Indeed, the surnames of cases 1 and 2 are of Slavic origin, suggesting an ancestral mutation propagated through Slavic migration to Northern Romania and Eastern Germany, where our patients are living. Nevertheless, the mutation affects a CpG dinucleotide, which has a high mutation rate from 5-methylated CG to TG and its complementary pair CA, suggesting that it could also be recurrent.

Altogether, we show that KS patients may harbor *FERMT1* deep-intronic mutations, which are missed in targeted and whole-exome sequencing, and require RNA analysis or whole-genome sequencing. Our results argue against a genetic heterogeneity of KS.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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Expanding the Phenotypic Spectrum of Olmsted Syndrome

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TO THE EDITOR

Palmoplantar keratodermas (PPKs) are a group of genetically heterogeneous genodermatoses. Recently mutations in *TRPV3* were identified as a cause of the rare form of PPK, Olmsted syndrome (OS; OMIM 614594; Lai-Cheong *et al.*, 2012; Lin *et al.*, 2012; Danso-Abeam *et al.*, 2013; Kariminejad *et al.*, 2014; Duchatelet *et al.*, 2014b). OS was first reported in 1927 in an Italian American boy with painful palmoplantar keratoderma, deep fissures, pseudoainhum, curved thickened nails, and periorificial hyperkeratosis with fissuring (Olmsted, 1927). About 50 clinical cases of OS have been described, and all generally exhibit the features described by Olmsted as well as some additional features (Mevorah *et al.*, 2005).

In this study, we report the case of six families, referred to the Pachyonychia Congenita Project for the evaluation of painful plantar keratoderma, but lacking pseudoainhum or significant periorificial keratoderma. In each case, after no mutations were identified in the PC-associated keratin genes, *KRT6A, KRT6B, KRT6C, KRT16*, or *KRT17*, and in some cases, after other candidate genes including *GJB6, DSP, DSG1, KRT5*, and *KRT14* had been screened, we identified heterozygous missense mutations in *TRPV3*, thus greatly expanding the phenotypic

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spectrum of OS. Samples were obtained with written, informed patient consent and ethical approval by a Western Institutional Review Board that complies with principles of the Helsinki Accord.

An 18-year-old girl of European ancestry from Family 1 initially noted focal callus formation on the soles at age 4. Severe, painful plantar keratoderma now necessitates periodic use of a wheelchair. She has mild keratoderma on the hands, thin nail plates with koilonychia, and fine slow-growing hair. She has no periorificial keratoderma (Figure 1a, b, c, Supplementary Figure S1 online and Supplementary Table S1 online). A likely diagnosis was PC, but no causative mutations were identified in the PC-related keratin genes nor in other candidate genes. Therefore, a whole-exome sequencing approach was performed (Supplementary Methods online), and data were analyzed for sequence variants in known keratoderma genes. A heterozygous missense mutation, p.Gly573Cys; c,1717G>T, was identified in *TRPV3* and confirmed by Sanger sequencing (Supplementary Methods online) but was not present in her unaffected parents or brother. This mutation has been reported in a sporadic case of Olmsted syndrome (Lin *et al.*, 2012).

TRPV3 was considered a candidate gene for five additional families in which no mutations were identified in the PC-associated keratin genes or in other candidate genes. Exons and intron/exon boundaries of *TRPV3* were amplified by PCR for Sanger sequencing (Supplementary Methods online).

A 7-year-old Brazilian girl in Family 2 presented with easily peeling hyperkeratosis on her toes and feet at about 18 months of age, and these have evolved into painful, focal hyperkeratosis. She has erythema and hyperkeratosis of the distal fingers and subungual hyperkeratosis. She has had transient periorificial hyperkeratosis and her nail plates are normal (Figure 1d, e, f, Table 1, Supplementary Figure S1 online). A previously unreported heterozygous missense mutation, p.Gly568-Val; c.1703G>T, was identified (Supplementary Figure S2 online); this mutation was not detected in either of her unaffected parents. Amino acid, p. Gly568 is highly conserved across several species. This mutation is not in the dbSNP database or the NHLBI Exome Variant Server (http://evs.gs.washington.edu/EVS/).

The proband from Family 3, a 38-year-old European female, developed calluses on her feet at the age of 8–9 years. She now has severe plantar pain and difficulty in walking (Figure 1g, h, i, Table 1,Supplementary Figure S1 online). She has thin nail plates with koilonychia. Her father, two paternal uncles and grandmother were similarly affected showing autosomal dominant inheritance of the disorder. A previously unreported heterozygous missense mutation, p. Gly568Asp;c.1703G>A (Supplementary Figure S2 online), was identified in the proband and in one affected paternal uncle; it was not present in an unaffected paternal uncle nor in her mother, (her father is deceased). This mutation is not listed in dbSNP or the NHLBI Exome Variant Server.

Interestingly, we found the same mutation, p.Gly568Asp, in Family 4 from South America. The first sign of a skin abnormality in the 25-year-old proband was peeling skin on her feet at age 4 years. Painful, focal keratoses formed on her feet and to a lesser extent on her hands. She has mild periungual hyperkeratosis on her fingers and toes, onychoschizia and longitudinal overcurvature of several toenails. She has no periorificial hyperkeratosis, and her hair is normal (Table 1). No clinical information or DNA samples were available from her parents or from other family members.

A 55-year-old man of European ancestry from Family 5 presented with painful calluses on the soles of his feet. Focal hyperkeratoses with thin surrounding rim of erythema started on his heels as a child when he started to walk and spread to the soles of his feet. He has thin nail plates with koilonychia and sparse, fragile hair. He develops severe hyperhidrosis accompanied by burning pain in the feet and bright erythema on the dorsal hands and feet in response to extremes of temperature. He has no palmar hyperkeratosis, but has had transient perioral and periauricular hyperkeratosis (Figure 1j, k, l, Table 1, Supplementary Figure S1 online). He believes that etretinate and acitretin have significantly improved his quality of life. His father was also affected. A heterozygous missense mutation, p.Gly573Ser; c.1717G>A, the most commonly reported mutation to date in *TRPV3*, was identified in this individual.

Mutation p.Gly573Ser, was also found in a 7-year-old girl of European ancestry (Family 6), who developed thickening of the skin on her heels at about 4 years of age (Table 1). She has severe plantar pain and now uses crutches to aid her mobility. Her parents are unaffected.

The genetic basis of autosomal dominant OS was recently elucidated (Lin *et al.*, 2012) when heterozygous missense mutation, p.Gly573Ser, was identified in *TRPV3* in a Chinese family. Mutations in *TRPV3* were subsequently identified in five additional Chinese families. All developed symptoms before 1 year of age, had varying severity of palmoplantar hyperkeratosis, periorificial hyperkeratosis, alopecia, and severe lesional pain and itch. All but one had constricting digital bands. Several heterozygous mutations have been reported at codons 573; p. Gly573Ser (Lai-Cheong *et al.*, 2012), p. Gly573Ala (Danso-Abeam *et al.*, 2013), and p.Gly573Cys (Lin *et al.*, 2012) and two mutations at codons 692; p. Trp692Gly (Lin *et al.*, 2012) and p. Trp692Cys (Kariminejad *et al.*, 2014). The heterozygous missense mutation p. Leu673Phe was found in a patient with OS and erythromelalgia (Duchatelet *et al.*, 2014b). Homozygous missense and compound heterozygous mutations in *TRPV3* have been shown to result in recessive OS with (Duchatelet *et al.*, 2014a) or without erythromelalgia (Eytan *et al.*, 2014). Recently, the heterozygous missense mutation p.Gln580Pro was identified in a family with focal palmoplantar keratoderma (He *et al.*, 2015), more reminiscent of the cases described here.

TRPV3 belongs to the family of transient receptor potential (TRP) cation channels and is widely expressed in keratinocytes and hair follicles (Peier *et al.*, 2002 Nilius *et al.*, 2013) as well as in other tissues including the brain, spinal cord, sensory neurons, and the cornea. Mutations in *TRPV3* causing autosomal dominant OS were shown to

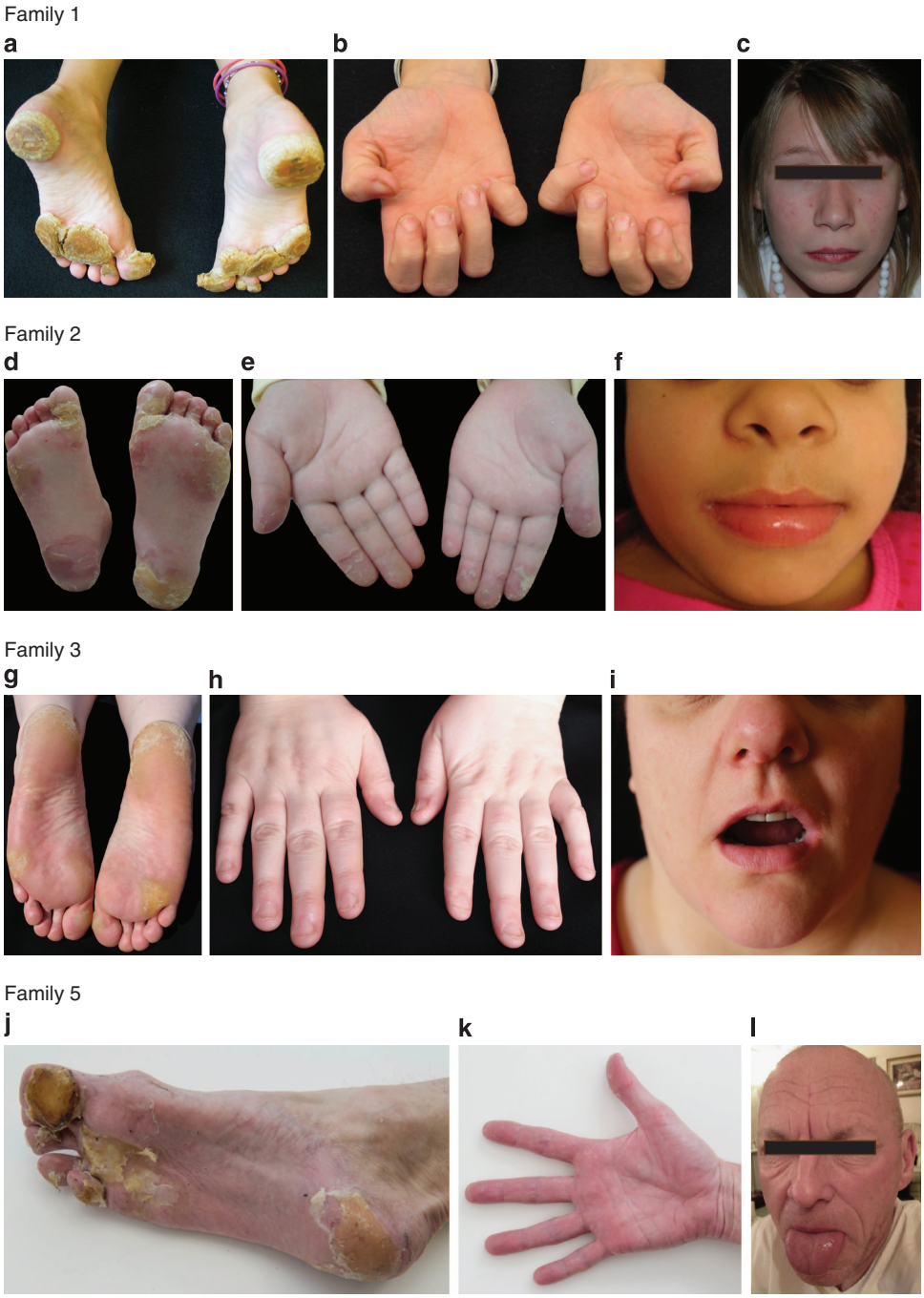

Figure 1. Clinical features. Proband of Family 1: (**a**) severe calluses on the weight-bearing areas of the soles (at age 9), (**b**) thin nail plates with koilonychia (age 9), and (**c**) no perioral keratoderma and fine hair, age 12. Proband of Family 2: (**d**) calluses on the soles of the feet, (**e**) blisters and peeling of skin on the fingertips, and (**f**) lack of perioral hyperkeratosis. Proband of Family 3: (**g**) calluses on the soles, (**h**) koilonychia of nails, and (**i**) no perioral lesions. Proband of Family 5: (**j**) hyperkeratosis on the soles, (**k**) no palmar hyperkeratosis, and (**l**) sparse fragile hair, mild lateral perioral fissuring, and no oral leukokeratosis. Images are published with patients' consent.

be gain-of-function mutations resulting in increased *TRPV3* activity (Lin *et al.*, 2012). In this study, two, to our knowledge previously unreported, mutations were identified at codon 568. Interestingly another amino acid substitution at this position, p.Gly568Cys, was recently reported in combination with a splice site mutation, exhibiting autosomal recessive inheritance in this case (Duchatelet *et al.*, 2014a). *TRPV3* forms a tetrameric complex, each subunit consists of six transmembrane domains (S1–S6) and a cytoplasmic amino and carboxy termini (Supplementary Figure S2 online). p. Gly568 is within the linker region between S4 and S5, near the boundary of S4. It is predicted that substitution

Table 1. Clinical findings in patients with mutations in *TRPV3*

Report	Inheritance	*TRPV3* mutation	Plantar keratoderma	Palmar keratoderma	Pseudoainhum	Periorificial keratoderma	Hair
Olmsted's patient			Diffuse-S	Diffuse-S	Present	Present	Dry
Lin *et al.*, 2012	AD	p.Gly573Ser (4)[1]	M(1)[2]; Mod(1); S(2)	M(1)[2]; Mod(1); S(2)	Present	M(1)[2]; Mod(1); S(2)	Alopecia - M(1); Mod (1); S (2)
Lin *et al.*, 2012	AD	p.Gly573Cys (1)	M	M	Absent	M	Alopecia - M
Lin *et al.*, 2012	AD	p.Trp692Gly (1)	Mod	Mod	Present	Mod	Alopecia - M
Lai-Cheong *et al.*, 2012	AD	p.Gly573Ser (1)	Diffuse-S	Diffuse-S	Present	M	Fine-dry
Danso-Abeam *et al.*, 2013	AD	p.Gly573Ala (1)	Diffuse-S	Diffuse-S	Absent	S	Alopecia-S
Duchatelet *et al.*, 2014b	AD	p.Leu673Phe (1)	Diffuse-S	Diffuse-S	Absent	Absent	Fine, dry
Duchatelet *et al.*, 2014a	AR	p.Gly568Cys; p.Gln216_ Gly262del (1)	Diffuse-S (1); Focal-Mod(1)	NR	Absent	Absent	Fine-dry
Eytan *et al.*, 2014	AR	p.Trp521Ser (1)	Diffuse-S	Diffuse-S	Absent	Present	Sparse
Kariminejad *et al.*, 2014	AD	p.Trp692Cys (1)	Diffuse-S	Diffuse-S	Present	Present (Mod)	Sparse; fragile
He *et al.*, 2015	AD	p.Gln580Pro (1)[2]	Focal-Mod	Focal-Mod	Absent	Absent	Normal
Family 1	AD	p.Gly573Cys (1)	Focal-S	Focal-M	Absent	Absent	Fine
Family 2	AD	p.Gly568Val (1)	Focal-Mod	Focal-M	Absent	M	Normal
Family 3	AD	p.Gly568Asp (2)[2]	Focal-Mod	M	Absent	M	Fine
Family 4	AD	p.Gly568Asp (1)	Focal-Mod	Focal-M	Absent	NR	Normal
Family 5	AD	p.Gly573Ser (1)	Focal-Mod	M/transient	Absent	M/transient	Fragile, sparse
Family 6	AD	p.Gly573Ser (1)	Focal-Mod	M	Absent	Absent	Normal

Report	Follicular keratosis	Erythema	Hyperhidrosis	Nails	Lesional itch	Lesional pain	Leukokeratosis
Olmsted's patient	NR	Lesion border; dorsal hands	Hands	Thickened	NR	Present	NR
Lin *et al.*, 2012	Scalp	Lesion border	NR	NR	S (4)[2]	Present	NR
Lin *et al.*, 2012	Scalp	Lesion border	NR	NR	S	Present	NR
Lin *et al.*, 2012	NR	Lesion border	NR	NR	S	Present	NR
Lai-Cheong *et al.*, 2012	NR	NR	NR	Dystrophy	No	"Functional impairment"	NR
Danso-Abeam *et al.*, 2013	NR	Lesion border	NR	Dystrophy	S	S	NR
Duchatelet *et al.*, 2014b	NR	Erythromelalgia	Present	Thin, brittle	S	S	NR
Duchatelet *et al.*, 2014a	M	Erythromelalgia	Present	Normal	S	S	NR
Eytan *et al.*, 2014	NR	Diffuse, palms and soles	NR	NR	Present	Present	Present
Kariminejad *et al.*, 2014	NR	NR	NR	Dystrophic/absent	S	S	NR
He *et al.*, 2015	NR	NR	NR	NR	NR	NR	NR
Family 1	M	Lesion border	Hands and feet	Koilonychia; thin plates	Absent	S	Absent
Family 2	Absent	Lesion border; distal digits (hands)	Feet	Normal	Absent	S	Absent
Family 3	M	Lesion border	Feet	Koilonychia; thin plates; onychoschizia	S	S	Present
Family 4	NR	Lesion border	NR	Onychoschizia	NR	S	Absent
Family 5	M	Lesion border; dorsal feet	Feet	Koilonychia; thin plates; onychoschizia	Absent	S	Absent
Family 6	NR	Lesion border	No	Normal	NR	S	Absent

Abbreviations: M, mild; Mod, moderate; NR, not reported; S, severe.
[1]Individual families.
[2]Individuals.

of this glycine is less damaging than substitutions further within the S4–S5 linker such as p.Gly573 (Duchatelet *et al.*, 2014a). *In silico* prediction tools (PolyPhen and Mutation Taster) predict all three variants at codon 568, p.Gly568Asp, p.Gly568Val (this study), and p.Gly568Cys (Duchatelet *et al.*, 2014a) to be damaging. In our families, no other mutations were identified in *TRPV3*, and in Family 2, the parents were wild-type for p.Gly568 indicating a *de novo* mutation, p.Gly568Val, in the proband. Mutation p.Gly568Asp was shown to be dominantly inherited in Family 3; the mutation was identified in the proband and an affected paternal uncle (affected father is deceased). However, in the family reported with p.Gly568Cys in combination with a splice site mutation (Duchatelet *et al.*, 2014a) the unaffected father was heterozygous for p.Gly568Cys and the clinical phenotype of the two affected brothers was significantly different. Overall, these findings suggest that environmental factors/modifier genes may also be involved in determining the phenotypic variability.

TRPV3 is involved in many cellular and physiological processes. Recently, Cheng *et al.* (2010) demonstrated the important role of *TRPV3* in regulating EGFR signaling in hair and skin barrier function using a *TRPV3* knockout mouse model that developed a wavy hair coat and curly whiskers in addition to a red, dry scaly skin at birth, reminiscent of mice with a defective skin barrier.

Although reported as a thermosensitive cation channel, activated at 30–33 °C, this thermosensory role is unclear (Nilius and Biro, 2013). Interestingly, coexistence of erythromelalgia with OS has been reported (Duchatelet *et al.*, 2014a, b), and one of our patients has findings compatible with erythromelalgia. Many OS patients report hyperhidrosis (including four of ours).

In this study, heterozygous missense mutations were identified in *TRPV3* in six families, (two previously unreported and two recurrent mutations) with painful, palmoplantar keratoderma. Clinically, none were as severe as typical OS (Table 1).

The cases we have described expand the phenotypic spectrum of Olmsted syndrome caused by mutations in *TRPV3*. Mutations in *TRPV3* should be considered as a cause of painful PPK even in the absence of periorificial hyperkeratosis and pseudoainhum as described by Olmsted. In contrast and to avoid confusion, painful PPKs caused by mutations in genes other than *TRPV3* probably should not be referred to as Olmsted syndrome.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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