Received: 5 April 2022 | Revised: 25 June 2022 | Accepted: 3 July 2022

DOI: 10.1111/exd.14640

Experimental Dermatology WILEY

RESEARCH LETTER

Familial primary cutaneous amyloidosis: Caspase activation may be involved in amyloid formation

Primary localized cutaneous amyloidosis (PLCA) is a rare form of cutaneous amyloidosis, characterized by the presence of flat-topped papules and macules with amyloid deposits in the superficial dermis. It is a purely cutaneous disease with no association with systemic forms of amyloidosis.[1] Although most cases are sporadic, familial cases (FPLCA) represent about 10% of total reports and show an autosomal dominant inheritance, with mutations described in the genes for the oncostatin M receptor (*OSMR*) and the interleukin-31 receptor A (*IL31RA*).[2] Herein, we present a family affected by FPLCA and underline the role of caspase activation in amyloid formation.

A 62-year-old woman presented with generalized hyperpigmented and hypopigmented macules since childhood (Figure 1A). The patient reported itching and dysesthesias. A brother and one of her two daughters had a similar clinical phenotype (Figure S1).

A skin biopsy was performed and histological study with haematoxylin–eosin showed the presence of extracellular deposits in the papillary dermis, which were positive for Congo red staining (Figure 1B). After obtaining written informed consent from the patient, whole-exome sequencing (WES) (Agilent SureSelect V6 Library + Novaseq6000 150PE [150 × 2 bp] 9 Gb/sample) (Figure S2) identified the following *OSMR* heterozygous missense sequence change: NM_003999.3 (OSMR): c.1891G>C p.(Val631Leu) that was confirmed by Sanger sequencing (Figure 1C). Molecular tests were suggested to be performed in the rest of the phenotypically affected relatives; however, they refused it. In addition to the proband, the genetic study was performed only on the daughter without the disease phenotype, and the mutation was not found.

Immunofluorescence of the patient affected skin with monoclonal antibodies against high molecular weight keratins (34βE12), OSMRβ and caspase-3 was also performed (Supplementary Data). OSMRβ mostly localized to the epidermis of normal skin with a nuclear pattern in the upper half and a cytoplasmatic pattern in the lower half. However, OSMRβ immunofluorescence in the affected skin of our patient was barely found in the nuclei and was mostly observed in the cytoplasm. Both caspase and 34βE12 cytokeratin expression were only observed in the papillary dermis of the affected skin (Figure 1D).

OSMR is a gene that encodes for the oncostatin M receptor β (OSMRβ), a component of two different cytokine receptors, OSM type II receptor and IL-31R, that bind two different ligands, OSM and IL-31, both members of the IL-6 cytokine family.[3] The OSM type II receptor represents a heterodimer of OSMR and a gp130 signalling receptor subunit, while the IL-31R receptor is formed by a heterodimer of the OSMRβ with IL31RA.

The OSMRβ protein is a component of a transmembrane cytokine receptor with several functional subdomains: an extracellular part with a cytokine binding domain followed by an immunoglobulin-like domain; a second complete cytokine binding domain and finally a region of fibronectin-III (FN-III) subdomains. Both the immunoglobulin-like domain and the cytokine binding domains are required for ligand binding and receptor complex formation, whereas the FN-III subdomains are required for the correct spacing of the receptor.[1,4]

The exact role of OSMRβ in FPLCA has not been fully elucidated. OSMRβ is expressed in numerous cell types, including keratinocytes, cutaneous nerves and nociceptive neurons of the dorsal root ganglia.[1] This observation raises the possibility that defective nerve signalling could be involved in the pathophysiology of FPLCA including pruritus and dysesthesias due to pathogenic sequence changes within the FIII-subdomain.[2,5]

To date, nine *OSMR* mutations have been reported in FPLCA, and five reside in the noncytokine binding FN-III domains of OSMRβ.[6] The heterozygous c.1891G>C mutation found in our patient was also localized in the FN-III subdomains of the OSMR gene (Figure S2) and to date has only been described once in a Dutch family.[2] It is not known if mutations in the FN-III subdomains could inhibit receptor dimerization for both the OSM type II and the IL31R receptors and induce alterations in epidermal differentiation and proliferation, leading to basal keratinocyte apoptosis and amyloid formation as observed in our patient.[3] Perhaps, keratinocyte destruction in FPLCA may occur as an initial result of apoptosis, leading to amyloid formation.[7,8] Furthermore, the expression of caspases and 34βE12 cytokeratin in the immunofluorescence study of the affected skin demonstrated that both apoptotic activity and cell death could be implicated in FPLCA.[9]

The caspase activity found in the skin lesions of our patient may add an additional factor involved in the skin of FPLCA patients in the same way that occurs in Alzheimer disease, a disorder characterized by apoptosis and neuronal death where the presence of caspases and amyloid deposits has been related.[10] Similarly, the relationship between OSMRβ and apoptosis has been observed in several cancers, demonstrating the apoptosis-inducing role of the

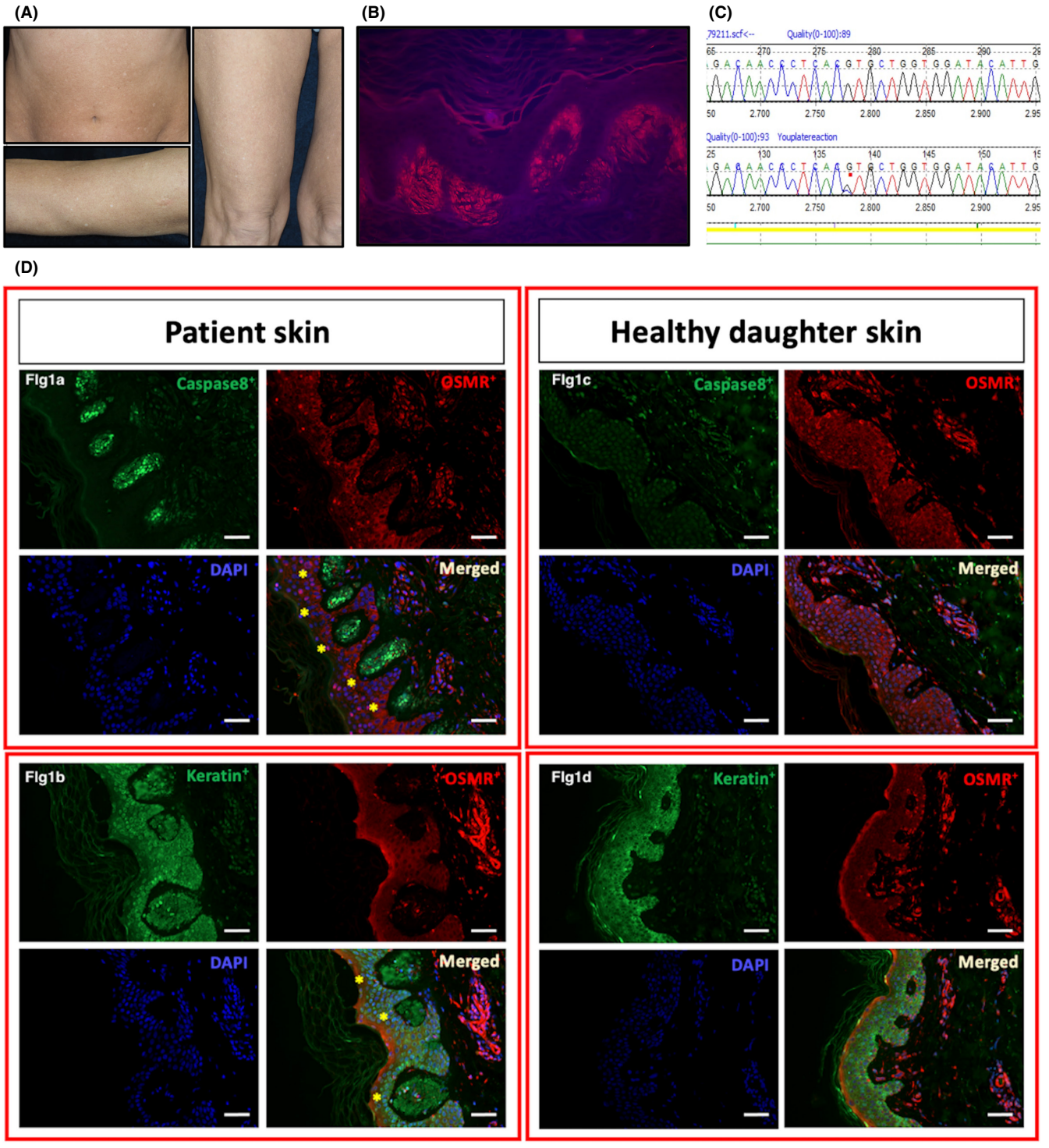

FIGURE 1 Clinical phenotype as well as the histological, immunohistochemical and molecular findings. (A) Hypopigmented and hyperpigmented macules in the proband with FPLCA. (B) Amyloid deposits with Congo Red staining (×100). (C) OSMR heterozygous missense sequence 1891G>C p.(Val631Leu) as detected by the Sanger method. (D) Immunofluorescence studies in proband and normal skin. (D-Fig1a) Presence of caspases in the dermis within the amyloid deposits. No OSMR is expressed in the amyloid material. Colocalized expression of caspases and OSMR is not found. (D-Fig1b) Presence of keratins of high molecular weight (34βE12) in the dermis, coinciding with the amyloid deposits. No OSMR expression is found in the amyloid material. (D-Fig1c) Absence of caspase expression in the dermis of normal skin. Deposits of OSMR are found in keratinocytes of the epidermis. (D-Fig1d) No expression of high molecular weight keratins (34βE12) in the dermis of the skin of a healthy daughter. Deposits of OSMR in keratinocytes of the epidermis. Caspase-3 and Keratin (green), OSMR (red), DAPI Nuclear staining (blue). Scale Bar = 50 μm.

OSMR mutations, similar to what occurs in FLCPA.[1] Additional factors involved in apoptosis in FPLCA lesions may also be related to high levels of insulin-like growth factor-binding protein 5 and to the activation of matrix metalloproteinases.[1]

In summary, although the pathophysiology of FPLCA requires further study, we show that pathogenic sequence changes within the OSMRβ protein could lead to abnormalities in OSM type II and IL-31R signalling, that probably give rise to alterations in basal keratinocyte differentiation, caspase activation and ultimately the induction of apoptosis and amyloid deposition. Pruritus and dysesthesias in patients with FPLCA could be explained by the fact that OSMRβ is also expressed within cutaneous nerves and nociceptive neurons of the dorsal root ganglia.

KEYWORDS

amyloidosis, apoptosis, caspases

AUTHOR CONTRIBUTIONS

Javier Antoñanzas performed the research, contributed essential reagents or tools, analysed the data and wrote the paper. **Beatriz Pelacho-Samper** performed the research, analysed the data and wrote the paper. **Gorka Alkorta-Aranburu** designed the research study, analysed the data and wrote the paper. **Jose I. Echeveste** analysed the data and contributed essential reagents or tools. **Agustín España Alonso** performed the research, designed the research study, contributed essential reagents or tools, analysed the data and wrote the paper. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors appreciate the predisposition of the patient involved in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Javier Antoñanzas[1]
Beatriz Pelacho-Samper[2,3]
Gorka Alkorta-Aranburu[4]
Jose I. Echeveste[5]
Agustín España Alonso[1]

[1]*Department of Dermatology, School of Medicine, University of Navarra, Pamplona, Spain*
[2]*Center for Applied Medical Research (CIMA), Regenerative Medicine Department, Universidad de Navarra, Pamplona, Spain*
[3]*Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain*
[4]*CIMA LAB Diagnostics, University of Navarra, Pamplona, Spain*
[5]*Department of Pathology, School of medicine, University of Navarra, Pamplona, Spain*

Correspondence
Agustín España Alonso, Clinica Universidad de Navarra, Av Pio XII, 36, 31008 Pamplona, Navarra, Spain.
Email: aespana@unav.es

REFERENCES

1. Tanaka A, Arita K, Lai-Cheong JE, Palisson F, Hide M, McGrath JA. New insight into mechanisms of pruritus from molecular studies on familial primary localized cutaneous amyloidosis. *Br J Dermatol*. 2009;161(6):1217-1224.
2. Tanaka A, Lai-Cheong JE, van den Akker PC, et al. The molecular skin pathology of familial primary localized cutaneous amyloidosis. *Exp Dermatol*. 2010;19(5):416-423.
3. Chen SH, Benveniste EN. Oncostatin M: a pleiotropic cytokine in the central nervous system. *Cytokine Growth Factor Rev*. 2004;15(5):379-391.
4. Heinrich PC, Behrmann I, Haan S, et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J*. 2003;374(1):1-20.
5. Bando T, Morikawa Y, Komori T, Senba E. Complete overlap of interleukin-31 receptor a and oncostatin M receptor β in the adult dorsal root ganglia with distinct developmental expression patterns. *Neuroscience*. 2006;142(4):1263-1271.
6. Adams R, Colmont C, Mukhtar A, Morgan H, Patel GK. A novel oncostatin M/interleukin-31 receptor mutation in familial primary localized cutaneous amyloidosis. *Clin Exp Dermatol*. 2020;45(2):254-256.
7. Chang YT, Wong CK, Chow KC, et al. Apoptosis in primary cutaneous amyloidosis. *Br J Dermatol*. 1999;140(2):210-215.
8. Liu J, Chen J, Zhong Y, et al. OSMRβ mutants enhance basal keratinocyte differentiation via inactivation of the STAT5/KLF7 axis in PLCA patients. *Protein Cell*. 2021;12(8):653-661.
9. Huilgol SC, Ramnarain N, Carrington P, Leigh IM, Black MM. Cytokeratins in primary cutaneous amyloidosis. *Australas J Dermatol*. 1998;39(2):81-85.
10. Allen JW, Eldadah BA, Huang X, et al. Multiple caspases are involved in β-amyloid-induced neuronal apoptosis. *J Neurosci Res* 2001;65(1):45–53.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1