


Case Report/Case Series

A New *TRPV3* Missense Mutation in a Patient With Olmsted Syndrome and Erythromelalgia

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IMPORTANCE Olmsted syndrome (OS) is a rare keratinizing disorder characterized by excessive epidermal thickening of the palms and soles, with clinical and genetic heterogeneity. Approximately 50 cases have been reported, with the molecular basis described in only 9. Recently, *TRPV3* (transient receptor potential vanilloid 3) mutations were identified in autosomal-dominant OS in 7 sporadic cases and 1 familial case, whereas an *MBTPS2* (membrane-bound transcription factor protease, site 2) mutation was reported in X-linked recessive OS. We report a new sporadic case of severe, atypical OS and its underlying genetic basis.

OBSERVATIONS Our patient is a young girl with severe nonmutilating (palmo)plantar keratoderma without periorificial keratotic plaques associated with intense acute flares of inflammation, itching, burning pain, vasodilatation, and redness of the extremities consistent with erythromelalgia. Whole exome sequencing of patient DNA identified a novel de novo heterozygous missense mutation within *TRPV3*, p.Leu673Phe, predicted to be damaging.

CONCLUSIONS AND RELEVANCE This case study further implicates *TRPV3* in OS pathogenesis. In addition, previous reports of OS have not described erythromelalgia as a clinical feature. Its occurrence in our patient could be a chance event, but, if associated with OS, the features of erythromelalgia may expand the phenotypic spectrum of this rare syndrome.

JAMA Dermatol. 2014;150(3):303-306. doi:10.1001/jamadermatol.2013.8709
Published online January 22, 2014.

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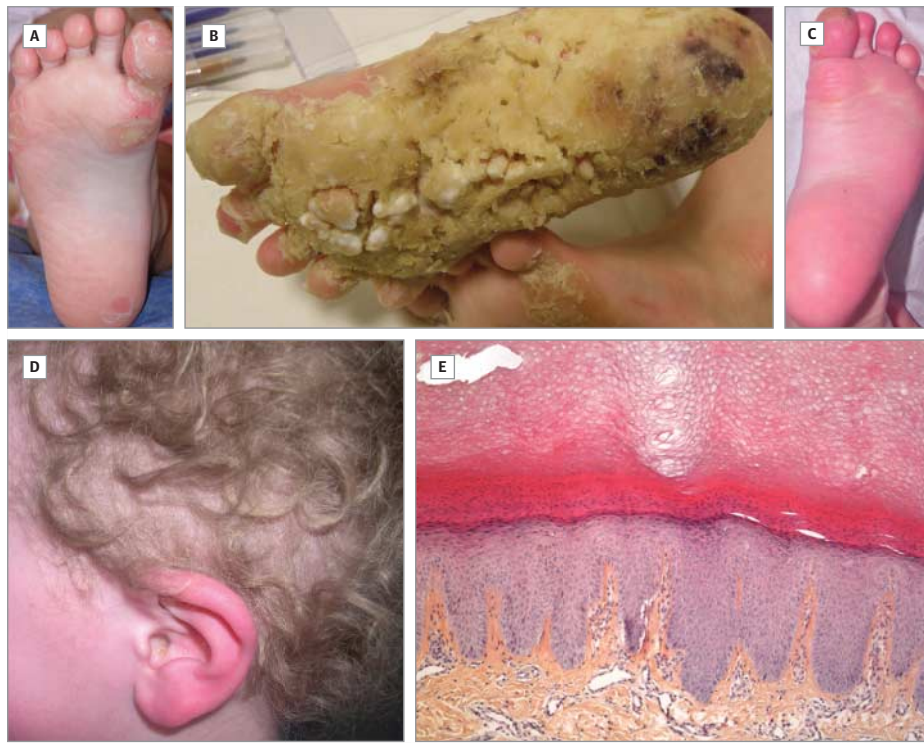
Olmsted syndrome (OS) (OMIM 14594) is a rare genodermatosis characterized by extensive palmoplantar keratoderma (PPK) and periorificial keratotic plaques.¹ Initially, these 2 features were considered diagnostic hallmarks of this syndrome. However, review of the literature reveals that OS encompasses a wide range of clinical manifestations, including variable features such as alopecia, constricting digital bands, or spontaneous digit amputation.^{2,3} This condition is therefore sometimes difficult to diagnose because of clinical overlap with other palmoplantar keratodermas. The total number of reported cases is approximately 50, of which 12 cases are familial, with different modes of inheritance. Recently, exome sequencing identified de novo heterozygous missense mutations in *TRPV3* (transient receptor potential vanilloid 3), encoding a cation channel, in autosomal-dominant OS.⁴⁻⁶ Three dominant gain-of-function mutations, p.Gly573Ser (4 patients), p.Gly573Cys (1 patient), and p.Trp692Gly (1 patient), were first described in 5 sporadic and 1 familial OS cases in Chinese patients.⁵ Subsequently, other exome studies identified the heterozygous p.Gly573Ser and p.Gly573Ala mutations in an Indian patient and a white patient with sporadic OS, respectively.^{4,6} Recently, a heterozygous missense mutation (p.Phe464Ser) in *MBTPS2* (membrane-bound transcription

factor protease, site 2), encoding a zinc metalloprotease, was detected in 2 related patients with X-linked recessive OS by means of exome sequencing, providing evidence for clinical and genetic heterogeneity in OS.⁷

Report of a Case

We studied a young girl, born at term after a normal pregnancy and delivery to healthy and nonconsanguineous parents. Her clinical symptoms started at birth with superficial peeling of the toes without hyperkeratosis or blistering. Plantar keratoderma developed after she started walking at 1 year of age, initially distributed in islands on the pressure points and gradually extending to most of the plantar surface, with no transgressions extension but dramatic thickening over time (Figure 1A and B). There was neither periorificial hyperkeratosis nor constriction or mutilation of the digits. A remarkable feature was that plantar keratoderma was associated at least since 3 years of age (age at diagnosis) with intense acute flares of severe itching, burning pain, erythema, and warmth in the extremities (hands, feet, and ears) and venous dilatation, consistent with erythromelalgia, triggered by heat

Figure 1. Clinical Features



A, Plantar keratoderma initially developed in islands on pressure points of the soles and first toes, with localized redness and peeling of the skin (2 years). B, The lesions rapidly extended to the bases of all toes, to heels, and to forefeet, associated with peripheral skin inflammation (5 years). Hyperkeratosis became massive and dramatic on the right sole, with intense itching and pain causing major disability. C and D, Ears, toes, and feet became red, swollen, and extremely painful during flares of erythromelalgia. D, Hair was thin, curly, and unmanageable. E, Skin biopsy showing hyperplastic epidermis with hyperkeratosis, parakeratosis, hypergranulosis, and papillomatosis. Capillaries are dilated in the upper dermis (hematoxylin-eosin, original magnification, $\times 100$).

(Figure 1C and D). Because of extreme foot pain, she walked on knees and hands, which resulted in mild palmar keratoderma, and has been using a wheelchair since the age of 3 years. Immersion in cold water, use of a fan, and treatment with systemic and topical steroids reduced pain. Her fingernails and toenails were thin and brittle. Her hair was fine, dry, curly, and unmanageable (Figure 1D). Microscopic examination of the hair showed superficial irregularities without specific abnormalities under polarizing microscopy. Sweating was enhanced. A skin biopsy sample stained with hematoxylin-eosin showed hyperplastic epidermis with hyperkeratosis, parakeratosis, hypergranulosis, and papillomatosis (Figure 1E).

Differential diagnoses included erythromelalgia; pachyonychia congenita (OMIM 167200 and OMIM 167210), in which nails can in rare cases show no thickening; and OS. However, no mutation in *SCN9A*, encoding the voltage-gated sodium channel α subunit Nav1.7, which is defective in primary erythromelalgia (OMIM 133020), or in *KRT6A*, *KRT6B*, *KRT16*, and *KRT17*, which are mutated in pachyonychia congenita, was identified in the patient by sequencing.^{8,9} Although our patient showed no periorificial hyperkeratosis, which was initially considered a major OS diagnostic feature but has also been reported to be absent in rare OS cases, the severity of plantar keratoderma seen in our patient, the cutaneous features, and the clinical course of the disease were highly suggestive of OS.^{3,4} When we initiated this study, the genetic basis of OS was unknown, and mutations in *TRPV3* and *MBTPS2* were reported during our analysis.

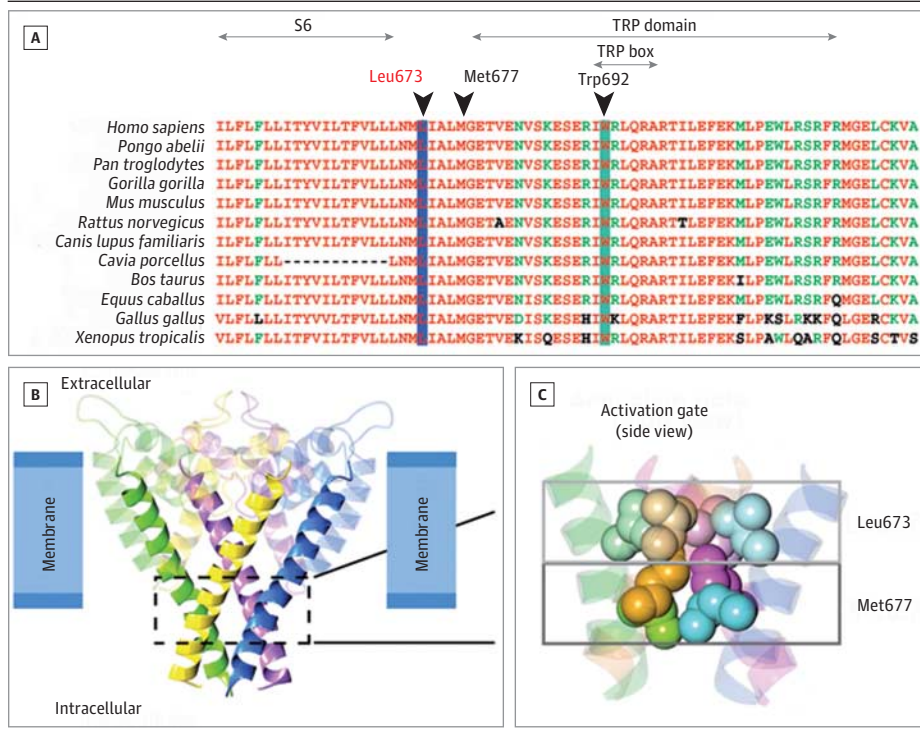
To identify the genetic cause underlying this disease, we performed whole-exome sequencing in this patient (see eMethods in Supplement). Analysis of exome data focused on

candidate genes, ie, keratin genes and other genes involved in PPKs. We identified no causative mutation except in *TRPV3*, which carried 1 heterozygous c.2017C>T substitution (NM_001258205.1) in exon 15 leading to p.Leu673Phe. We first confirmed the occurrence of this genetic variant in the patient by means of Sanger sequencing of genomic DNA and messenger RNA (see eMethods in Supplement). Sequencing showed that the c.2017C>T variation was absent in both parents, indicating that it was a de novo missense mutation. This variant was not found in 6503 individuals from the National Heart, Lung, and Blood Institute Exome Sequencing Project, in 100 normal controls, or in 253 in-house exomes.

TRPV3 is a thermosensitive cation nonselective channel, predominantly expressed in keratinocytes and in sensory neurons. This polymodal channel assembles as tetramers and is activated by temperature (31°C–39°C) and several chemical ligands.¹⁰ Remarkably, the 3 dominant missense gain-of-function *TRPV3* mutations (p.Gly573Cys, p.Gly573Ser, and p.Trp692Gly) recently identified in patients with OS lead to constitutive activity in mutant channels, resulting in enhanced keratinocyte apoptosis and hyperkeratosis.^{4,5}

The p.Leu673Phe variant identified in our patient was predicted to be damaging by in silico prediction tools (SIFT, Polyphen2, PANTHER, LRT, and MutationTaster). In addition, alignment of *TRPV3* orthologues showed that Leu673 is highly conserved among species, suggesting functional importance (Figure 2A). The p.Leu673Phe and the p.Trp692Gly mutations are located in the cytoplasmic C-terminal of the molecule. However, in contrast to the p.Trp692Gly mutation, p.Leu673Phe is not located in the transient receptor potential (TRP) box of the TRP domain. The TRP domain, a conserved

Figure 2. Localization and Modeling of the TRPV3 Mutation



A, Alignment of TRPV3 orthologues showing part of the C-terminal domain. Transmembrane domain S6 and the TRP domain and box are indicated. Leu673 (indicated in blue) is a highly conserved residue. The mutated residue (Trp692Gly) previously identified in Olmsted syndrome is indicated in green. B, Overview of a homotetrameric TRPV3 channel (each color represents a different TRPV3 molecule). Non-S6 segments are transparent to highlight S6 helices. Leu673 is located at the S6 base (dashed black rectangle). C, Enlarged representation of the TRPV3 activation gate sealed by Met677, which is directly below Leu673.

cytoplasmic region of all TRP channel families, has been proposed to have a role in subunit multimerization, channel conformation and gating, functional coupling of stimulus sensing, and pore opening.^{11,12} The p.Leu673Phe nonconservative missense mutation predominantly changes the size rather than the chemistry of residue 673 (the Phe side chain is 22.7 Å² larger in surface area than Leu). A TRPV3 homology model was generated to locate the mutated residue within an assembled channel complex (Figure 2B) (see eFigure and eMethods in Supplement). The energy-minimized model revealed that Leu673 was situated immediately above the predicted activation gate residue (Met677) on the preceding helical turn (Figure 2C). Whereas a direct effect on channel gating is conceivable, several segments capable of influencing channel activity intersect at this position (the S4-5 linker, S6 transmembrane helix, and the TRP domain). The mechanism by which the p.Leu673Phe mutation alters TRPV3 function must await future studies. Thus, all these results suggested that this variant is likely to be the mutation responsible for PPK in our patient.

Discussion

Because of the limited number of OS cases with known genetic basis, genotype-phenotype correlations remain elusive. However, noticeable differences are observed even among patients with OS with *TRPV3* mutations. These discrepancies include the severity of symptoms and the presence or absence of constricting digit bands, spontaneous digit amputation, hair anomalies, nail defects, and/or periorificial keratosis.²⁻⁶ Hair involvement varies, ranging from alopecia to thinning, coarse,

dry, and curly hair.^{2,3} In contrast to our patient, previously reported patients with OS had normal, absent, or more commonly dystrophic nails.^{2,3} Therefore, phenotypic variability in OS can result from allelic or nonallelic genetic heterogeneity, modifier genes, and/or environmental factors.

None of the previously reported OS cases had features suggestive of erythromelgia. Most cases of erythromelgia are idiopathic (primary erythromelgia); others occur secondary to medical conditions.¹³ Primary erythromelgia is an inherited condition with autosomal-dominant inheritance and is mostly caused by mutation in *SCN9A*, but other genes remain to be identified.⁸ Reported secondary causes of erythromelgia include disorders such as neurological, autoimmune, or hematological diseases for which we have no evidence in our patient.¹³ Because we report a sporadic case, we could not explore cosegregation of erythromelgia with OS in this family. Thus, we cannot establish whether cooccurrence of erythromelgia and OS in our patient is coincidental or is part of the phenotypic spectrum of OS. Although no mutation in *SCN9A* was identified, we could not formally exclude the occurrence of an additional de novo mutation in a second gene in our patient with no familial history of erythromelgia. Conversely, *TRPV3* is implicated in skin inflammation and nociceptive signaling, suggesting that symptoms of erythromelgia could also result from the consequences of the *TRPV3* mutation identified in our patient.¹⁴ Atypical cases lacking classical OS clinical features and presenting with additional unusual manifestations, such as corneal dysplasia, hearing loss, or squamous cell carcinoma, have been previously reported, supporting clinical heterogeneity in OS.^{2,3,15} The identification of similar cases with OS associated

with erythromelalgia will be necessary to link erythromelalgia to OS and *TRPV3* mutation.

Conclusions

In summary, our findings identify a novel missense mutation in *TRPV3* and corroborate that *TRPV3* mutations are recur-

rent in autosomal-dominant OS. Our findings further support the notion that *TRPV3* is a major gene in OS physiopathogenesis. We report for the first time, to our knowledge, the association of OS with severe erythromelalgia in 1 sporadic case, which could be incidental or expands the spectrum of atypical manifestations associated with OS. The molecular mechanisms through which this *TRPV3* mutation alters channel function and leads to OS are yet to be determined.

ARTICLE INFORMATION

Accepted for Publication: September 26, 2013.

Published Online: January 22, 2014.
doi:10.1001/jamadermatol.2013.8709.

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Author Contributions: Dr Hovnanian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Critical revision of the manuscript for important intellectual content: Duchatelet, Pruvost, de Veer, Fraitag, Bodemer, Hovnanian.
Obtained funding: Hovnanian.
Administrative, technical, or material support: Pruvost, Bole-Feysot, Bodemer.
Study supervision: Bodemer, Hovnanian.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by a donation from the BDE-Bulle d'encre association.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are indebted to the young patient and her parents for their participation in this study and to the BDE-Bulle d'encre association for supporting part of this work.

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