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A possible association between a dysfunctional skin barrier (filaggrin null mutation status) and diabetes

Reviewer 1: Schalock, Peter

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No conflicts of interest

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

If you answered No to any of the above, please supply details below.

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?	✓	
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?	✓	
Is the message clear?	✓	

If you answered No to any of the above, please supply details below.

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

req Recommendation	
✓	Accept
	Minor Revision

Would you be willing to review a revision of this manuscript?	
✓	Yes
	No

Comments

If you have any further comments for the authors please enter them below.
Excellent, well written article. Very interesting results - useful for both primary care and dermatology No concerns other than a few spelling errors which will be corrected in typesetting.

Reviewer 2: Gao, Peisong

Peisong Gao
Assistant Professor of Medicine
Johns Hopkins University School of Medicine
USA

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?		

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?	✓	
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?	✓	
Is the message clear?	✓	

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?		✓
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

If you answered No to any of the above, please supply details below or contact the editorial office.
All samples were from Danish citizens born in Denmark, Do they have the same ethnic background?

req Recommendation	
	Accept
✓	Minor Revision
	Major Revision
	Reject

Would you be willing to review a revision of this manuscript?	
✓	Yes
	No

However, the null mutation frequency in this group is higher (12.8%) as compared to the screen-detected diabetes group (9.1%), type 1 diabetes group (6.7%), and type 2 diabetes group (9.8%). It is likely that those participants with higher frequency from the self-reported group may be due to high frequency of AD. Furthermore, the sample size in this group is limited (n=133). A power calculation is needed.

3. All samples were from Danish citizens born in Denmark, Do they have the same ethnic background? If not, how was the population admixture controlled?

4. What is the quality control used for the filaggrin genotyping?

5. Data presented in the figure seem to be overlapped with those in Table 2.

6. There is lack of overall interpretation of results considering objective, novel findings, and clinical implication in the Discussion.

Authors Response to Decision Letter for (BMJ Open.2011.000062)

A possible association between a dysfunctional skin barrier (filaggrin null mutation status) and diabetes

Dear Editor

We are very pleased with the positive review of our article on the possible association between filaggrin null mutations and diabetes. We have tried to answer the questions and we sincerely hope that you find this suffi-cient. If not, please don't hesitate to contact us.

Sincerely, on behalf of the authors,

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University of Copenhagen
Denmark

Reviewer: Peisong Gao
Assistant Professor of Medicine
Johns Hopkins University School of Medicine
USA

Comments:
Dr. Thyssen et al studies a possible association between filaggrin null mutations and diabetes by genotyping R501X and 2282del4 null mutations in a random sample of 3335 adults from the general population in Den-mark. Additional genotyping was performed in two independent study populations of patients with type I (n=104) and 2 (n=774). They found an association for type-2 diabetes and self-reported diabetes. They con-cluded that filaggrin mutation may relate to diabetes, particularly type 2 diabetes. In the meantime, the au-thors have addressed several weaknesses in their studies, such as filaggrin mutation selection, criteria for disease diagnosis, sample size, and potential confounders. Overall, the report is clear and the findings should be of interest to the BMJ audience.

Several issues that should be addressed:

1. As the authors stated in the Introduction, several studies have suggested an inverse relationship between atopic dermatitis (AD) and type 1 diabetes, but very few for type 2 diabetes. However, in this study, the as-sociation was observed for type 2 diabetes, it is possible the finding is either novel or type-I error. It would be of great interest and impotance if this finding is true. Thus, a detailed discussion is needed.

Response:

Inserted in introduction: "To our knowledge, no studies have so far investigated the possible association between diabetes type 2 and atopic dermatitis". This was done to clarify that this is the first study on this topic.

In the discussion section, we have tried to better interpret and discuss the results. Also, we have included a sentence about type 1 error.

2. The association with diabetes was mainly observed in the self-reported diabetes group. However, the null mutation frequency in this group is higher (12.8%) as compared to the screen-detected diabetes group (9.1%), type 1 diabetes group (6.7%), and type 2 diabetes group (9.8%). It is likely that those participants with higher frequency from the self-reported group may be due to high frequency of AD.

Response: This is an important aspect. The prevalence of self-reported atopic dermatitis in participants from the general population study was 13.5% in those with self-reported diabetes, 9.1% in those with screen-detected diabetes and 9.9% in the control group. Thus, just as for the filaggrin haplo-insufficiency, the preva-lence of atopic dermatitis varied across sub groups and tended to be higher in subjects with self-reported diabetes. These numbers have been already been inserted in table 1 in the first draft that we submitted. In an adjusted analysis (table 3), we took into consideration that the

frequency of atopic dermatitis may vary be-tween the groups and still found the variations. To make these data findings even more clear to the reader, we have inserted the frequencies in the results section. However, it should be underscored that we did not have access to information on atopic dermatitis status for the patient cohorts (Type I and II diabetes patients).

Furthermore, the sample size in this group is limited (n=133). A power calculation is needed.

Response: Prior to genotyping the cohorts of type 1 and 2 diabetes patients, we made a power calculation to estimate the necessary sample size. Power calculation (power 0.8, significance level 0.05) revealed that we needed 800 patients with type 2 diabetes to replicate the difference observed in the general population study. 2 independent diabetes patient cohorts had already been characterized at the Hagedorn Center (an outpatient setting), respectively, 104 patients with type 1 diabetes and 774 patients with type 2 diabetes. Thus, we in-cluded and genotyped these cohorts, but it should be emphasized that our primary aim was not to investigate the association between filaggrin haplo-insufficiency and type 1 diabetes.

3. All samples were from Danish citizens born in Denmark, Do they have the same ethnic background? If not, how was the population admixture controlled?

Response: All participants and patients from the cohorts were Caucasians born in Denmark and with Danish citizenship. This is stated in the M&M section.

4. What is the quality control used for the filaggrin genotyping?

Response: The filaggrin genotyping procedure has been validated using appr. 450 individual samples of filaggrin sequenced DNA from the the Epithelial Genetics Group, Human Genetics Unit, Division of Pathol-ogy and Neuroscience, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. The PCR technique applied is currently under evaluation for a novel patent.

5. Data presented in the figure seem to be overlapped with those in Table 2.

Response: Agree. It has been removed.

6. There is lack of overall interpretation of results considering objective, novel findings, and clinical implica-tion in the Discussion.

Response: We have tried to make the discussion more clear and concise. Please see the “discussion” section.