

## REVIEW

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# Olmsted syndrome: clinical, molecular and therapeutic aspects

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## Abstract

Olmsted syndrome (OS) is a rare genodermatosis classically characterized by the combination of bilateral mutilating transgradient palmoplantar keratoderma (PPK) and periorificial keratotic plaques, but which shows considerable clinical heterogeneity. The disease starts usually at birth or in early childhood. About 73 cases have been reported worldwide. OS is observed in both sexes, although male cases are more frequent. The most suggestive symptoms associate PPK with pseudoainhum and periorificial keratotic plaques. Frequently associated features include hair and nail abnormalities, leukokeratosis, corneal defect and recurrent infections. Pain and itching are variable but can be severe. Most of reported OS cases are sporadic, although familial cases with different mode of inheritance were also described. Mutations in *TRPV3* (Transient receptor potential vanilloid-3) gene have recently been identified as a cause of autosomal dominant (gain-of-function mutations) or recessive OS. Mutations in *MBTPS2* (membrane-bound transcription factor protease, site 2) gene were identified in a recessive X-linked form. The diagnosis relies mainly on clinical features associating severe PPK and periorificial keratotic plaques, but can be challenging in patients with incomplete phenotype or atypical features. OS has to be differentiated from other severe forms of PPK including Vohwinkel, Clouston, Papillon-Lefèvre or Haim-Munk syndromes, Mal de Meleda, pachyonychia congenita, Tyrosinemia type II and acrodermatitis enteropathica. When differential diagnoses are difficult to exclude, genetic studies are essential to search for a *TRPV3* or *MBTPS2* mutation. However, additional genes remain to be identified. No specific and satisfactory therapy is currently available for OS. Current treatments of hyperkeratosis (mainly emollients, keratolytics, retinoids or corticosteroids), either topical or systemic, are symptomatic and offer only temporary partial relief. Specific management of pain and itching is important to reduce the morbidity of the disease. The disease is debilitating and progressive keratoderma and auto-amputation of digits can prevent patients from grasping and walking, and confine them to a wheelchair. New therapeutic options are therefore crucial and are expected from a better understanding of the disease mechanisms. The use of TRPV3 antagonists would represent such a targeted and potentially powerful strategy.

**Keywords:** Olmsted syndrome, Palmoplantar keratoderma, Periorificial keratotic plaques, Clinical heterogeneity, TRPV3, MBTPS2

## Résumé

Le syndrome d'Olmsted (SO) est une génodermatose rare et sévère, classiquement caractérisée par une kératodermie palmo-plantaire (KPP) bilatérale transgrédiente et mutilante associée à des plaques kératosiques péri-orificielles. Il existe une grande hétérogénéité clinique. Des anomalies des cheveux et des ongles, une leukokératose, des anomalies de la cornée et de fréquentes infections peuvent être associées. La douleur et le prurit sont variables, mais peuvent être sévères. La maladie (Continued on next page)

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débutent généralement à la naissance ou pendant la petite enfance. Environ 73 cas ont été rapportés à travers le monde. La maladie touche les deux sexes. La plupart des cas sont sporadiques, bien que des cas familiaux avec différents modes de transmission aient également été décrits. Des mutations du gène *TRPV3* (Transient receptor potential vanilloid-3) ont récemment été identifiées dans les formes autosomiques dominante (mutations gain-de-fonction) et récessive. Des mutations du gène *MBTPS2* (membrane-bound transcription factor protease, site 2) ont été rapportées dans une forme récessive liée à l'X. Le diagnostic est essentiellement clinique, reposant sur l'association d'une KPP sévère et de kératoses péri-orificielles ; mais il peut être difficile chez les patients ayant une présentation incomplète ou des symptômes atypiques. Le SO doit être différencié des autres KPP sévères telles les syndromes de Vohwinkel, de Clouston, de Papillon-Lefèvre ou de Haim-Munk, le Mal de Meleda, la pachyonychie congénitale, la tyrosinémie de type II et l'acrodermatite entéropathique. Lorsque le diagnostic est difficile à établir, les études génétiques sont essentielles afin de rechercher une mutation des gènes *TRPV3* ou *MBTPS2*. Cependant, d'autres gènes restent à identifier. Il n'existe à ce jour pas de traitement spécifique du SO. Les traitements actuels de l'hyperkératose comprennent essentiellement des émoullissants, kératolytiques, rétinoïdes et corticoïdes, locaux ou systémiques. La prise en charge spécifique de la douleur et du prurit représente un aspect important du traitement. La KPP massive et l'auto-amputation des doigts peuvent être très invalidants. Le développement de nouveaux traitements est crucial et attendu d'une meilleure compréhension des mécanismes pathologiques de la maladie. L'utilisation d'antagonistes de TRPV3 représenterait une nouvelle option thérapeutique prometteuse.

## Introduction

Olmsted syndrome (OS) is a rare genodermatosis belonging to the heterogeneous group of palmoplantar keratoderma (PPK). OS shows marked clinical and genetic heterogeneity. The aim of this article is to give an updated review of clinical features, genetics, pathological mechanisms, diagnostic criteria, differential diagnosis and current treatment.

## Methods

### Literature review

This review is based on a literature search using PubMed. To identify all publications related to Olmsted syndrome and summarize reported cases, a comprehensive search of PubMed was performed for all studies published prior to December 1, 2014, using the search terms "Olmsted syndrome", "mutilating palmoplantar keratoderma" or "periorificial keratoderma". We then checked the bibliography of each article to identify additional references. Altogether, 59 reports containing a total of 73 OS were identified from 1927 until December 1, 2014.

## Review

### Disease name and synonyms

Mutilating palmoplantar keratoderma with periorificial keratotic plaques (ORPHA659, MIM #614594 and #300918)

Olmsted Syndrome (OS)

Palmoplantar and periorificial keratoderma

### Definition

Olmsted syndrome is a rare keratinizing disorder characterized by the combination of bilateral mutilating trans-gredient palmoplantar keratoderma and periorificial keratotic plaques. This syndrome was first described in 1927 by Olmsted [1]. Since that date, similar cases have

been reported in the literature under the heading of Olmsted syndrome.

### Epidemiology

Olmsted syndrome is a rare genodermatosis. The prevalence of the syndrome is unknown. To date, about 73 cases have been reported in the literature (Table 1). Although the number of cases is probably underestimated, the prevalence is likely to be less than 1/1000000.

The disease seems to occur worldwide and is observed in both sexes, although male cases (~63% of OS patients) have been predominantly reported (Table 1).

### Clinical description

The classical clinical phenotype of OS consists of bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques. However, OS shows high clinical variability and a wide range of inconsistent clinical manifestations have been reported [36,44]. Other features associated with this condition have been described subsequently and continue to be reported. Clinical manifestations described in detail below are not specific for OS, they can be rarely observed and can also vary in severity. In addition, some features observed in OS patients may be fortuitous and not a part of this syndrome. The disease starts usually at birth, in neonatal period or in early childhood, when the child starts to walk and grasp, and worsens over time. The disease has a slow but progressive course.

### Skin

Initially, the hallmarks for the diagnosis of OS are bilateral mutilating palmoplantar keratoderma (Figure 1A) associated with periorificial keratotic plaques (mouth, nose, eyes, genital, anal, ears, navel) (Figure 1B) [1]. Indeed, progression of the keratoderma may lead to flexion deformities,

**Table 1 Reported Olmsted syndrome cases in the literature**

Reference	Number of cases	Sex	Mutation
Olmsted, 1927 [1]	1	Male	Not reported
Costa, 1962 [2]	1	?	Not reported
Keir, 1967 [3]	1	Female	Not reported
Ruiz-Maldonado et al., 1972 [4]	1	Female	Not reported
Michalowski, 1983 [5]	1	Male	Not reported
Poulin et al., 1984 [6]	1	Male	Not reported
Barnett et al., 1985 [7]	1	Male	Not reported
Harms et al., 1985 [8]	1	Male	Not reported
Rivers et al., 1985 [9]	4 (child, father, paternal aunt and grandmother)	2 females, 2 males	Not reported
Battini et al., 1989 [10]	1	Male	Not reported
Georgii et al., 1989 [11]	1	Female	Not reported
Atherton et al., 1990 [12] and Armstrong et al., 1997 [13]	1 (son of case reported in Keir, 1967 [3])	Male	Not reported
Judge et al., 1991 [14]	1	Male	Not reported
Hausser et al., 1993 [15]	1	?	Not reported
Ueda et al., 1993 [16] and Yoshizaki et al., 2001 [17]	1	Male	Not reported
Lucker et al., 1994 [18]	1	Male	Not reported
Cambiaghi et al., 1995 [19]	2 (twins)	Male	Not reported
Kress et al., 1996 [20] and Raskin and Tu, 1997 [21]	1	Female	Not reported
Dogra et al., 1997 [22]	1	Male	Not reported
Frias-Iñiesta et al., 1997 [23]	1	Male	Not reported
Santos et al., 1997 [24]	1	Male	Not reported
Sirka et al., 1999 [25]	1	Male	Not reported
Larregue et al., 2000 [26]	2	Male	Not reported
Fonseca et al., 2001 [27]	1	Female	Not reported
Koch et al., 2001 [28]	1	Female	Not reported
Requena et al., 2001 [29]	1	Male	Not reported
Bergonse et al., 2003 [30]	2	Male	Not reported
Dessureault et al., 2003 [31]	1	Female	Not reported
Ogawa et al., 2003 [32]	1	Female	LOR excluded
Batra and Shah, 2004 [33]	1	Male	Not reported
Inamadar et al., 2004 [34]	1	Male	Not reported
Al-Mutairi et al., 2005 [35]	1	Female	Not reported
Mevorah et al., 2005 [36] and Eytan et al., 2014 [37]	1	Male	TRPV3 p.Trp521Ser
Ziaaddini et al., 2006 [38]	1	Male	Not reported
Ali et al., 2007 [39]	3 (2 brothers)	2 Males, 1 ?	Not reported
Yaghoobi et al., 2007 [40] and Haghighi et al., 2012 [41]	2 (uncle, nephew)	Male	MBTPS2 p.Phe464Ser
Bedard et al., 2008 [42]	2	Female	Not reported
Kumar et al., 2008 [43]	1	Female	Not reported
Tao et al., 2008 [44]	1	Male	Not reported
Nofal et al., 2010 [45]	2 (sister)	Female	Not reported
Vosynioti et al., 2010 [46]	1	Male	Not reported
Tharini et al., 2011 [47]	2	Female	Not reported

**Table 1 Reported Olmsted syndrome cases in the literature (Continued)**

Elise Tonoli <i>et al.</i> , 2012 [48]	1	Female	Not reported
Lai-Cheong <i>et al.</i> , 2012 [49]	1	Male	TRPV3 p.Gly573Ser
Lin <i>et al.</i> , 2012 [50]	6	5 females, 1 male	TRPV3 p.Gly573Ser (4 cases), p.Gly573Cys (1 patient) and p.Trp692Gly (1 case)
Tang <i>et al.</i> , 2012 [51]	1	Male	Not reported
Attia <i>et al.</i> , 2013 [52]	1	Male	Not reported
Danso-Abeam <i>et al.</i> , 2013 [53]	1	Female	TRPV3 p.Gly573Ala
Alotaibi <i>et al.</i> , 2014 [54]	1	Male	Not reported
Duchatelet <i>et al.</i> , 2014a [55]	1	Female	TRPV3 p.Leu673Phe
Duchatelet <i>et al.</i> , 2014b [56]	2 (brother)	Male	TRPV3 p.Gly568Cys and p.Gln216_Gly262del
He <i>et al.</i> , 2014 [57]	2 (father and son)	Male	TRPV3 p.Gln580Pro
Kariminejad <i>et al.</i> , 2014 [58]	1	Male	TRPV3 p.Trp692Cys
Wang <i>et al.</i> , 2014 [59]	1	Male	MBTPS2 c.671-9 T > G
<b>Total</b>	73	26 Females, 44 Males	14 TRPV3 mutations 2 MBTPS2 mutations

constrictions of digital bands and even spontaneous digit amputations. However, this pseudoainhum feature is in fact inconsistently reported in OS patient [45]. In addition, in rare cases, periorificial keratotic plaques are absent [55,56]. Keratoderma is initially focal and distributed on the pressure points, gradually extends to most of the surface and becomes diffuse, massive and thicker with time with painful deep fissures. The keratotic lesions are pruritic and can be painful with pressure. Some cases present with focal or punctuate keratoderma [45,57]. A clear improvement of the keratoderma during febrile diseases may occur [19]. Other

patients are reported with nonperiorificial keratotic lesions involving the thighs, arms, elbows, knees and intertriginous folds. Hyperkeratotic linear streaks [45,52], follicular keratosis [40], pachyderma, cheilitis [47], ichthyotic lesions or chronic blepharitis [14,23,40] may be also observed.

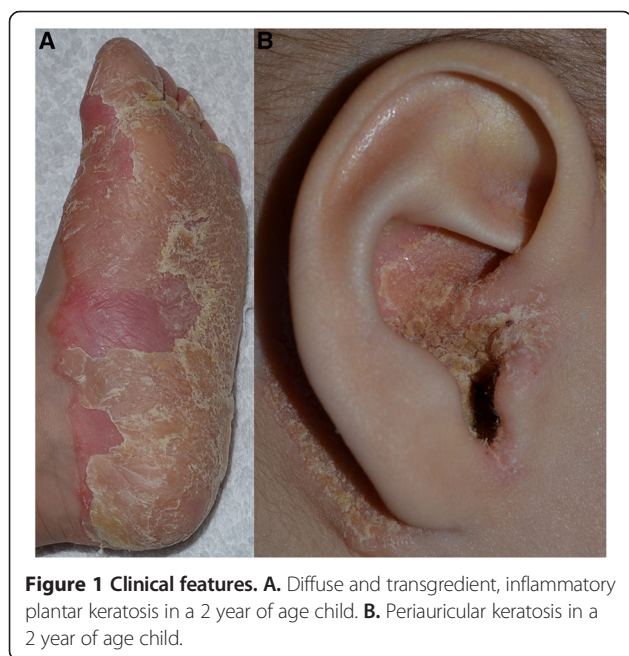
**Pain and itching**

Slight to severe pain with variable intensity is a frequent feature of OS [6,9,18,36,44,45]. Painful PPK is reported in around 50% of OS cases, it can be disabling causing most of the time the patient to avoid walking and grasping. In the less severe patients, only slight pain not interfering with hand and feet activities (walking, writing, grasping objects) is mentioned [45].

Itch has also been reported, although less frequently [36,44]. Pruritus, which can be severe, is mentioned in around 16% of OS cases.

Thus, pain and itch represent major causes of morbidity resulting in insomnia and interfering with walking and grasping.

Atypical OS, with nonmutilating PPK and no periorificial keratotic plaques, associated with erythromelalgia is rarely observed [55,56]. Pain and itching are reported to be particularly severe in uncommon OS patients with erythromelalgia which lead to acute flares of hyperalgesia, severe itch, erythema, vasodilatation and warmth of the legs and extremities (hands, feet and ears) [55,56]. Erythromelalgia is triggered by heat and pain and is reduced by immersion in cold water. In these patients presenting with dysesthesia (tingling or burning sensations) and allodynia with increased sensitivity to thermal and mechanical stimuli, the pain has clearly features of neuropathic pain. The extend to which similar but less



**Figure 1 Clinical features. A.** Diffuse and transgredient, inflammatory plantar keratosis in a 2 year of age child. **B.** Periauricular keratosis in a 2 year of age child.

severe features could be present in other cases of OS remains to be evaluated.

#### Hair and nails

The vast majority of patients present with hair abnormalities including alopecia (diffuse, universal or patchy), hypotrichosis, sparse, thinning, curly, woolly, coarse, dry or easily broken hair [22,36,44,47,51]. Microscopic Hair examination may show pili torti, trichorrhexis nodosa type defects, reduced pigment, as well as longitudinal ridges and transverse fractures of the hair shaft [19,22,36]. Rare OS cases have normal hair.

Sparse and thin eyebrows and eyelashes but also madarosis are also reported [19,40]. In contrast, eyelash trichomegaly is also observed in OS patients [56].

OS patients often show nails abnormalities including dystrophic, lusterless, ridged, rough nails, hyperkeratosis, onychogryphosis, leukonychia, irregular curvatures, onycholysis, paronychia, subungual hyperkeratosis and even absence of nails [22,32,36,43–45,60].

#### Oral cavity

Leukokeratosis of the tongue or buccal mucosa have been noted [2,6,11,16,24,27,33,36].

#### Sweating

Sweating abnormalities such as palmoplantar hyperhidrosis or anhidrosis, acral hyperhidrosis are reported in OS patients [29,61].

#### Eye

Eyes lesions are frequently described in OS patients, including corneal dystrophy, epithelial dysplasia and opacity [10,14,40]. Inflamed lacrimal glands/ducts or meibomian glands dysfunction are also observed.

#### Growth

Delayed physical development leading to short stature is frequently described in OS patient [32,36,59].

#### Recurrent infections

OS patients are prone to recurrent bacterial or candidal infections in keratotic areas [11,14,20,26,27,30]. Perionychial infections are also mentioned.

#### Immunity

The immunological phenotype was assessed in one OS patient and demonstrated immune dysregulation leading to frequent dermal infections, inflammatory infiltrate in the affected areas, hyper IgE production and elevated follicular T cells and eosinophils in the peripheral blood [53]. Immunodeficiency of an unknown origin has been also reported in another patient [11].

#### Predisposition to malignancies

OS patients may have a higher susceptibility to develop malignant tumors in keratotic areas such as verrucous carcinoma (a squamous cell carcinoma) and its variant epithelioma cuniculatum located on the sole of the foot, and malignant melanoma [7,15,17,31,32,62].

#### Teeth

Abnormal dentition with absence of premolar teeth [6], mammilations on the free margins of the incisors [34] or periodontal disease leading to premature teeth loss [54] are mentioned.

#### Hearing

Hearing loss for high frequencies and congenital deaf-mutism are noted in few OS patients [6,11,29,48].

#### Bone

Deformed lower extremities (bow legs) as well as ankylosis (knee and ankles joints), likely resulting from long-term impeded mobility due to painful hyperkeratosis, are described [51]. Osteoporosis and osteolysis of hands and feet [2,3,6,24,26,32] have been also reported.

#### Other abnormalities

Other abnormalities including joint laxity [6,11,16,26], primary sclerosing cholangitis [11], intellectual disability [1,12] and haemangioma [35] are also rarely observed in OS patients.

Thus, OS syndrome may result from multiple defects in embryonic structures with a major ectodermal involvement as found in ectodermal dysplasia, with possible minor mesodermal abnormality as manifested by hyperlaxity of joints in some cases.

#### Aetiology

##### Genetics

Most reported OS cases are sporadic, although familial cases with different modes of inheritance (dominant or recessive autosomal or X-linked inheritance) were also reported.

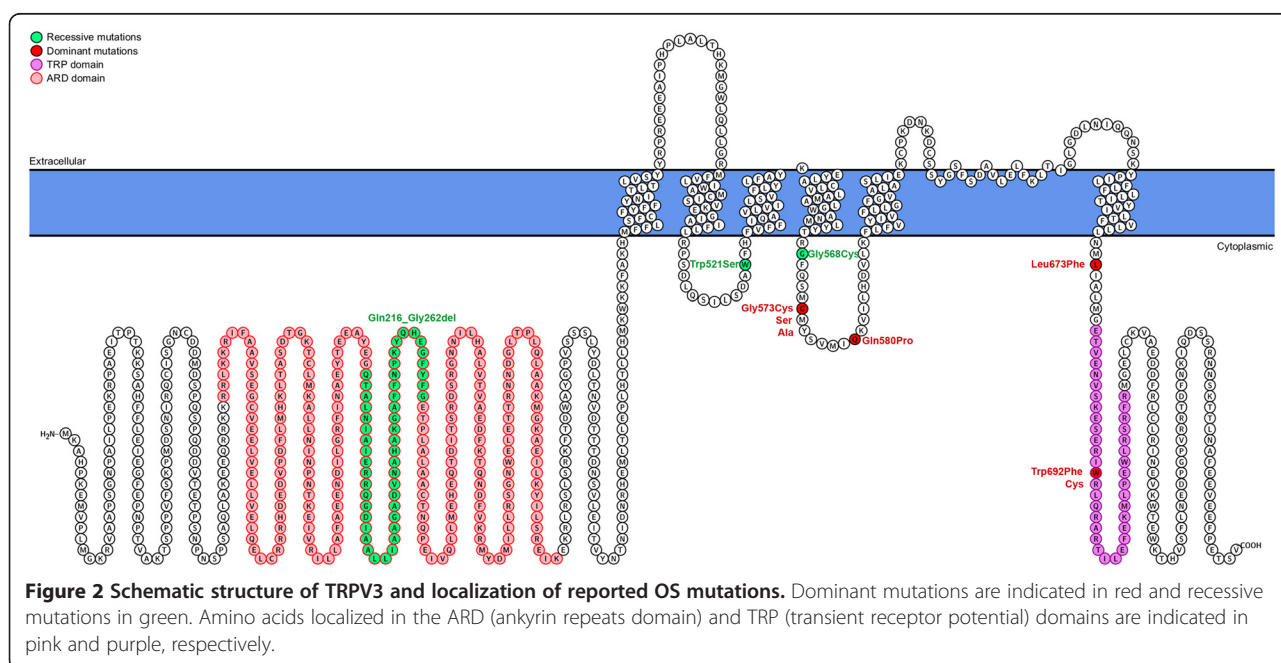
Recently, the genetic basis has been partially elucidated by the identification of mutations in *TRPV3* (Transient receptor potential vanilloid-3) in 14 OS patients with different genetic background (Chinese, Indian, Iranian, Arabic, Caucasian) [37,49,50,53,55–58]. *TRPV3* has been reported as a thermosensible cation non selective channel, activated by temperature and several chemical ligands, predominantly expressed in keratinocytes, and in sensory neurons [63,64]. *TRPV3* is a transmembrane channel belonging to the family of TRP (Transient receptor potential) [63,64] and consists of 6 transmembrane domains with cytoplasmic N and C-termini, assembling as tetramers. *TRPV3* mutations are responsible for autosomal dominant but also

recessive OS (Figure 2). To date, 7 dominant mutations (p.Gly573Ser in 5 unrelated patients, p.Gly573Cys, p.Gly573Ala, p.Gln580Pro, p.Leu673Phe, p.Trp692Gly and p.Trp692Cys each in a unique case) have been reported (Figure 2). Several dominant mutations were demonstrated to be gain-of-function mutations leading to an increased intracellular Ca<sup>2+</sup> [50,57]. Three recessive mutations (p.Trp521Ser in a homozygous state in one patient, and p.Gly568Cys and p.Gln216-Gly262del in a compound heterozygote state in two brothers) were also reported (Figure 2) [37,49,50,53,55–58]. Thus, the Gly573 residue, and Trp692 to a lesser extent, are recurrently mutated. In addition, all mutations, except for two recessive mutations, are located in the S4-5 linker or in the C-terminal part of the protein (Figure 2). The recessive p.Trp521Ser and p.Gln216-Gly262del (resulting from the splicing site mutation c.784 + 1G > A) mutations are located in the S2-3 linker and in the N-terminal part of the protein respectively (Figure 2). OS caused by *TRPV3* mutations shows clinical heterogeneity. Indeed, OS patients with *TRPV3* mutations present either with typical OS hallmarks or incomplete phenotype with atypical features. Genotype-phenotype correlations are difficult to establish at present because of the few reported cases. However, the 5 patients with the same p.Gly573Ser mutation present with a similar phenotype including mutilating PPK with variable severity, hair abnormalities (from dry hair to alopecia) and keratotic plaques (periorificial or only in the natal cleft). In the other hand, other mutations, located in the same part or in different domains of the protein, are associated with atypical features (Figure 2). The p.Leu673Phe (dominant), p.Gly568Cys (recessive) and p.Gln216-Gly262del (recessive)

mutations lead to atypical OS, with nonmutilating PPK and no periorificial keratotic plaques, associated with erythromelalgia [55,56]. The patient with the p.Gly573Ala presents with immune dysregulation [53]. The 2 related patients with the p.Gln580Pro mutation have a very mild phenotype with only focal PPK even at 37-year-old for the father [57].

Mutations in *MBTPS2* (membrane-bound transcription factor protease, site 2) gene (p.Phe464Ser and c.671-9 T > G), encoding a zinc metalloprotease essential for cholesterol homeostasis and endoplasmic reticulum stress response, have also been reported in recessive X-linked OS [41,59]. Mutations in *MBTPS2* also lead to IFAP (Ichthyosis follicularis - atrichia - photophobia) syndrome with or without BRESHECK syndrome (MIM #308205, ORPHA2273) [65]. BRESHECK syndrome is a multiple congenital malformation characterized by intellectual disability, brain anomalies, Hirschsprung disease, corneal opacifications, kidney dysplasia, cryptorchidism, cleft palate, and skeletal malformations, particularly of the vertebrae. The OS patient with the c.671-9 T > G mutation also presents with classic IFAP syndrome [59], whereas previously reported patients with the same mutation in *MBTPS2* has no OS features. The mechanism by which *MBTPS2* mutations lead to IFAP or OS is currently unclear.

There is no obvious clinical difference between OS caused by *TRPV3* and *MBTPS2* mutations despite the mode of inheritance. In addition, clinical variability is observed even in patients from the same family or unrelated patients harbouring the same mutation, suggesting the implication of modifier genes, epigenetics and/or environmental factors.



Finally, some patients do not carry detectable mutations in either gene, indicating further genetic heterogeneity.

**Pathogenesis**

The pathogenesis of OS is poorly understood. However, a defect in the expression of mature epidermal keratins (1 and 10) and persistence of basal keratins (5 and 14) was reported [20,21,27,45], as well as increased expression of Ki-67, a mitotic activity marker in basal and suprabasal layers [29,44,48]. Thus, involved areas remain in an immature state and continue to proliferate in an improper fashion. This excessive epithelial proliferation may result in hyperkeratosis. The mechanism by which *TRPV3* mutations lead to OS pathogenesis is unknown. Functional studies of four *TRPV3* mutations (p.Gly573-Ser, p.Gly573Cys, p.Trp692Gly and p.Gln580Pro) using patch clamp analysis on transfected HEK293 cells expressing *TRPV3* mutants were performed [50,57]. These studies have shown that these mutations lead to much larger inward currents probably because of the constitutive opening of the mutants [50]. Thus, these mutations are gain-of-function mutations and result in elevated intracellular Ca<sup>2+</sup> inducing increased apoptosis, suggesting that enhanced cell-death could drive OS [50]. In addition, murine models have shown that *TRPV3* is also associated with TGF- $\alpha$ /EGFR signaling, which plays a role in keratinocyte differentiation control [66]. Reported immune dysregulation in OS suggests a primary (as *TRPV3* is expressed by Langerhans cells) or secondary role of immunological processes in OS pathogenesis [53]. Transcriptomic and proteomic investigation in patients with the p.Gln580Pro mutation, leading only to focal PPK, showed decreased expression of proteins involved in keratinocyte differentiation, in gap junction, tight junction and desmosome formation, but increased expression of proteins involved in keratinocyte proliferation and cell death [57]. Thus, the *TRPV3* p.Gln580Pro gain-of-function mutation disrupts the balance between keratinocyte proliferation and differentiation, and compromises cell adhesion. In addition, previous studies on murine models have also demonstrated that *TRPV3* mediates release of pro-inflammatory cytokines including interleukin IL-1 $\alpha$  [67], an important mediator of cutaneous inflammation, but also prostaglandin E2 [68]. Of note, *TRPV3* is expressed in nociceptive neurons. Thus, it is also likely that *TRPV3* over-activation leads to local overproduction of inflammatory cytokines which could affect the somatosensory system, leading to a peripheral neuropathic pain.

**Diagnosis and diagnostic methods**

Olmsted syndrome diagnosis relies on the clinical presentation. Initially, the diagnostic hallmarks of OS are the association of bilateral transgredient mutilating

palmoplantar keratoderma and periorificial keratotic plaques (mouth, nose, eyes, genital, anal, ears, navel) which allows exclusion of other hyperkeratotic related disorders. However, subsequent reports showed that this full-blown OS is not always observed, making the diagnosis challenging for patients with partial cutaneous expression of OS. Unfortunately, the histopathology of skin sections shows epidermal hyperplasia, orthohyperkeratosis, focal parakeratosis, hypergranulosis, acanthosis, and inflammatory infiltration in upper dermis, which are unspecific and of limited use to orientate the diagnosis. In the absence of specific biologic markers, molecular genetics is the most powerful approach to establish the diagnosis when the clinical presentation is unusual.

**Differential diagnosis**

The diagnosis of Olmsted syndrome is supported by clinical criteria that require the exclusion of other diseases. OS has to be differentiated from other severe forms of PPK, such as Vohwinkel syndrome (MIM#124500 and 604117, ORPHA494 and ORPHA79395), Mal de Meleda (MIM#248300, ORPHA87503), Clouston syndrome (MIM#129500, ORPHA189), Papillon-Lefèvre syndrome (MIM#245000, ORPHA678), pachyonychia congenita (MIM#167200 and 167210, ORPHA2309), Tyrosinemia type II (MIM#276600, ORPHA28378) and Haim-Munk syndrome (MIM#245010, ORPHA2342) (Table 2) [52]. The periorificial involvement is the unique characteristic of OS that allows exclusion of the above syndromes. However, because of periorificial involvement, OS is easily confused with acrodermatitis enteropathica (MIM#201100, ORPHA37) which however can be excluded by measurement of zinc levels. Indeed, low plasma level of zinc is diagnostic of acrodermatitis enteropathica which shows improvement after oral zinc therapy, unlike OS. Thus, the full-blown OS with its typical association of mutilating bilateral PPK and periorificial keratotic plaques is distinctive enough to lead to the correct diagnosis.

**Table 2 Differential diagnosis and underlying molecular basis**

Disease	Gene	Mode of inheritance
Vohwinkel syndrome	<i>GJB2, LOR</i>	Autosomal dominant
Mal de Meleda	<i>SLURP1</i>	Autosomal recessive
Papillon-Lefèvre syndrome	<i>CTSC</i>	Autosomal recessive
Clouston syndrome	<i>GJB6</i>	Autosomal dominant
Pachyonychia congenita	<i>KRT6A, KRT6B, KRT16 and KRT17</i>	Autosomal dominant
Tyrosinemia type II	<i>TAT</i>	Autosomal recessive
Haim-Munk syndrome	<i>CTSC</i>	Autosomal recessive
Acrodermatitis enteropathica	<i>SLC39A4</i>	Autosomal recessive

However, the diagnosis becomes challenging for patients with partial and moderate cutaneous expression because of clinical overlap with other PPK mentioned above. In this case, OS diagnosis should be considered and molecular genetics and the mode of inheritance may help to discriminate these disorders (Table 2). The difficult clinical and histopathological distinction between different PPK makes genetic testing important in the diagnostic approach to these patients.

#### Genetic counselling and antenatal diagnosis

Most reported OS cases are sporadic, although familial cases were also reported. For familial cases, the mode of inheritance of OS has not been clearly established. Thus, different modes of inheritance have been suggested including dominant or recessive autosomal pattern but also dominant or recessive X-linked inheritance.

As with all severe genetic disorders, genetic counselling and psychological support are appropriate and requested for the families, to discuss the aetiology, the probability of occurrence in future pregnancies, the possibilities of early prenatal diagnosis and current treatment available.

#### Management including treatment

There is currently no specific nor satisfactory treatment for OS. Skin lesions are usually refractory to therapy. Different treatments have been tried with varying success to reduce hyperkeratosis. Topical treatments including emollients (white petrolatum), keratolytics (urea, salicylic acid), wet dressing, boric acid, tar, retinoid acid, shale oil, corticosteroids, steroids are attempted with poor to moderate improvement. In several OS patients, systemic retinoids (acitretin, etretinate), corticosteroid or methotrexate were used with poor to moderate relief [9,15,16,51]. Repeated partial excision of palmoplantar keratosis or full-thickness excision with skin grafting have been also performed for few patients but was usually followed by recurrence of the hyperkeratosis after initial improvement [42].

Until now, treatments either topical or systemic only offer temporary partial symptomatic relief of pain and fissures by reducing the thickness keratotic palmoplantar skin lesions. Specific treatments of pain and itching are essential to reduce the morbidity of the disease. Painkillers and topical lidocaine can be effective, but for patients with severe pain and especially when erythromelalgia and/or neuropathic pain are present, anti-inflammatory drugs, anticonvulsants (carbamazepine, gabapentin, pregabalin), tricyclic antidepressants (amitriptyline, nortriptyline) and lastly opioid analgesics (tramadol) are required to alleviate the pain of these patients. Prolonged soaking of the affected parts in cold water may reduce pain. However, these treatments are ineffective in arresting the course of the disease. The identification of

TRPV3 gain-of-function mutations indicates that TRPV3 antagonists may be an effective therapeutic approach to treat the OS patients harbouring such mutations.

#### Prognosis

The natural history of the disease can lead to severe morbidities. Progressive keratoderma and auto-amputation of digits worsens the disability by preventing patients from grasping and walking, and can confine them to a wheelchair. Severe pruritus and pain increase the discomfort and can result in insomnia. Corneal dystrophy can cause blindness. In addition, OS patients may have a higher susceptibility to develop tumors in keratotic areas. No reduced life expectancy has been reported.

#### Unresolved questions

There have been recently many major advances in our understanding of the genetic basis of OS, with the identification of *TRPV3* and *MBTPS2* mutations, although other causal genes remain to be identified. Several questions remain unanswered with regards to the great variability of clinical expression of the disease, the lack of phenotype/genotype correlation and the exact pathophysiological mechanism(s) underlying OS. The broad spectrum of OS clinical features raises the question whether atypical reported cases really belong to OS. Mutations within *TRPV3* can cause both typical and atypical OS cases. Thus, OS may be a heterogeneous syndrome with variable clinical features.

#### Conclusion

For 87 years after its first description, around 73 OS cases have been reported, increasing the spectrum of clinical features associated with this condition and disclosing variable clinical expression. OS diagnosis may be challenging in the absence of the full-blown cutaneous phenotype associating bilateral mutilating PPK and periorificial keratotic plaques. The recent advances in the genetics of OS has lead to a better understanding of the aetiology of the disease and make possible the use of diagnostic genetic testing. Currently available drugs are nonspecific and poorly effective. The identification of the molecular basis of OS will permit the development of specific therapeutic strategies such as TRPV3 antagonists, and better patient management. However, other genes remain to be identified and next generation sequencing is likely to permit to further elucidate the genetics of OS and its clinical spectrum in patients with no *TRPV3* or *MBTPS2* mutation.

#### Abbreviations

OS: Olmsted syndrome; PPK: Palmoplantar keratoderma; TRPV3: Transient receptor potential vanilloid-3; MBTPS2: Membrane-bound transcription factor protease, site 2; IFAP: Ichthyosis follicularis atrichia photophobia.

#### Competing interests

The authors declare that they have no competing interests.



**Authors' contributions**

SD performed the literature search and wrote the draft of the initial manuscript. AH critically revised the manuscript. All authors read and approved the final manuscript.

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