Author’s response to reviews

Title: Familial autoimmunity: a meta-analysis

Authors:

Jorge Cárdenas-Roldán (jorge.cardenas.roldan@gmail.com)
Adriana Rojas-Villarraga (adrirojas@gmail.com)
Juan-Manuel Anaya (juan.anaya@urosario.edu.co)

Version: 2 Date: 24 October 2012

Author’s response to reviews: see over
Reviewer's report

Reviewer: Noel Rose

Autoimmune diseases have long been known to aggregate. A patient with one autoimmune disorder appears to have a greater risk of a second or even third autoimmune disease. In addition, in a family in which one case of autoimmune disease is diagnosed, a second or third genetically related member of the family is at somewhat greater risk of the same or even a different autoimmune disorder.

The purpose of this review article is to “reintroduce” the term “familial autoimmunity” for this latter form of autoimmune disease aggregation. The article is dedicated mainly to reviewing the large body of published literature describing the co-occurrence of autoimmune diseases within the family. There is also an extensive discussion of “polyautoimmunity” defined as the expression of more than one disease in a single affected individual.

The topic of the article is of great importance in the understanding of autoimmune disease. On the practical side, information about co-occurrence of autoimmune diseases is of great value in determining the risk of additional autoimmune disorders with some specificity and precision in a patient. Similarly, such studies are of great potential value in quantitating the risk of an autoimmune disease in related family members. From an investigative point of view, the information from studies of co-occurrence of autoimmune diseases has already been shown to be of value in identifying genetic traits that are common to several autoimmune disorders, including those that have a relatively modest genetic effect. Unfortunately, this review as presented does not well serve these purposes. The studies are listed with little or no evaluation. Most of them are too small to be of biologic or statistical significance and often lack controls. In addition, with respect to familial autoimmunity, no distinction is made between genetically based inheritance and common environmental exposures. No attention is given to degree of relatedness as an approximation of genetic concurrence. The data are useful only if related to the prevalence of each disease at a comparable age in the particular geographic area. Since most of the autoimmune diseases are relatively uncommon, large-scale studies in a particular population are necessary. The results are most useful if expressed quantitatively where the risk of a second or third disorder can be determined. With a few notable exceptions (e.g., type 1 diabetes and autoimmune thyroid disease), the relative risk of co-morbidity is usually very low. The recent studies by Eaton, et al provide a model of how these investigations can be appropriately carried out. The present review would be greatly strengthened if the authors go back to the original studies and determined whether they are large enough to draw statistically valid conclusions and whether appropriate control data on the epidemiology of each disease in the geographic area are provided. In assessing family histories, it is essential to consider confounding factors such as the likelihood that patients and families with multiple autoimmune disorders are more likely to receive medical attention and that family histories are likely to be biased if they are based on questioning only probands rather than normal controls.

Answer to reviewer: Noel Rose

Many thanks for your review and for your insights in our paper.

Our objective with this report is to make aware clinicians and researchers about the importance of Familial Autoimmunity. However we feel it is important to introduce the term of polyautoimmunity, multiple autoimmune syndrome, and familial autoimmune disease for the non expert reader. This leads us to reviewing the apparently large body of literature on autoimmune diseases. However, regarding familial autoimmunity, this literature is scarce, and as you mention in yours papers, the quality of such studies are not the best. We hypothesize that there is a lack of attention of clinicians and researchers for the presence of familial autoimmunity, and as such, few studies have been devised for this purpose. Although we cannot do much about it we can try to get across the message to clinicians and researchers in order to raise the quality of study design to be able to analyze familial autoimmunity as a trait i.e. re introduce the term familial autoimmunity.

As you suggested, we went back and reviewed the articles that were retrieved with our literature search, and for the purpose of quantifying familial autoimmunity in ADs that were chosen, we performed a meta analysis. We are aware of the limitations that the meta-analysis may have due to the fact of poor quality of the studies found. Nevertheless we must deal with this and we mention that constraint in our article. All your comments and queries were answered and incorporated into the revised manuscript.

We hope that the corrections done to our paper satisfy your doubts and enquiries. Again we are very grateful for your suggestions, comments, and criticisms.
**Answer to reviewer: Didac Mauricio**

We were delighted to have such a thorough review of our paper. Many thanks for your review and for your insights.

We will proceed to answer point by point in an ordered fashion.

- **Major Compulsory Revisions**

1. The authors performed a literature search with a systematic approach. There are essential data concerning the search that should be provided for any researcher potentially interested in reproducing the literature search. Please, provide the following information in the text:

   - Clarify whether only Medline and Embase were searched.
     
     *A/ Corrected. You can find this on page 10*

   - Also, please specify to which year the search dates back in each database.
     
     *A/ Corrected. You can find this on page 10*

   - State whether there was any language restriction (where articles in any language included?).
     
     *A/ Corrected. You can find this on page 11*

   - Did the authors search the reference lists of the 46 articles included to identify any additional relevant studies?
     
     *A/ Corrected. You can find this on page 11*

   - Concerning the 1,746 references identified, did the authors assess the abstracts (this is the usual way) or the full articles? Was each reference assessed only by one author or in duplicate?
     
     *A/ Corrected. The flow chart (fig 3) illustrates the search done. Pages 11-12 also offers more info on this particular issue.*

   - In systematic reviews, the use of truncating search terms is usual (for example, famil* instead of familial). This strategy is aimed at not missing potentially relevant studies. Did the authors use this strategy for the words (non-MeSH terms) familial, clustering and aggregation?
     
     *A/ Corrected. You can find this on page 11*

2. The literature search strategy included only the specific search terms for five autoimmune diseases. However, the authors state that they “did not constrain the search for the 5 ADs” and decided to include articles “if familial autoimmunity was assessed in other ADs”. The identification of articles on these other ADs probably retrieved a number of potential studies well below the number that could be obtained using a specific search for each given disease.
(as was done with the main five diseases). This means that the risk of bias is high and, also, that the conclusions reached may not be solid. Therefore, this should be acknowledged as an important limitation of the information provided for these other diseases. Actually, I would recommend to focus on the five major diseases proposed and to rearrange the content of the review. The authors may alternatively choose to include all other ADs under ‘Other ADs’ and they should then acknowledge the limitation of the information retrieved on these diseases.

A/ We appreciate your insights on this matter. If you could be so kind and read page 29 where we state this flaw that is caused by an arbitrary decision of choosing these five index diseases just as you suggested. As you may also read we focused even more on these index diseases. However, we feel that is important to show the articles we found for other autoimmune diseases. After all, this paper aims to draw attention on familial autoimmunity and to make clinicians aware of these entities.

- Minor Essential Revisions

1. In the second section of the article (The mosaic of autoimmunity), the second paragraph describes mainly the potential use of autoantibodies in disease prediction and prevention. Actually, this does not belong to the subject of the review. Thus, I would recommend to delete this section.

A/. Although it may seem that this deviates from the main purpose of our review we kindly ask the reviewer to allow us to keep this information. The reason for this is also an observation you did in a later part of your review; we believe that that part would benefit from a practical point of view for clinicians, as many clinicians who do not see autoimmune patients every day, may not be aware of the importance of auto-antibodies and the clinical importance of it.

2. Please, to be consistent throughout the different diseases, state at the beginning of all disease subheadings how many studies where identified.

A/. Corrected. You may find the number of articles at the beginning of each section

3. The information provided in figure 2 is already included in table 1. Therefore, the figure might be deleted.

A/. Even though it appears that the information is being repeated, we believe that the figure you mention (now figure 8 and updated) gives the non-expert reader a better understanding of familial autoimmunity. This is also aimed for clinicians who with a simple glimpse of the figure may be aware of which diseases first degree relatives may suffer.

4. The term ‘Grave’s disease’ should be changed to ‘Graves disease’ throughout the text.

A/. Corrected

- Discretionary Revisions
1. For the non-expert reader, it would be nice to have a more specific definition of the term ‘autoimmune tautology’ (second paragraph, page 4).

A/. Many thanks for interesting on the definition of “The autoimmune tautology”. A better definition was inserted in page 4.

2. At the beginning of page 7, the authors state that they adopt the terms polyautommunity and familial autoimmunity and refer the reader to figure 1. In my opinion, the figure does not add relevant information. Instead, it would be preferable to have additional text that expands on the two terms adopted.

A/. Both terms are concisely yet thoroughly described in the last part of page 5. Figure 1 is used to make conceptually clearer these definitions, how they do present in pedigrees and to show risk alleles such as HLA-DRB1

3. Under T1D (line 4), the authors probably meant ‘replicated’ instead of ‘duplicated’.

A/. Corrected

4. For the clinician, it would be relevant to have a section of the manuscript that summarizes the available evidence for screening of first-degree relatives of probands with any of the diseases. A section describing any available recommendations for or against screening in relatives would be very interesting.

A/. Besides the clinical importance from the section discussed earlier, and in agreement with your observation, we feel it is important to connect research with the clinical practice. Therefore the second paragraph of page 25 is devoted to this aspect of screening.

5. To the opinion of this reviewer, the use of an excessive number of abbreviations is not desirable (in the main text and also in figures and tables). The number of abbreviations should be restricted to those terms that are used more frequently in the text. Further, the abbreviation SSc is not defined under the list of abbreviations.

A./ We understand that there are a high number of abbreviations and it may be not be desirable for certain readers. However, it makes easier to convey the message to the reader as it is shorter than writing the whole words i.e. autoimmune disease, first degree relatives, autoimmune thyroid disease, systemic lupus erythematosus. Thus we rather keep the abbreviations in order to be clearer throughout the text. The systemic sclerosis abbreviation is added to the abbreviation list

Again Dr. Mauricio we are delighted with your review and we hope that the new concept and these answers satisfy your doubts and suggestions.
Reviewer's report

Reviewer: jean roudier

This article seems to be a review. Although it concerns an interesting topic, it fails to make the difficult field of familial autoimmunity any clearer. Is it a review? Is it an original article reporting a family or a study? Please give the reader a chance to find his way through this text!

Answer to reviewer: Jean Roudier

Many thanks for your review Dr. Roudier

This article was conceived originally as a review of the term familial autoimmunity which is embedded within “The autoimmune tautology”. This is refers to the fact that autoimmune diseases share several clinical signs and symptoms, physiopathologic mechanisms and genetic factors. This is a newly acquired term and as such it has to be thoroughly described. That is the reason we have sections devoted to polyautoimmunity, familial autoimmunity and multiple autoimmune syndrome. Definitions of these entities may be found in the revised manuscript. The main objective with this article is to make clinicians and researchers aware of the lack of studies, and the lack of adequate studies that assess familial autoimmunity. Therefore we conducted a systematic search, and afterwards a meta-analysis, in order to summarize the evidence available in the medical literature and to objectively quantify the risk of the presence of other autoimmune diseases within the nuclear family of affected probands. We constructed figure 2 which gives an overview of the text in order for the reader to have a better experience.

We hope you enjoy reading this new version of the paper and we also hope you find it more suitable and self guiding