc.
We obtained Risk Ratios and Odds Ratios depending on the type and acquisition of data revised. As mentioned in the “Methods” section: “Effect size was calculated based on studies that reported an OR with its respective 95% CI and from raw data given by case-control and cohort studies”. A second effect size was calculated with studies that only showed the RR and the respective 95% CI and if raw data from cohort studies was available.”

We added into the paper a new paragraph: “In order to perform the analyses, the association measures were transformed to log values, and then the results were converted back to ratio values for presentation.”

5. Statistics: You state that "Additional meta-analyses were done for studies with complex data structure and noncumulative results since the information for the different effects was not totally independent." This needs further explanation. What do you mean with complex data, and what do you mean with non-cumulative results? What kind of meta-analyses did you do in this situation?

R/ We refer to cases where studies contribute more than one effect size to the meta-analysis. These usually fall into one of the following types: multiple independent subgroups within a study, multiple outcomes or time-points within a study or more than one comparison group within a study (Introduction to Meta-Analysis -Statistics in Practice. Eds.: Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Part 5. Complex Data Structures. p 215-244. John Wyley & Sons, ltd. United Kingdom 2009. ISBN-10: 0470057246).

The first case of a complex data structure is the case where studies report data from two or more independent subgroups. This was the most prevalent case in our analyses.

As an example, Heminki et al (2009) reported separately the aggregation. For type 1 diabetes in offspring whose parents were diagnosed with autoimmune disorders, they gave RR for son and daughter by father and mother. In conclusion, they gave four results for a same disease. The subgroups were included in the analysis. An additional example corresponds to subgroups published into the same paper where the authors showed different ORs for each autoimmune disease in first degree relatives of a proband with a specific autoimmune disease (i.e. Deretzi 2010, showed more than 20 different ORs corresponding to each autoimmune disease in FDR of probands with multiple sclerosis).

We modified the sentence as follows: “Additional meta-analyses were done for studies with complex data structure and noncumulative results since the information for the different effects was not totally independent. This is the case of studies reporting multiple independent subgroups (i.e., aggregation for son and daughter separately) within a study”

6. Statistics: Fixed and random effects models were both used. I would prefer to
use random effects models in general, unless we can assume that there is neglectable between study heterogeneity which is rarely the case. You state that "The selection of the computational model was done based on the expectation that the studies shared a common effect size." This sentence should be re-written or deleted, it is not very clear what it means here. A common effect size is assumed in a fixed effects model. I am not sure whether this is what you wanted to explain? Again, in general I would prefer random effects models.

R/ We certainly agree. The random model was used, and the text was revised. The following paragraph was deleted: "The selection of the computational model was done based on the expectation that the studies shared a common effect size." And "Fixed and random effects models were both used."

The following sentence (included in the previous version) agrees with the reviewer opinion and remains in the revised manuscript: “The random effect model was preferred because it accepts that there is a distribution of true effect sizes rather than one true effect, and assigns a more balanced weight to each study. It was also used because all the studies were considered to be unequal in terms of specific ADs.” Data show in Table 2 as well as in all the forest plots correspond to results obtained by the random effect model.

7. The method used for the fixed or random effects model needs to be mentioned (for example, DerSimonian&Laird approach?)

R/ The method implemented for estimating the variance between studies was the “method of moments” or the “DerSimonian and Laird method”. This method has the virtue that it is always qualitatively consistent with the heterogeneity test based on the Q statistic (that is, statistically significant heterogeneity is always accompanied by a positive estimate of $T^2$). (Borenstein M, Hedges LV, Higgins J PT and Rothstein HR. 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Method, 1: 97–111. doi: 10.1002/jrsm.12)

The following sentence is now in the revised manuscript: "Heterogeneity was calculated by means of Higgins’s ($I^2$) tests. The variance between studies was estimated by the “DerSimonian and Laird method”.

8. In the abstract, you use odds ratios, in the result section, there are risk ratios. This is confusing. I would prefer consistent effect size measures throughout. If there were also case-control studies included and not only prospective studies as described in the method section, risk ratio is not appropriate effect size measures.

R/ Abstract was revised accordingly. In the revised manuscript a clarification about risk ratios and odds ratios was done. We detailed the respective effect size in the table 2 as well as in the supplementary material “Forest plots depicting risk ratios for familial autoimmunity in FDRs” which shows all the analyses resulting from the studies that included RR as an effect size.
9. The paper evolved from a narrative review which influenced its current shape. Nevertheless, the manuscript should be written more concisely and more clearly. The introduction should be shorter, the results section should focus more on the meta-analysis.

R/ The manuscript was modified accordingly

10. Table 2: number of studies is smaller than number of subgroups. What was the unit of analysis, the subgroups or the entire studies?

R/ See response to query 17

11. Table 2: Subject "FDR" versus "proband" is confusing. The proband is the index patient? The association is between index patient and his first degree relatives FDR? What does "subject" mean here?

12. Table 2: what exactly does table 2 show? The association between a specific disease and any autoimmune disease in a FDR?

R/ Table 2 was omitted because of redundancy. Figures 4-7 give the reader the same information. In addition, supplementary material contains all the analyses.

13. Table 3: worldwide prevalence of autoimmune disease. This is very important and interesting information but we have to make sure it is accurate. Worldwide would mean that the studies include a very broad range of countries, we know that AID vary considerably among different countries, for example MS prevalence with its north-south decrease etc. Second, you calculated a mean value based on ranges. This may be possible if you had confidence intervals, but for a range, this seems a little questionable, without any information on data distribution.

R/ Table 3, now Table 2, shows data according to refs. [2, 29-32].

14. Table 3: the statistical section does not describe how you calculated the pooled worldwide prevalence values.

R/ We previously included the description of this calculation in the results section: "In order to study aggregation we determined worldwide prevalences of ADs from four studies mentioned earlier [2, 29-32]. (Now Table 2). If a range was reported we arbitrarily calculated the mean." Now, we moved this paragraph to the methods section.

The modified paragraph in the results section corresponds to:

Aggregation
Several studies retrieved only reported prevalences of ADs in FDRs. Aggregation based on four studies mentioned earlier [2, 29-32] is shown in Table 3. Information on calculated aggregation for diverse ADs, in AITD, T1D, SLE, RA and MS, can be found on Table 3.
15. Table 4: This is very difficult to read and understand. The idea of a meta-analysis is to pool, summarise and digest current evidence. What do these numbers mean? You state that these are aggregations lambda. What does that mean exactly? The reader needs to see, what the likelihood of first degree relative is, if the index patient has a certain autoimmune disease.

R/ Table 4 (now Table 3) shows Aggregation results, also referred to as recurrence risk or lambda, $\lambda$. Meta-analyses are shown in figures 4-7.

16. It is not clear how many patients were included in these studies.

R/ A new supplementary table containing this information was included in the revised manuscript.

17. Forest plots: for figure 5 and 6 for example, it seems as if you have used subgroups as the unit of analysis. I am not sure why occasionally two subgroups have the exactly same characteristics (same Proband disease and same disease in FDR). What is the difference between these subgroups?

R/ Subgroups are the unit of analysis. In some cases there are more than one subgroups with the same characteristics (same Proband disease and same disease in FDR). Several papers report data from two or more independent subgroups in the same article (i.e., son and daughter separately; hypothyroidism and hyperthyroidism; simplex and multiplex families, etc).

18. A table with baseline characteristics of the individual studies (size, setting, design such as case-control or cohort study, etc) would help to get a better understanding and overview for the reader.

R/ A new supplementary table containing this information was included in the revised manuscript.

Minor discretionary revisions:

1. Abstract: multiple sclerosis (S), I would prefer to use MS as abbreviation for MS which makes more sense and is used in general.

R/ Abstract was revised.

2. Page 19: be consistent with decimal marker/separator, sometimes you use a comma, sometimes points ("a p-value 2-tailed: 0,047",...) Since the manuscript is written in American English, it should be points (0.047).

R/ Points are used as decimal marker/separator in the revised manuscript.
Quality of written English: Needs some language corrections before being Published

R/ Manuscript was revised by an English native speaker

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

Declaration of competing interests: None

Reviewer’s report

Title: Familial autoimmunity: a meta-analysis

Version: 2 Date: 12 November 2012

Reviewer: Didac Mauricio

Reviewer’s report:

The authors made substantial changes to the paper. Most of the changes requested by this reviewer were made. I have few additional comments to this new version of the manuscript.

-Minor essential revisions

I would recommend that the legends to figures 4 to 7 include enough information to be self-explanatory, i.e. the reader does not have to go back to the main text to interpret the content of the figures.

R/ We have modified the legends to figures 4 to 7 according to the reviewer suggestion (please see at the end of this text).
-Please, in the reference list, check the abbreviations of the journal titles. There are many that are not abbreviated. Please, follow the instructions for authors.

R/ We have modified the references according to the instruction for authors.

-Please, see my previous comment concerning figure 2. I strongly feel that this figure (now figure number 8) should be deleted. Alternatively, this could be included as additional supplementary material.

-Also, I recommend to delete figure 1.

R/ We consider both figures as illustrative and academic for clinicians interested in this manuscript. We kindly request the reviewer to allow us keep these figures. As mentioned previously, we believe that the figures give the non-expert reader a better understanding of familial autoimmunity as well as the distinction between similar familial syndromes.

-In the discussion, the authors seem to recommend screening of first-degree relatives of probands affected by these autoimmune diseases. As far as this reviewer knows, there is not consistent evidence-based information for recommending screening of autoimmune diseases in relatives of most autoimmune diseases. The main conclusion concerning this issue should be that further research is needed.

R/ The recommendation was omitted

-Discretionary revisions
I still think that the authors used too many abbreviations.

R/ Abbreviations were limited as much as possible.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests