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Letter to the Editor

A combination of low-dose systemic etretinate and topical calcipotriol/betamethasone dipropionate treatment for hyperkeratosis and itching in Olmsted syndrome associated with a *TRPV3* mutation

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To the Editor:

Most cases of Olmsted syndrome (OS, OMIM#614594) are inherited in autosomal dominantly, although autosomal recessive and X-linked cases have been reported [1]. Pathogenic mutations in *TRPV3* cause the dominant and recessive subtypes of OS, and those in *MBTPS2* lead to the X-linked form of OS [2]. Clinically, there are 2 major skin manifestations of OS: symmetrical keratoderma on the palms and soles, and symmetrical hyperkeratotic plaques around bodily orifices. Several additional cutaneous manifestations have been reported: constriction bands on the fingers and toes (pseudoainhum), diffuse alopecia, skin infections, onychodystrophy and increased risk of squamous cell carcinoma [1, 3].

TRPV3 encodes a transient receptor potential (TRP) vanilloid cation channel that is primarily expressed in the skin, hair follicles, brain and spinal cord. Mutant TRPV3 may function dominant-positively to increase the constitutive TRPV3 activity and elevate Ca^{2+} in keratinocytes, leading to severe keratoderma and intolerant itching sensation [4]. TRPV3 is a Ca^{2+} entry pathway tightly associated with the TGF-α/EGFR signaling complex orchestrating keratinocyte terminal differentiation [4]. There are no specific or satisfactory treatments for OS. Specific treatments for pain and itching are essential to reduce the morbidity of the disease [5, 6]. Here, we report a pedigree of OS in which severe itching and hyperkeratosis were effectively controlled by a topical ointment of calcipotriol/betamethasone dipropionate with low-dose systemic retinoids.

A 39-year-old male presented with partial hyperkeratosis in both soles from his infancy. Clinical examination revealed mild hypotrichosis with some thinning of the hair (Fig. 1A). Light microscopy of cut and plucked hairs did not reveal any gross abnormalities. Focal palmar hyperkeratosis was seen along the friction-prone sites of his

dominant right hand. His palms showed slight hyperhidrosis. Plantar hyperkeratosis was observed on the big toes and on the edges of the soles (Fig. 1B). Histologically, marked hyperkeratosis without granular degeneration was seen (Fig. 1D). He was treated with a low-dose etretinate (10 mg/day) in combination with a topical calcipotriol/betamethasone dipropionate ointment, leading to sufficient control without adverse effects. To reduce a risk of adverse effects of etretinate treatments including liver dysfunction, conjunctivitis, cheilitis, and hair loss, the patient chose the low-dose etretinate treatment. After 4 months of treatment, his plantar skin became smoother and greatly improved (Fig. 1C).

In contrast to the proband, his 5-year-old daughter had a history of hyperkeratosis from 1 month of age. Examinations showed slight hypotrichosis with thin, curly hair (Fig. 1E). We found scaly hyperkeratosis with peripherally inflamed erythema on the palms, and severe diffuse hyperkeratosis on the soles (Fig. 1F and H). All fingers showed moderate contracture, and X-ray of the right hand revealed increased permeability in the distal phalanx (Fig. 1I). Her palms and soles exhibited moderate hyperhidrosis. Notably, she had severe itching on the erythematous lesions of the palms and soles. We used moderate dose of systemic etretinate (10 mg/day), leading to mild improvement of her eruptions (Fig. 1G).

Following informed consent and ethical approval, and with all research conforming to the *Declaration of Helsinki* principles, genomic DNA from the father was subjected to whole-exome sequencing analysis. Whole-exome sequencing revealed a previously reported heterozygous missense mutation in *TRPV3* (c.2017C>T; p.Leu673Phe), which was detected by Sanger sequencing in the affected daughter. The mutation was not present in DNA from the unaffected mother, nor in 777 ethnically

matched control chromosomes (data not shown).

TRPV3 channel contains six transmembrane domains with an intramembrane region between the fifth (S5) and sixth (S6) segments, and both C and N terminus are intracellularly located (Figure 2). The mutation p.Leu673Phe in *TRPV3* here has been reported previously as a pathogenic substitution in an individual with OS [7]. In addition, a missense mutation of the adjacent methionine residue, p.Met672IIe, has been reported [8]. They are not located in TRP box of the TRP domain of TRPV3, but are highly conserved amino acids among diverse species [7]. Thus far, no strong correlation has been observed between a specific mutation in *TRPV3* and the severity of OS. There were differences in the phenotype between our pedigree and the other p.Leu673Phe case with regard to the presence or absence of erythromelalgia. The clinical features across all cases of OS, including those with the same *TRPV3* pathology, show some variation, for example, in terms of periorificial keratoderma, leucoplakia, diffuse alopecia and pseudoainhum. In the present pedigree, there was intrafamilial phenotypic heterogeneity with respect to the severity and distribution of eruptions in two affected individuals. We hypothesized that mutations in other genes or environmental factors might have affected their phenotypes through modifier effects.

Our pedigree had severe itching on the palms and the soles, especially on the erythematous lesions. TRPV3 is known to play essential roles in skin keratinization, hair growth and possibly itching sensation in humans [4]. Topical treatments including emollients, keratolytics, wet dressings, boric acid, tar, retinoic acid, shale oil and corticosteroids are attempted, producing poor to moderate improvement [5]. In several OS patients, systemic retinoids, corticosteroid or methotrexate were used, producing poor to moderate relief [4].

Our cases were significantly improved by the topical calcipotriol/betamethasone dipropionate and low-dose systemic retinoids. This has two important clinical implications: It suggests that topical calcipotriol/betamethasone dipropionate is a potentially useful treatment for OS and that combination therapy of topical calcipotriol/betamethasone dipropionate and low-dose systemic retinoids is a promising treatment for OS. Oral retinoids have been described as efficient therapeutic agents for severe ichthyotic disorders; however, we sometimes hesitate to use systemic retinoid treatments because they have several adverse effects. Topical calcipotriol/betamethasone dipropionate is an effective treatment for psoriasis vulgaris [9]. Akasaka *et al.* reported that efficient oral etretinate and local injection of bleomycin as therapeutic options for punctate palmoplantar keratoderma type 1 [10].

In the present case, a combination of low-dose systemic etretinate and topical calcipotriol/betamethasone dipropionate treatment was effective for skin lesions of OS caused by *TRPV3* mutation. Although it is difficult to evaluate its efficacy from only the present case, our finding suggests this combination therapy might be a useful and powerful tool for controlling severe itching and improving quality of life for OS patients.

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Figure legends

Figure 1. Various clinical features are seen in the present family with autosomal dominant Olmsted syndrome.

(A) The father has mild hypotrichosis and thinning of hair on the scalp. (B) He shows diffuse hyperkeratosis on the plantar aspect of the big toe (before treatment). (C) After combination treatment, the hyperkeratosis is improved and thick scales are not seen on the big toe. (D) A skin biopsy sample from the right sole shows marked hyperkeratosis without granular degeneration. Scale bar: 100 μm. (E) His daughter has slight hypotrichosis with thin, curly hair. (F) Her palms show scaly hyperkeratotic plaques with erythema on their edges (before treatment). (G) After moderate dose of etretinate treatment, her palmar hyperkeratosis is improved mildly. (H) Her soles show diffuse, severe hyperkeratosis. (I) An X-ray image of her right hand shows increased permeability in the distal phalanx.

Figure 2. Schematic of the TRPV3 domain structure.

The yellow areas mark the transmembrane segments (from S1 to S6). The intramembrane region (green area), the transient receptor potential domain (TRP) and the ankyrin repeat domain (ARD) are indicated. The present mutation is marked by a red arrow. The black numbers indicate the numbering of the amino acids in the TRPV3 amino acid sequence.

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