Reviewer's report

Title: Genetic loci linked to Type 1 Diabetes and Multiple Sclerosis families in Sardinia

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Reviewer: David Dyment

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RE: Genetic loci linked to Type 1 Diabetes and Multiple Sclerosis families in Sardinia

By the authors:
Maristella Pitzalis, Patrizia Zavattari, Raffaele Murru, Elisabetta Deidda, Magdalena Zoledziewska, Daniela Murru, Loredana Moi, Costantino Motzo, Valeria Orru, Gianna Costa, Elisabetta Solla, Elisabetta Fadda, Lucia Schirru, Maria Cristina Melis, Marina Lai, Cristina Mancosu, Stefania Tranquilli, Stefania Cuccu, Marcella Rolesu, Maria Antonietta Secci, Daniela Corongiu, Daniela Contu, Rosanna Lampis, Annalisa Nucaro, Gavino Pala, Adolfo Pacifico, Mario Maioli, Paola Frongia, Margherita Chessa, Rossella Ricciardi, Stanislao Lostia, Anna Maria Marinaro, Anna Franca Milia, Novella Landis, Maria Antonietta Zedda, Michael B. Whalen, Federico Santoni, Maria Giovanna Marrosu, Marcella Devoto and Francesco Cucca

Overview:

It was a pleasure to review this paper by Pitzalis et al.

The authors performed a genome-wide screen for linkage in a sample of 58 MS families and 120 diabetes (T1D) families. Key to this study is the Sardinian sample. This island has a high prevalence of MS as well as a twin concordant rate similar to populations of Northern European extraction. The population has been convincingly shown (by this same group) to aggregate both diabetes and MS together. With the low DR2 frequency and high DR3 in this population it could be hypothesized that the aggregation may be solely to the effects at the HLA. The group has also shown that this is not the case. As such, they propose that there are non-MHC linked autoimmune (MS and diabetes) loci increasing a Sardinians risk to these conditions.

The results of their genome scan are not significant. Unfortunately, this is par for the course in MS and diabetes genetic research. More specifically, the authors tested the diabetes and MS families separately and then together. The diabetes screen showed significant linkage to the HLA and non-significant evidence of linkage at 1p31, 6q26, 10q21 and 22q11. None of these results overlapped with the MS results linkage findings. The MS families showed non-significant evidence of sharing at 1q42, 18p11 and 20p12.
When the two traits are analysed together, the authors continue to find evidence for sharing at the HLA, 6q26, 10q21, 20p12 and 22q11. A denser set of markers were genotyped in the candidate regions and an increase in LOD scores, when analyzed jointly, was observed at 10q21 and 20p12.

Major Concerns:
I have no major issues or comments for this manuscript.

Minor concerns and comments:
I will lay out my comments as per the BMC guidelines.

1. Is the question posed by the authors new and well defined?
The question is posed clearly. While the question is not novel, the Sardinian population is one of the few populations where diabetes and MS risk are convincingly present together. We do not see this in the Canadian population and in other outbred populations the question is equivocal. To my knowledge the first genome-wide investigation into common autoimmune susceptibility loci was a meta-analysis by Becker et al. (PNAS 1998). The study identified 9 IDDM + MS loci -none of which overlap here. This present study is an improvement as this analysis considers the data together versus an inspection of the end results.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The methods are described well and in sufficient detail. The authors are world leaders in the genetics of complex traits and their genotyping and statistical methods are sound.

3. Are the data sound and well controlled?
As above, the data are sound and well-controlled. Like any complex trait, we would love a sample size of hundreds to thousands of families. Unfortunately this is rarely feasible and often requires international collaboration. This kind of collaboration would defeat the purpose of the study as it would take away from the proposed homogeneity and uniqueness of the Sardinian sample.

I would be interested in the amount of the genome that is excluded at various lambda values (lambda=2, =3)given the sample size in the MS, the diabetes and the combined samples.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? And, 5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes and yes. The authors present their non-significant findings in a balanced and realistic manner. They discuss previous work in other autoimmune conditions, sample size, power and, of course, the benefits of the Sardinian population.

6. Do the title and abstract accurately convey what has been found? 7. Is the
writing acceptable?
This is actually one of the better written manuscripts I have reviewed. The title, abstract etc. are clear and do not misrepresent the findings of the study.

8. Common autoimmunity loci?
There are only 12 families segregating both conditions. These families are germane to the possibility of common susceptibility alleles posed by the authors. I would like to have some background data of these families presented in text format (it doesn’t need a table). Were there any differences in age of onset, the sex ratio or, perhaps, even the presence of other autoimmune conditions?

Moreover, one can make a case that families with only-MS (n=58) or only diabetes would actually take away from the original hypothesis of common susceptibility loci increasing risk to both conditions.

There are only 12 families with both conditions, and if I understand the number correctly, this should equate to 30+ affected-relative pairs (diabetes and MS both counted as affected). While I do not suggest a genome-wide scan be repreformed on so few families, I am interested in linkage at certain candidate loci.

Chromosome 10q21 and 20p12 would be of interest in this limited subset of MS+T1D families. IL2R at chromosome 10p15 has been convincingly shown in recent genome-wide association studies of MS and T1D to be a mild risk allele. I would like to see if there is any increased linkage here. This should be relatively straightforward to accomplish and may warrant a line or two in the results section.

Perhaps more to the point, if the reviewers genotyped the families for the IL2RA SNPs, the results would also be worth presenting. However, I realize this is beyond the scope of this publication.

In closing, I do not have any significant criticism of this manuscript. The results are non-significant but it is difficult to find a replicable positive finding in this field. Overall the study was well performed. I would only ask for the additional information on the families segregating both multiple sclerosis and diabetes.

It should be noted that with the rapid advance in genotyping and sequencing technologies, this kind of linkage study in samples of <200 outbred or heterogeneous families would not be published. But, as stated by the authors, the Sardinian population is unique and may continue to provide further insight into the genetics of both diabetes and MS.

Sincerely,
David Dyment
DPhil, MD

What next?: Accept after minor essential revisions
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