Reviewer’s report

Title: Meta-analysis derived atopic dermatitis (MADAD) transcriptome confirms core AD characteristics and presents novel pathogenic insights

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Reviewer: Joseph Arron

Reviewer’s report:

Ewald and colleagues describe a meta-analysis of non-lesional and lesional AD skin, employing sophisticated analytical methods. These analyses are potentially important in synthesizing a robust molecular phenotypic description of AD skin.

Major

1. Reference 9 describes matched non-lesional, acute and chronic lesions from 10 AD patients from their previous study, in which they reported intensification of pathway expression between non-lesional, to acute and chronic lesions. When assessing individual study effects in this manuscript, were acute lesions considered? If so, what were the methods employed? If hierarchical models were utilized and non-lesional, acute, and chronic lesions were analyzed, were acute and chronic lesions considered as separate levels of the tissue factor? See related Minor comment 3.

2. Potentially important differences in clinical characteristics of the studies included this meta-analysis are not clearly described in this manuscript, nor is it obvious from the comparison of the original published papers. Differences in severity and current therapies may be important sources of gene expression variation with implications for the meta-analysis. The authors need to more thoroughly address this to facilitate interpretation of these analyses. For example, the Methods section describes that data “subject to treatments” were not included in these analyses; does this include TCS and calcineurin inhibitors at time of sample collection? For example, were samples described by reference 10 only from studies M4A, M4B, and M12 which excluded “Treatment with topical glucocorticosteroids, tacrolimus, and/or pimecromilus within 1 week before baseline visit”?

3. We commend the authors for addressing dataset level effects, i.e. batch-effects which are potentially significant technical sources of variance in preparing the data for meta-analysis. The authors employed the ComBat method from the sva package to address this. Related to major comment 2, please address the implication of this method in the context of bona fide (if any) biological, i.e. transcriptional study-level differences, which are potentially confounded by batch.

4. The authors analyze the molecular phenotype of AD skin in the context of therapeutic treatment, Dupilumab, Cyclosporin, and UVB having potentially
distinct mechanisms of action, utilizing 19 discriminating genes. In this important and interesting analysis, the authors describe the extent of molecular phenotype recovery by treatment in terms of an average gene-based metric. Upon inspection of Table 2, it appears that there is substantial heterogeneity of individual gene responses to specific therapies, which may have implications for these therapies and the importance of these discriminating genes. For example, MUC7, HSD11B1, and MMP3 appear affected by these treatments. Please discuss the potential implications of these important observations more thoroughly.

Minor

1. Why weren’t down-regulated genes included in the analysis underlying Figure 1A?

2. Figure 3 appears to be erroneously labeled as Figure 4.

3. The supplementary methods state that hierarchical linear models were utilized to assess individual study effects while the main text methods stated paired t-tests were employed. Could you clarify?

4. Figure 2 legend erroneously refers to panel C, which appears to describe panel B. Related to figure panel B, are the significance levels adjusted for multiple testing? A description in the figure legend or text cannot be found in reference of the right section of panel B which appears to be a schematic of gene set analysis correlation analysis of Th2 and Lipid gene sets – please clarify.

5. Figure 3A reports correlations of WGCNA with age, SCORAD, and IgE. Are P-values corrected for multiple testing?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.