Reviewer's report

Title: Genome-wide copy number variation (CNV) in patients with autoimmune Addison's disease

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Reviewer: Anna L Mitchell

Reviewer's report:

This paper details, to my knowledge, the first genome-wide study in autoimmune Addison's disease patients to date. A cohort of 26 individuals with isolated Addison's were genotyped on the Affymetrix SNP Array 6.0 platform. In addition to analysing the genome-wide CNV data, more than 20 candidate genes were selected and the data from these regions manually analysed. Individual CNV assays for these candidate genes were then performed by duplex Taqman real-time PCR assays in a cohort of 352 cases and 353 controls. From the genome-wide scan, the authors identified that that low copy number of UGT2B28 was significantly more frequent in Addison's patients compared to controls while a high copy number of ADAM3A was associated – these findings are novel and of interest. CNVs in the selected candidate genes were not associated with Addison's on the genome wide scan or by Taqman. The authors propose that the mechanism by which susceptibility is conferred but may involve steroid inactivation in the case of UGT2B28 and T cell maturation for ADAM3A.

Major compulsory revisions:

1) My major concern with this study relates to the power of the genome-wide scan. Was a pre-study power calculation considered or were 26 samples analysed because of cost-constraints? To improve the study power, more isolated Addison’s patients would need to be analysed on the Affymetrix chips. This limitation is not really acknowledged in the manuscript, however I believe that the authors would agree that this study is underpowered because they undertook to select candidate genes and analyse the chip data for these separately (these were not associated in the genome wide scan). For this reason, this manuscript, although very well-written, does read a little like separate genome wide and candidate gene studies merged together.

Instead of presenting the data on the candidate gene analyses in which no associations were identified either by GWAS or by candidate gene analysis, the manuscript might be improved by presenting the genome-wide data, the Taqman replication of loci identified in the genome wide scan and then by undertaking some additional work to characterise the protein products of these two genes.

2) With regard to the genome wide study, can the authors clarify the size of the CNVs associated and whether there were other genes or micro RNAs in the associated CNVs that might also account for the associations seen?
3) The genome-wide scan did turn up some positive associations and of the CNVs that were taken forward to replication, two were found to be association with AAD. With regard to the P values presented in table 1, were corrections made for multi-testing? If so, how was this done?

**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