OPEN PEER REVIEW

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Archives of Clinical Infectious Diseases
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Peer Review Report for "Alternation of *HWP1* and *PLB1* mRNA Expression Level in Progression of *Candida albicans* in Different Anatomical Sites"

Author(s): Ensieh Lotfali, Azam Fattahi, Fatemeh Noorbakhsh, Saham Ansari, Reza Ghasemi, Mohammad Mahdi Rabiei

Review Timeline:

Submit Date: 5 Mar 2019
Revised Date: 27 Oct 2019
Accepted Date: 1 Dec 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 31 May 2019

Dear AE,
The manuscript is good for publication however it needs some revisions. I highlighted some of them in the PDF file.
1. Why the authors have emphasized on systemic candidiasis in different parts of the manuscript, whereas the most sample has been collected from mucocutaneous candidiasis?
2. In the discussion section, the authors must interpret their results not express their results.
Regarding the authors worked on C. albicans, they should present a precise method to differentiate this species from C. dublliniensis.
For more details, refer to the PDF file.
Sincerely

REFEREE: Reviewer | **Revision** (0) 11 Jun 2019

Dear AE,
Thanks for inviting me to review the article entitled "Expression analysis of the Candida

albicans HWP1 and PLB1 genes during candidiasis".

Minor Comment:

a- The editing of the manuscript has to be revised.

b- Revision is needed in terms of grammar and structure. Some sentences are unclear.

1. TITLE:

- It reflects the major content of the article.

2. ABSTRACT:

- It gives a clear delineation of the research background, including important data and conclusions, however; the following item has to be considered:

- In the keywords section, the usage of “hyphal wall protein” is better than “fungal proteins”.

3. INTRODUCTION:

- It provides sufficient background regarding the studied topic. The aim of the work is clearly identified.

4. MATERIALS AND METHODS:

- Partially full description is provided for this section. Some important issues have to be considered:

- Were the samples cultured in “Sabouraud Dextrose Agar” or “Sabouraud Dextrose Ager with Chloramphenicol”?

- What are the diagnostic tests for the differentiation of Candida albicans from others? Did the authors use only the CHROM Agar media to differentiate Candida Species?

5. RESULTS:

- The information given in the results section is well organized and provides sufficient experimental data. However; in Fig.1 please use the logarithmic chart to show the mean of expression of HWP1 and PLB1 genes.

6. DISCUSSION:

- An overall constructive theoretical analysis of the study results is nearly covered.

7. REFERENCES:

- Finally, relevant and sufficient references were included, however, some references are old. Please replace it with new researches.

Thanks

REFEREE: Reviewer | **Revision** (0) 9 Jul 2019

Dear AE,

The manuscript entitled “Expression analysis of the Candida albicans HWP1 and PLB1 genes during candidiasis “investigated the virulence markers expressed by HWP1 and PLB1 genes. Some changes are necessary:

- The article text strongly requires detailed proof-reading and corrections of the English language. The conclusions are weak; it is not clear what the base for these conclusions is? Thus, no conclusion on any correlations between clinical form and gene expression should be drawn from those results. More specifically as follow:

1. It is preferable to use Medical Subject Headings (MeSH) keywords.

Abstract

1. Remove sp. After Candida species.

2. The usage of technical terms eg. Candida seems to be incorrect. Please write all these words in italics.

3. Please identify the respective phrases and change accordingly. Eg The HWP1 expression was up-regulated in mucosal samples as compared to cutaneous samples. Should say The HWP1 expression was up-regulated in mucosal samples compared to cutaneous samples?
4. In general, for introduction part, it is better to describe the relation between the HWP1 gene and vulvovaginal Candidiasis due to Candida africana and add newly published papers relate to polymorphism analysis add a reference in the text, and discuss in the discussion part also: Whole Genome-Based Amplified Fragment Length Polymorphism Analysis Reveals Genetic Diversity in Candida africana. Front Microbiol. 2017, 3;8:556. DOI: 10.3389/fmicb.
5. Why Hwp1, should be in regular. The GENE NAMES are supposed to be in italic with capital letter HWP1 (see: DOI: 10.2353/jmoldx.2007.060081. Standard Mutation Nomenclature in Molecular Diagnostics: Practical and Educational Challenges. Shuji Ogino)
Materials and methods
1. The company name of some materials are not provided.
2. Full name of C. albicans at the beginning of the sentence.
3. How did you distinguish between colonization and infection? By which guideline? Please give a reference.
Discussion
1. What does it mean? 'Respiratory isolates from sputum, BAL and lung tissue may illustrate colonization of Candida sp. rather than infection"
2. It seems that one such a paper is missing; please refer the following reference which mentioned: “Molecular Characterization of Highly Susceptible Candida africana from Vulvovaginal Candidiasis” has been published by Yazdanparast et al. Mycopathologia. 2015 Dec;180(5-6):317-23. DOI: 10.1007/s11046-015-9924-z.
3. According to the title (Expression analysis of the Candida albicans HWP1 and PLB1 genes during candidiasis), there are not enough discussion about limitations of virulence testing.
4. The study could be improved in the discussion section. This sections seemed to have gone in a different direction. The authors should compare their study with recently published papers mention above. In greater detail for differences that might explain their findings, so comparing their findings to these studies in particular would be most helpful to the reader. Thanks.

REFEREE: Reviewer | **Revision** (0) 10 Aug 2019

Dear AE,
1. ABSTRACT
Abstract needs to Major revision.
- What’s the Aim of the study?
- What’s the meaning of the word “increased mRNA levels” in the first line on the Result section?
- Conclusion: The expression rates of HWP1 and PLB1 genes were significantly different at the four sites. Which sites?
2. Methods
- What’s the role of the housekeeping gene ACT1?

- How the authors find the RNA of the strain which has not undergone invasion condition as a positive control? This positive control is not true.

3. Results

- According to the Results" PLB1 expression was observed less frequently in clinical samples (Table 2)". All the samples in this study were clinical.
- What's the meaning of N.S in Table 2?
- According to Table 2, this sentence needs to revision "HWP1 up-regulation was found in the four sites (oral, vaginal, BAL, and cutaneous) of clinical samples as 70, 83.3, 43.3, and 33.3%, respectively".
- Table 2 needs to Major revision. Please describe all rows and sums.

According to Fig. 1. Mean expression (%) of HWP1 and PLB1 in cutaneous, vaginal, oral, BAL samples, there is only significant differences in Up-regulated PLB1 between cutaneous specimens and other samples. Also, down-regulated PLB1 is the lowest in oral samples.

4. Conclusions

- The conclusion is not suitable.

Thanks.

Bita Pourkaveh: Associate Editor | **Revision** (0) 25 Sep 2019

Dear EIC

The reviewer(s) have recommended publication, but also suggest some major revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.

Kind regards,

Associate Editor

Masoud Mardani: EIC | **Revision** (0) 29 Sep 2019

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs major revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Prof. Mardani

Please find our accompanying manuscript 92285. It has been revised according to the reviewer's suggestions. The individual issues raised by the reviewer are listed below together with our actions and comments. Also, each modification in the text was highlighted in yellow color.

Action/Comment:

We thank Editor in chief and reviewer omments for what, we believe, accurately encapsulates the value of the present manuscript.

Referee(s)' Comments to Author:

Reviewer 1:

Dear Professor Mardani

The manuscript is good for publication however it needs some revisions. I highlighted some of them in the PDF file.

Why the authors have emphasized on systemic candidiasis in different parts of the manuscript, whereas the most sample have been collected from mucocutaneous candidiasis?

Action/Comment: Text was edited.

in discussion section, the authors must interpret their results not express their results. Regarding the authors worked on C. albicans, they should present a precise method to differentiate this species from C. dublliniensis.

Action/Comment: Text was edited. All samples were identified as *C. albicans*

Reviewer *2:*

Comments to the Editor:

Thanks for inviting me to review the article entitled "Expression analysis of the Candida albicans HWP1 and PLB1 genes during candidiasis".

Minor Comment:

-The editing of the manuscript has to be revised.

Action/Comment: Text was edited.

-Revision is needed in term of grammar and structure. Some sentences are unclear.
Action/Comment: Text was edited.

1. TITLE:
   -It reflects the major content of the article.
   Action/Comment: Text was edited.

   2. ABSTRACT:
   -It gives a clear delineation of the research background, including important data and conclusions, however; the following item has to be considered:
   -In keywords section, the usage of "hyphal wall protein" is better than "fungal proteins".
Action/Comment: Text was edited.

   3. INTRODUCTION:
   -It provides sufficient background regarding the studied topic. The aim of the work is clearly identified.
Action/Comment: Text was edited.

   4. MATERIALS AND METHODS:
   -Partially full description is provided for this section. Some important issues have to be considered:
   -Were the samples cultured in "Sabouraud Dextrose Agar" or "Sabouraud Dextrose Ager with Chloramphenicol"?
   Action/Comment: The samples were cultured in "Sabouraud Dextrose Agar
   -What are the diagnostic tests for differentiation of *Candida albicans* from others? Did the authors use only the CHROM Agar media to differentiate *Candida* Species?
   Action/Comment: The *HWP1* gene amplification were used to discrimination of *Candida albicans* complex. The text was edited
   5. RESULTS:
   -The information given in the results section is well organized and provides sufficient experimental data. However; in Fig.2&3 please use the logarithmic chart to show the mean of expression of HWP1 and PLB1 genes.
. ***Action/Comment***: Text was edited.

   6. DISCUSSION:
   -An overall constructive theoretical analysis of the study results is nearly covered.

7. REFERENCES:

-Finally, relevant and sufficient references were included, however, some references are old. Please replace with new researches.

.

Action/Comment: Text was edited.

Reviewer 3:

ABSTRACT

Abstract needs to Major revision.

Action/Comment: Text was edited.

- What's the Aim of the study?

- What's the meaning of the word "increased mRNA levels" in the first line on Result section?

Action/Comment: Text was edited.

- Conclusion: The expression rates of HWP1 and PLB1 genes were significantly different at the four sites. Which sites?

Action/Comment: The anatomical sites were described in the text previously.

Methods

- What's the role of the housekeeping gene ACT1?

Action/Comment: The *ACT1* gene was used as house-keeping to normalize the data. Text was edited.

- How the authors find the RNA of the strain which has not undergone invasion condition as a positive control? This positive control is not true. The RNA were extacted

Action/Comment: To ensure that mRNA expression related to the infection in clinical and standard control, total RNA of all clinical isolates and ATCC strain was extracted in the early stage of the growth. The samples with no changes in mRNA expression level were closed as positive control.

Results

- According to the Results" PLB1 expression was observed less frequently in clinical samples (Table 2)". All the samples in this study were clinical.

Action/Comment: all samples isolated from clinical samples.

- What's the meaning of N.S in Table 2?

Action/Comment: Not Significant. This column was deleted.

- According to Table 2, this sentence needs to revision "HWP1 up-regulation was found in the four sites (oral, vaginal, BAL, and cutaneous) of clinical samples as 70, 83.3, 43.3, and 33.3%, respectively".

Action/Comment: Text was edited.

- Table 2 needs to Major revision. Please describe all rows and sums.

Action/Comment: Text was edited.

According to Fig. 1. Mean expression (%) of HWP1 and PLB1 in cutaneous, vaginal, oral, BAL samples, there is only significant differences in Up-regulated PLB1 between cutaneous specimens and other samples. Also, down-regulated PLB1 is lowest in oral samples.

Conclusions

Action/Comment: Text was edited.

- Conclusion is not suitable.

Action/Comment: Text was edited.

Reviewer 4:

Dear Editor in Chief

Manuscript entitled "Expression analysis of the Candida albicans HWP1 and PLB1 genes during candidiasis "investigated the virulence markers which expressed by HWP1 and PLB1 genes. Some changes are necessary:

The article text strongly requires detailed proof-reading and corrections of the English language. The conclusions are weak; it is not clear what the base for these conclusions is? Thus, no conclusion on any correlations between clinical form and gene expression should be drawn from

those results. More specifically as follow:

It is preferable to use Medical Subject Headings (MeSH) keywords.

Action/Comment: Text was edited.

Abstract

Remove sp. After Candida species.

Action/Comment: Text was edited.

The usage of technical terms eg. Candida seems to be incorrect. Please write all these words in italics.

Action/Comment: Text was edited.

Please identify the respective phrases and change accordingly. Eg The HWP1 expression was up regulated in mucosal samples as compared to cutaneous samples. Should say The HWP1 expression was up regulated in mucosal samples compared to cutaneous samples?

Action/Comment: Text was edited.

In general, for introduction part, it is better describe relation between HWP1 gene and vulvovaginal Candidiasis due to Candida africana and add newly published papers relate to polymorphism analysis add reference in text and discus in discussion part also: Whole Genome-Based Amplified Fragment Length Polymorphism Analysis Reveals Genetic Diversity in Candida africana. Front Microbiol. 2017, 3;8:556. doi: 10.3389/fmicb.

Action/Comment: Text was edited.

Why Hwp1, should be in regular. The GENE NAMES are supposed to be in italic with capital

letter HWP1 (see: doi: 10.2353/jmoldx.2007.060081. Standard Mutation Nomenclature in Molecular Diagnostics: Practical and Educational Challenges. Shuji Ogino)

Action/Comment: Text was edited.

Materials and methods

The company name of some materials are not provided.

Action/Comment: Text was edited.

Full name of C. albicans at the beginning of the sentence.

Action/Comment: Text was edited.

Discussion

What does it mean? 'Respiratory isolates from sputum, BAL and lung tissue may illustrate colonization of Candida sp. rather than infection"

Action/Comment: Text was edited.

It seems that one such a paper is missing; please refer the following reference which mentioned "Molecular Characterization of Highly Susceptible Candida africana from Vulvovaginal Candidiasis" has been published by Yazdanparast et al. Mycopathologia. 2015 Dec;180(5-6):317-23. doi: 10.1007/s11046-015-9924-z.

Action/Comment: This reference was added.

According to the title (Expression analysis of the Candida albicans HWP1 and PLB1 genes during candidiasis), there are not enough discussion about limitations of virulence testing.

Action/Comment: Text was edited.

The study could be improved in discussion section. This sections seemed to have gone to a different direction. The authors should compare their study with recent published papers mention above. In greater detail for differences that might explain their findings, so comparing their findings to these studies in particular would be most helpful to the reader.

Action/Comment: Text was edited.

We hope the above answers to comments help to promote the context of manuscript. If you have any question/comment doesn't hesitate to contact us.

Regards,

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 10 Nov 2019

Dear AE,
The current manuscript (Manuscript ID:91258), entitled" Alternation of HWP1 and PLB1 mRNA Expression Level in Progression of Candida albicans in Different Anatomical Sites" has been much improved over the previous version. The authors made all the corrections as revised. Therefore, in my opinion, it would be considered for publication.
Regards

Bita Pourkaveh: Associate Editor | **Revision** (1) — 1 Dec 2019

Dear EIC
The reviewer(s) have recommended publication.
Kind regards,
Associate Editor

Masoud Mardani: EIC | **Revision** (1) — 1 Dec 2019

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.