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# Two familial cases of Olmsted-like syndrome with a G573V mutation of the *TRPV3* gene

**Y. P. Zhi,[1] J. Liu,[2] J. W. Han,[2] Y. P. Huang,[2] Z. Q. Gao,[1] Y. Yang[3] and R. N. Wu[1]**

[1]*Department of Dermatology, International Mongolian Hospital of Inner Mongolia, Hohhot, Inner Mongolia Autonomous Region, PR China;* [2]*Department of Dermatology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region, PR China; and* [3]*Department of Dermatology, Peking University First Hospital, Beijing, PR China*

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## Summary

Olmsted syndrome (OS) is a rare disease, characterized by symmetrical, sharply defined, hyperkeratotic, mutilating plaques on the palms and soles, which are associated with periorificial keratotic plaques. Other clinical manifestations of OS include diffuse alopecia, leucokeratosis of the oral mucosa, onychodystrophy, hyperkeratotic linear streaks, follicular hyperkeratosis and constriction of the digits. A recent study identified *de novo* mutations in the gene for transient receptor potential vanilloid 3 (*TRPV3*), causing constitutive activation of the TRPV3 channel, as a cause of OS. We report familial inheritance of OS in a family from Mongolia, which was caused by a previously undescribed G573V point mutation in *TRPV3*. To date, mutations in the G573 residue of *TRPV3* have been reported in seven cases of OS: G573S in five cases, and G573C and G573A mutations in one case each. We present a Mongolian familial case of G573V point mutation in *TRPV3*.

Olmsted syndrome (OS) is a rare disease characterized by symmetrical, sharply defined, hyperkeratotic, mutilating plaques on the palms and soles, which are associated with periorificial keratotic plaques.[1] Other clinical manifestations of OS include diffuse alopecia, leucokeratosis of the oral mucosa, onychodystrophy, constriction of the digits, hyperkeratotic linear streaks and follicular hyperkeratosis. The onset of OS begins in the neonatal period or in childhood. The disease has a slow but progressive and extremely disabling course that includes deformities and constrictions, eventually leading to spontaneous amputations. A recent study identified *de novo* mutations of the transient receptor potential vanilloid 3 gene (*TRPV3*), causing constitutive activation of the TRPV3 channel, as a cause of OS.[2] In the present report, we describe a Mongolian family with OS caused by a previously undescribed point mutation, G573V, in *TRPV3*.

*Correspondence*: Dr Ri-Na Wu, Department of Dermatology, International Mongolia Hospital of Inner Mongolia, 83 University Road, Hohhot, Inner Mongolia, PR China
E-mail: 1036094003@qq.com

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## Report

The proband was a 39-year-old woman who presented with a 36-year history of symmetrical, sharply marginated, massive palmoplantar keratoderma affecting her palms, soles, and perioral area (Fig. 1). Her lesions had started to develop at 3 years of age, and had caused flexion deformities to the distal interphalangeal joints. The phalangeal joints became thinner and showed annular narrowing. The patient exhibited signs of hypotrichosis, nail dystrophy and hypohidrosis. Her general health was good and her physical, mental and hearing development was normal. There was no evidence of associated systemic disease. She was the first child of nonconsanguineous healthy parents.

Patient 2 was a 4-year-old boy, the only child of Patient 1, who presented with symmetrical, sharply marginated, palmoplantar keratoderma on his soles. He also had erythema and crusting of the nail edges and part of the left hand between the thumb and

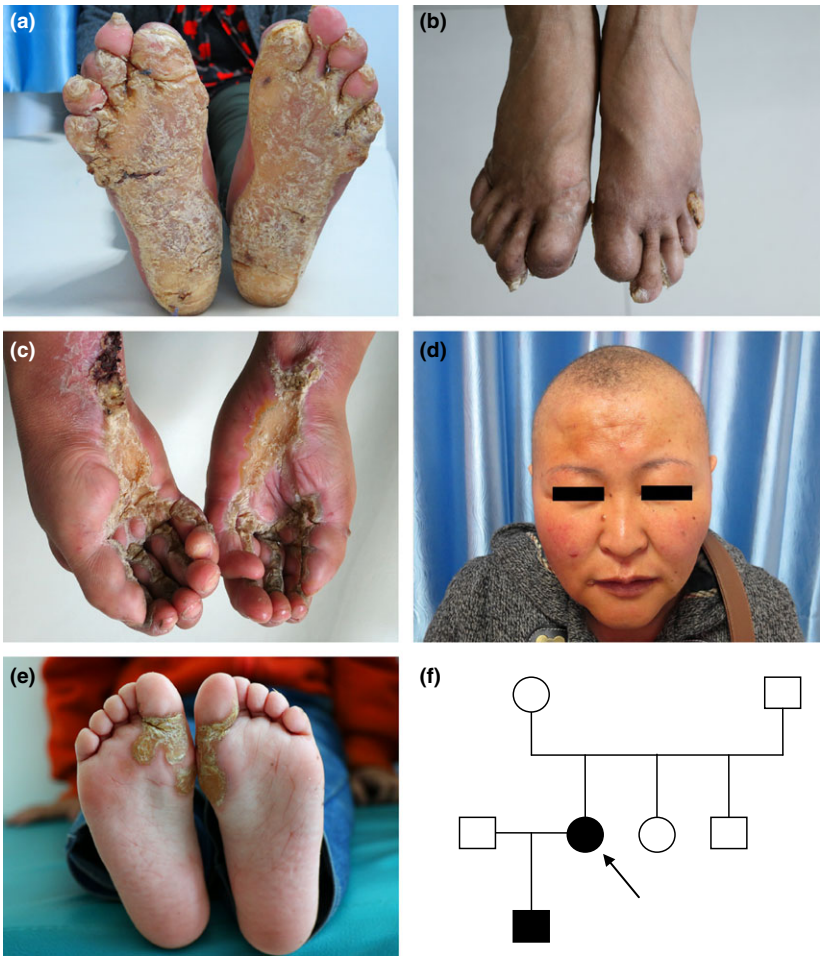


**Figure 1** (a–c) Patient 1 had bilateral, mutilating palmoplantar keratoderma, flexion deformities, and constriction of digits; and (d) dfiffuse alopecia with follicular papules. (e) Patient 2, showing bilateral palmoplantar keratoderma. (f) Family pedigree (arrow indicates the proband).

forefinger (Fig. 1), along with exhibited diffuse alopecia, hypotrichosis, nail dystrophy and hypohidrosis. He had normal teeth and oral mucosa, and normal physical, mental and hearing development.

Based on these clinical presentations, both cases were diagnosed as having OS.

Genetic studies were planned. Informed consent for publication of this report and blood sample collection were obtained in accordance with the protocols approved by our institutional review board.

DNA sequencing of the whole coding region of the *TRPV3* gene of the proband, her parents and son (Patient 2) revealed a heterozygous missense mutation of c.1718G>T (p.G573V) in the proband and her son (Fig. 2), but this mutation was not found in the proband's parents. These results indicate that this mutation occurred *de novo* in the proband and was inherited by her son.

OS is a rare congenital disorder characterized by bilateral, sharply circumscribed, palmoplantar keratoderma and periorificial keratotic plaques. Although a definite mode of inheritance remains uncertain, autosomal dominant, X-linked dominant and X-linked recessive modes of inheritance have been proposed.[3–5] The familial case of OS discussed in this report was possibly due to autosomal dominant transmission. Previous studies have demonstrated that gain-of-function mutations within TRPV3 might lead to increased apoptosis of keratinocytes and consequent skin hyperkeratosis in affected individuals, suggesting that TRPV3 plays essential roles in skin keratinization, hair growth and possibility itching sensation in humans.[6] In our two cases, a previously undescribed G573V point mutation was identified, which may render the TRPV3 channel spontaneously active. To date, mutations in the G573 residue of TRPV3 have been reported in seven cases of OS: G573S in five cases, and G573C and G573A mutations in one case each. These data, combined with our case, indicate that the G573 residue may be a mutation hotspot in *TRPV3*. This

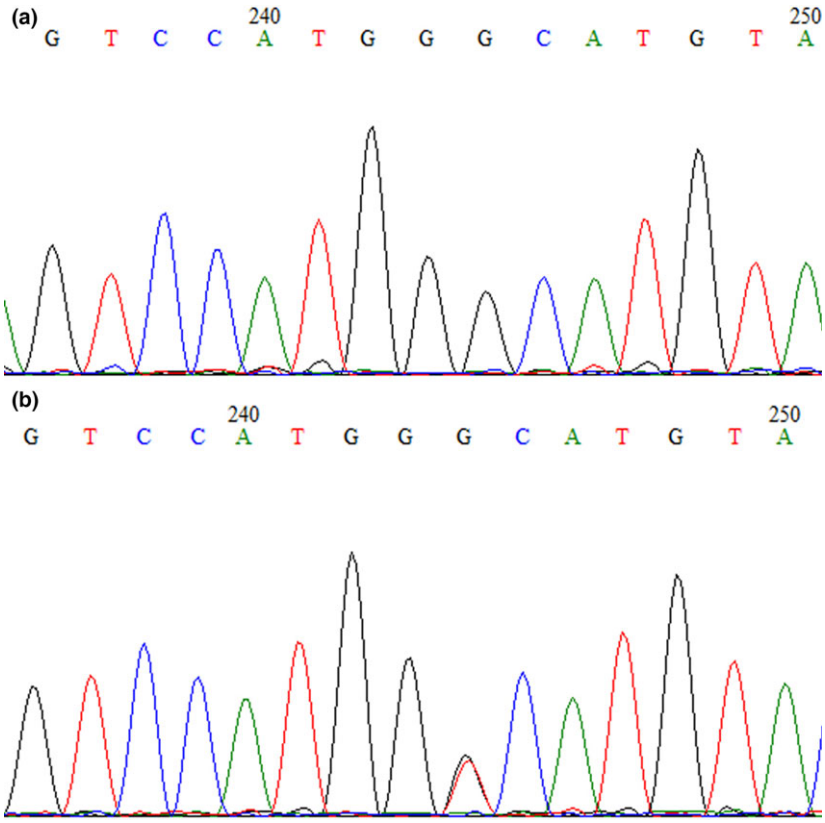


**Figure 2** (a) Normal schematic structure of TRPV3. (b) Sequencing results identified a heterozygous missense mutation, c.1718G>T (p.G573V), in the proband and her son.

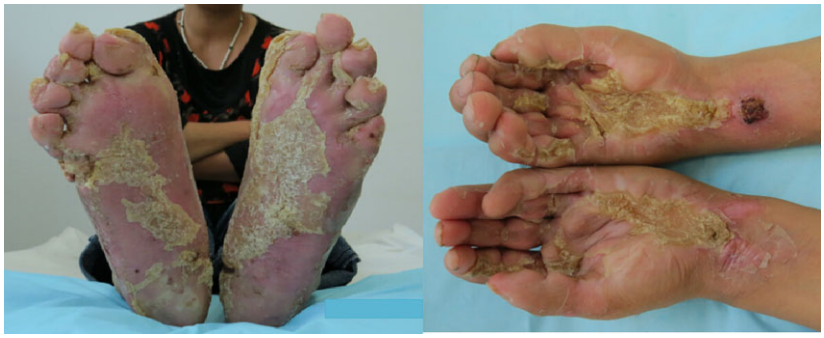

**Figure 3** Patient 1 had improvement of symptoms after 3 months of oral retinoid administration.

mutation illustrates the characteristic clinical features and complications that can present in OS, and further expands the molecular basis and indicates the therapeutic potential of this genodermatosis.

OS must be differentiated from other severe forms of palmoplantar keratoderma syndromes, such as mal de Meleda syndrome, Vohwinkel syndrome, tyrosinaemia type II, pachyonychia congenita and Papillon–Lefèvre syndrome. Acrodermatitis enteropathica can also be excluded by measurement of zinc levels.

Although there is no satisfactory treatment for OS, topical treatments, including potassium permanganate solution, wet dressings, salicylic acid in various concentrations, boric acid, urea, tar, retinoic acid, shale oil, corticosteroid therapy and prolonged soaking of the affected parts in warm water[2,7] may offer temporary symptomatic relief. For our Patient 1, the symptoms were relieved after 3 months of oral retinoid administration (Fig. 3). For nonresponsive patients, full-thickness excision of hyperkeratotic plaques followed by skin grafting presents another therapeutic option to alleviate pain.[8]

However, although this treatment may improve flexion contracture of the fingers, the risk of recurrence remains.

## Learning report

- We describe two cases of OS syndrome in a Mongolian family.
- The underlying cause was a previously undescribed G573V point mutation in TRPV3.

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