REPLY TO THE REVIEWERS

Manuscript number: 13266-R1

Knowledge explosion for monogenic skin diseases by Nikoletta Nagy, Katalin Farkas, Lajos Kemény, Márta Széll

Reviewers' comments:

REVIEWER 1 (Reviewer No: 506525)

Comment 1

If possible upgrade to 2014.

Reply 1

Thank you for the comment. In order to upgrade the manuscript to 2014, we have carefully checked the literature and added the four more papers to the manuscript and to the list of the references: Vanecek et al., Am J Dermatopathol, 2014; Wu et al., Arch Dermatol Res, 2014; Guardoli et al., J Eur Acad Dermatol Venereol, 2014; Qian et al., Australas J Dermatol, 2014

Comment 2

Putting the figure caption the meaning of the acronym.

Reply 2

Thank you for your comment. The meaning of the acronym has been added to the text of the figure caption.

REVIEWER 2 (Reviewer No: 2150997)

In this manuscript, the authors present the knowledge explosion for genodermatoses caused by CYLD mutations. The authors give the opinion that BSS, FC and MFT1 are clinical variants of a disease spectrum of CYLD-associated disease, rather than different entities. But them seems to not perfectly reach this goal, and the manuscript is not in-depth enough, especially in the DISCUSSION. The authors should provide more information to increase the readability of the manuscript. So, I think that this manuscript could be reconsidered for publication if the authors are prepared to incorporate major revision. In addition, we give some specific advice to improve this manuscript.

Comment 1

The authors need a native English expert to enhance this manuscript.

Reply 1

Thank you for the suggestion. The manuscript has been corrected by a native English expert, Shannon Frances (shannon@sourceoutsource.de; www.sourceoutsource.de).

Comment 2

As the requirement of this journal, standard abbreviations should be defined in the abstract and on first mention in the manuscript.

Reply 2

Thank you for the comment. The abbreviations have been defined on first mention in the revised version of the manuscript. Changes have been underlined and highlighted in the abstract and in the introduction.

Comment 3

In DISSCUSION, the sentence “they are currently considered part of a phenotypic spectrum of the same entity” should be changed to “they are currently considered as part of a phenotypic spectrum of the same entity”.

Reply 3

Thank you for the suggestion, in the revised version of the manuscript the sentence “they are currently considered part of a phenotypic spectrum of the same entity” has been changed to “they are currently considered as part of a phenotypic spectrum of the same entity”.

Comment 4

It is that mutations in the same gene could lead to different clinical phenotypes has been described previously. In this manuscript, the authors mentioned that several CYLD mutations lead to the development of all three clinical variants. It could be better if they give some more discussion on mechanism that why same mutation causes different phenotypes and why different mutations in the same gene cause the same clinical phenotype.

Reply 4

In general, nonsense mutations exhibit the largest phenotypic diversity (Table II). Presumably, this is due to the fact that nonsense mutations of the CYLD gene are in general recurrent ones and many of them develop due to *de novo* events indicating mutational hotspots on the gene (Nagy et al., Acta Derm Venereol, 2013). Patients carrying the same nonsense mutation from different mutational events often exhibit extreme differences in their clinical manifestations. These differences might be the consequences of yet unknown genetic factors that modify the development of the phenotype. This explanation has been added to the revised text of the manuscript.

Comment 5

It would be better if the author provide more information about that 95 disease-causing CYLD mutations have been reported worldwide.

Reply 5

Thank you for your comment. In this review our aim was to give an impression about the recent advancements in the field of monogenic skin diseases due to the recent discoveries of human genetics and genetic investigative methods. We used the CYLD mutation caused spectrum as an example to demonstrate these developments. We agree with the comment that a detailed review of the so far identified CYLD mutations would be interesting, but this was not in the scope of this paper.

Comment 6

The label of the table “Table I” is not consistent with the description in the Figure legend. In addition, the table should be changed to the standard three-line table.

Reply 6

Thank you for the comment, Table I has been changed according to the suggestion.

Comment 7

The reference should be update.

Reply 7

Thank you for the comment. In order to upgrade the manuscript to 2014, we have carefully checked the literature and added the four more papers to the manuscript and to the list of the references: Vanecek et al., Am J Dermatopathol, 2014; Wu et al., Arch Dermatol Res, 2014; Guardoli et al., J Eur Acad Dermatol Venereol, 2014; Qian et al., Australas J Dermatol, 2014

Comment 8

The figure 2 is not meaningful enough, and it could be deleted.

Reply 8

Figure 2 has been deleted according to the suggestion.