THE JOURNAL OF DERMATOLOGY
JAPANESE DERMATOLOGICAL ASSOCIATION

Familial or sporadic porokeratosis as an autoinflammatory keratinization disease

Journal:	*The Journal of Dermatology*
Manuscript ID	Draft
Wiley - Manuscript type:	Letter to the Editor
Date Submitted by the Author:	n/a
Complete List of Authors:	Takeichi, Takuya; Nagoya University Graduate School of Medicine, Dermatology Akiyama, Masashi; Nagoya University Graduate School of Medicine, Department of Dermatology
Keywords:	autoinflammatory keratinization diseases, mevalonate pathway, porokeratosis, MVK, keratinization diseases

Abstract:

We read with great interest the very recent excellent report of familial or sporadic porokeratosis by Leng et al (J Dermatol 2018; 45: 862-866). Their findings extend the mutation spectrum of porokeratosis and provide further evidence for its genetic basis. In 2017, we proposed the new umbrella term "autoinflammatory keratinization diseases" (AIKD) to encompass inflammatory keratinization disorders with autoinflammatory pathogenic mechanisms. Inspired by the report by Leng et al., we propose that porokeratosis be categorized as an autoinflammatory keratinization disease.

Porokeratosis has a number of unique characters as an AIKD. At first, porokeratosis is undeniably a keratinization disorder, and it has been considered a skin-specific autoinflammatory disease. In addition, so far, four mevalonate pathway genes including *MVK* have been found to be associated with porokeratosis. Indeed, *MVK* is also known to be causative for the conventional autoinflammatory disease, hyperimmunoglobulinemia D and periodic fever syndrome. The defective mevalonate metabolism might lead to both hyperkeratosis and autoinflammation in porokeratosis.

Journal of Dermatology

Letter to the editor

Familial or sporadic porokeratosis as an autoinflammatory keratinization disease

Takuya Takeichi and Masashi Akiyama*

Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

***Correspondence**:
Masashi Akiyama MD, PhD
Tel: 81-52-744-2314, Fax: 81-52-744-2318
E-mail: makiyama@med.nagoya-u.ac.jp

Short title: Porokeratosis as AIKD

Abbreviations: autoinflammatory keratinization diseases (AIKD)

KEY WORDS: autoinflammatory keratinization diseases, mevalonate pathway, porokeratosis

Funding statement: This work was supported by Grant-in-Aid for Scientific Research (B) 2618H02832 to M.A. and by Grant-in-Aid for Young Scientists 18K16058 to T.T. from the Japan Society for the Promotion of Science (JSPS).

The authors have no conflicts of interest to declare.

Word count: 500/500 words in the main text, 5/5 references, 1 table

We read with great interest the mutation report of familial or sporadic porokeratosis by Leng *et al*.[1] Porokeratosis (OMIM_175800) comprises heterogeneous keratinization diseases which show one or more atrophic plaques with hyperkeratosis forming a ridge-like border.[1] Porokeratosis is a skin-specific autoinflammatory disease that is often inherited and is linked to ultraviolet light exposure and immunosuppression.[2] Porokeratosis is a genetically heterogeneous disorder that can be caused by mutations in any of the four genes involved in the mevalonate pathway (*MVK*, *MVD*, *PMVK* and *FDPS*) and *SLC17A9* encoding the solute carrier family 17 member 9.[1] Leng *et al*.[1] studied seven families affected with porokeratosis and five sporadic patients of the disease in a Chinese population and detected six mutations in the *MVK*, *MVD* and *PMVK*.[1] Their findings extend the mutation spectrum of porokeratosis and provide further evidence for its genetic basis.[1] Inspired by their report, we propose that porokeratosis be categorized as an autoinflammatory keratinization disease.

In 2017, we proposed the new umbrella term "autoinflammatory keratinization diseases" (AIKD) to encompass inflammatory keratinization disorders with autoinflammatory mechanisms.[3,4] AIKD have primary and main inflammation sites in the epidermis and upper dermis, and the inflammation leads to the main and characteristic AIKD phenotype: hyperkeratosis. In the pathogenesis of AIKD, primary genetic causative factors associated with the hyperactivation of innate immunity (autoinflammation) play important roles, mainly in the epidermis and upper dermis.[3]

Porokeratosis has a number of unique characters as an AIKD. Cornoid lamellae, vertical 'columns' of parakeratosis, are a histological hallmark, and the cornoid lamella pattern relates to epidermal hyperplasia and dermal inflammation.[2] Porokeratosis is undeniably a keratinization disorder, and it has been considered a skin-specific autoinflammatory disease.[2] For example, eruptive pruritic papular

porokeratosis exemplifies the inflammatory manifestation, and complications to inflammatory conditions such as localized cutaneous amyloidosis are seen in porokeratosis patients.[2]

Since mutations in the mevalonate pathway gene *MVK* were identified as causative for disseminated superficial actinic porokeratosis, four mevalonate pathway genes have been found to be associated with porokeratosis.[1] It is noteworthy that one of the major causative genes of porokeratosis, *MVK*, is also known to be causative for the conventional autoinflammatory disease, hyperimmunoglobulinemia D and periodic fever syndrome (OMIM_260920). In fact, heterozygous *MVK* mutations cause porokeratosis and homozygous or compound heterozygous *MVK* mutations result in hyperimmunoglobulinemia D and periodic fever syndrome. The mevalonate pathway of isoprenoid biosynthesis provides precursors of isoprenoids, which serve as precursors of cholesterol, heme A, ubiquinones, dolichol, and isoprenylated proteins (e.g., RAS and Lamin B).[2] The isoprenylated proteins regulate cell growth, division and differentiation, and are probably associated with retention of nuclei in the stratum corneum (i.e., parakeratosis).[2] Van der Burgh *et al*.[5] reported that a shortage of a non-sterol isoprenoid product of the mevalonate pathway, geranylgeranylpyrophosphate, leads to aberrant activation of the small GTPase Rac1 and inflammasome activation. Thus, we hypothesize that the defective mevalonate metabolism might lead to both hyperkeratosis and autoinflammation in porokeratosis (Table 1).

In conclusion, we propose that porokeratosis is a new member of AIKD, which expands the clinical spectrum of AIKD.

Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research (B)

2618H02832 to M.A. and by Grant-in-Aid for Young Scientists 18K16058 to T.T. from the Japan Society for the Promotion of Science (JSPS).

References

1. Leng Y, Yan L, Feng H, et al. Mutations in mevalonate pathway genes in patients with familial or sporadic porokeratosis. *J Dermatol* 2018; **45**: 862-866.
2. Zhang Z, Li C, Wu F, et al. Genomic variations of the mevalonate pathway in porokeratosis. *Elife* 2015; **4**: e06322.
3. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases. *J Allergy Clin Immunol* 2017; **140**: 1545-1547.
4. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization diseases: An emerging concept encompassing various inflammatory keratinization disorders of the skin. *J Dermatol Sci* 2018; **90**: 105-111. Review.
5. van der Burgh R, Ter Haar NM, Boes ML, Frenkel J. Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clin Immunol* 2013; **147**: 197-206. Review.

TABLE I. Current hypothesized pathogenesis of porokeratosis in AIKD

Disease	Genetic causative factor (frequency)	Hypothesized pathogenic inflammatory mechanisms and pathways
Porokeratosis		
	MVK mutations (prevalent)	5-phosphomevalonate↓
	PMVK mutations (rare)	→5-Pyrophosphomevalonate↓
	MVD mutations (prevalent)	→Geranylgeranylpyrophosphate↓
	FDPS mutations (rare)	→small GTPase↓→IL-1β↑?

Abbreviation: AIKD, autoinflammatory keratinization diseases