Expanding the clinical spectrum of erythrokeratolysis hiemalis

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Introduction

- Erythrokeratolysis hiemalis (EH) also known as keratolytic winter erythema is a rare dominantly inherited disorder of cornification. It manifests with recurrent episodes of skin peeling and palmoplantar erythema, often more visible during the winter season.
- EH was recently found to be caused by genomic duplications in a non-coding region which regulates *CTSB*, a gene encoding the cysteine protease cathepsin B¹. As a consequence, Cathepsin B expression is increased which in turn causes EH.
- In this study, we aimed at identifying the genetic basis underlying an atypical disorder of cornification.

Clinical features and mutation analysis

We studied a family featuring severe diffuse transgradient hyperkeratosis involving the palms and soles accompanied by mild diffuse redness of palms (a-c). Examination of a skin biopsy obtained from the palmar area revealed orthohyperkeratosis and multiple areas of intra and subcorneal separation (d). Pedigree analysis suggested autosomal dominant inheritance (e). Using whole-exome and direct sequencing analysis, we identified in the affected individual VI-1 a heterozygous missense mutation (c.763G>A, p.V255M) in *CTSB* (f). The mutation affects a highly conserved residue and is predicted to be pathogenic.

Functional consequences of *CTSB* mutation by protein modeling

We modelled cathepsin B structure based on the HUC1 structure deposited in the PDB database². Two histidine residues critical for catalytic activity and the mutation site are shown (oxygen and nitrogen shown in red and blue, respectively).

The V255M mutation is causing the substitution of amino acid valine 255 (a) to methionine (b). This substitution fills the active site cleft and becomes proximal to the occluding loop. The cathepsin B active site cleft is partially blocked by the occluding loop. The mutation is predicted to push the occluding loop away thus increasing endo over exopeptidase activity.

Functional consequences of *CTSB* mutation on cathepsin activity

In order to ascertain in vivo the predicted consequences of the mutation, we transfected HELA cells with either wild type (WT) or a p.V255M mutation-carrying (p.V255M) vector, and measured cathepsin B activity. The p.V255M mutation was found to significantly induce cathepsin activity. This is in agreement with a previous report which indicated increased cathepsin B expression and is associated with abnormal cornification¹.

Conclusion

A gain-of-function missense mutation in *CTSB*, rather than a genomic change, was found to result in an unusual EH-like phenotype.

References

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- DEMBO J, 1991, 10:2321