Reviewer's report

**Title:** Rare hereditary pattern in sisters with epidermodysplasia verruciformis: a case report

**Version:** 5  
**Date:** 15 May 2014

**Reviewer:** Bettina Burger

**Reviewer's report:**

Major compulsory revision

**TITLE:** In most EV families the pattern of inheritance is autosomal recessive. This is also the case in the reported siblings. Therefore I suggest a new title, e.g. “Familiar epidermodysplasia verruciformis without mutations in TMC6 or TMC8”

**ABSTRACT, para3, conclusion, lines 15-18:** The conclusion is wrong! Please see the detailed comments in Discussion and Conclusions

**BACKGROUND, para2, line 14:** TMC6/EVER1 and TMC8/EVER2 are both localized on chromosome 17q25, named as EV1 locus (Ramoiz et al JID 2000; 114:1148-1153). The second susceptibility locus for EV is mapped to 2p21-224, but the gene still remains unknown. Please delete the chromosome 2 locus

**CASE 2, para1, line 8:** “Interestingly, neither parent of the two patients showed EV lesions, but both were carriers” Please verify, how you get that conclusion.

**GENETIC INVESTIGATIONS, para2, line 32:** “We did not identify any point mutations in any of the eight target bands” Do you mean nonsense, frameshift, and splice site mutations? Or do you mean any missense mutation? That would be remarkable as both genes contains many common SNPs. Please verify the type of mutation you did not find and mention if there is no missense mutation indeed. If so, please discuss this point.

**DISCUSSION, para1, line 14:** “The parents of the patients in our study were carriers, but did not develop EV lesions.” Do you mean that the parents are carrier of a heterozygous mutation? In that case, it is quite normal that they don not develop EV.

**DISCUSSION, para1, line 15 – 17:** “Based on autosomal recessive patterns of inheritance, we would expect 25% of children to develop EV lesions. In this family, these sisters are the only offspring, and the mother does not have a history of miscarriage.”

This conclusion is completely wrong! The expectance of only 25% affected offsprings is a question of statistic and number of offsspring. In families with parents who are carrier of a mutation causing an autosomal recessive disease you can observe that all children are affected or half of children are affected or no children is affected. The risk is for each embryo 25% but you can not expect that
a family with one affected child will not get a second affected child. So the inheritance pattern in the family you describe is absolutely common for an autosomal recessive disease.

DISCUSSION, para2, line 27-28: “In the elder sister, the lack of EVER gene mutations suggests that she may have a low risk for the development of cutaneous squamous cell carcinoma.” Currently, we just know the two genes TMC6 and TMC8 which are causative for EV. But in only 75% of all EV-patients causative mutations are found in these genes. As other genes remain unverified in correlation with EV does not decrease the individual risk for cancer development in EV-patients.

CONCLUSION, para1, line 5: “... both parents were carriers and the disease showed a rare hereditary pattern.” Please compare the comment above regarding the carrier status of the parents. The hereditary pattern in this family is normal for an autosomal recessive disease.

Minor essential revision

ABSTRACT, para2, case presentation, line 11: In addition, we detected the EVER1 and EVER2 genes without any point mutations from peripheral blood of the elder sister using PCR with eight different primers. # In addition, we examined the EVER1 and EVER2 genes using eight different primer pairs without finding any nonsense or frameshift mutation in the gDNA from lymphocytes of the elder sister.

BACKGROUND, para1, line 10/11: Also the HPV9 is often involved in EV.

CASE 1, para1, line 28/29: “No abnormalities were observed upon examination of the hair, nails, mucosal membranes, and other systems showed no abnormalities.” Please verify “other systems”.

GENETIC INVESTIGATIONS, para2: it remains unclear, whether you sequenced both TMC genes completely or only in part. Please, complete that information.

DISCUSSION, para2, line 21-22: “The presence of EVER gene mutations in patients with EV suggests that beta-HPV infection is linked to the progression of non-melanoma skin cancer.” The mutation itself leads to an increased susceptibility to beta HPV which are associated with the skin cancer. It is not possible to conclude that due to the mutation the HPV is linked to skin cancer. Please correct the relationship of the single factors.

DISCUSSION, para2, line 22-23: “Some reports indicate that mutations in the EVER2 gene increases the risk of cutaneous squamous cell carcinoma [13,14].” Do you mean polymorphisms or disease-causing mutations here? In case you mean the SNPs also common in the general population you should remove reference 14 and replace it behind the previous sentence. In case you mean the disease-causing mutations you have to delete reference 13.

DISCUSSION, para2, line 25: “we did not observe any point mutations” Please
correct this similar to the upper comment

DISCUSSION, para2, line 32: “…in immunocompetent patients…” In both cited publications EV patients were treated with imiquimod, but EV-patients are not immunocompetent.

FIGURE 1: One figure is not labelled (4 images but only A-C)

FIGURE 1: Please add arrows in the histopathology picture

Discretionary revision

CASE 1, para1, line 25/26: “…since the age of five years old as well as… # ..since the age of five as well as….

CASE 2, para1, line 1: “The 23-year-old sister of Case 1 has had similar cutaneous lesions since the age of six years old” # The 23-year-old sister of case 1 has had similar cutaneous lesions since the age of six”

CASE 2, para1, line 2: The figure 1C does not support “mild” erythematous lesions. I suggest to delete this word.

DISCUSSION, para2, line 18: “EVER1 and EVER2 genes associated with EV belong to…” # EVER1 and EVER2 genes causing EV belong to…

Minor issues not for publication

BACKGROUND, para2, line 17: “examination. We also…” space is missing

DISCUSSION, para2, line 27: The reference has the wrong format

FIGURE 2: The picture I received does not indicate the viruses by arrow

Level of interest: An article of limited interest

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.