Table I. Bivariate analysis of tumor characteristics and treatment modalities*

Variable	Low-volume (<1 case/y), n = 4,049 (49.1)	Moderate-volume (≥1 and ≤3 cases/y), n = 2,336 (28.3)	High-volume (>3 cases/y), n = 1,867 (22.6)	*P* value
Primary site				
Head and neck	1792 (44.9)	1169 (50.6)	1047 (56.5)	<.001
Trunk	623 (15.6)	339 (14.7)	218 (11.8)	<.001
Extremities	1572 (39.4)	801 (34.7)	588 (31.7)	<.001
Stage				
0 (in situ)	66 (1.6)	48 (2.1)	39 (2.1)	.333
I	2580 (63.7)	1610 (68.9)	1404 (75.2)	<.001
II	1403 (34.7)	678 (29.0)	424 (22.7)	<.001
Tumor size, cm				
<1	1152 (32.1)	763 (37.8)	780 (47.8)	<.001
≥1 and <2	1115 (31.0)	654 (32.4)	465 (28.5)	.037
≥2	1326 (36.9)	603 (29.9)	388 (23.8)	<.001
Academic facility	634 (16.1)	1450 (64.4)	1676 (92.5)	<.001
Geography				
Metropolitan	3213 (81.7)	1944 (86.4)	1472 (81.3)	<.001
Urban	658 (16.7)	260 (11.6)	306 (16.9)	<.001
Rural	64 (1.6)	46 (2.0)	32 (1.8)	.488
Management				
Surgery alone	2393 (59.1)	1565 (67.0)	1406 (75.3)	<.001
Radiation alone	105 (2.6)	33 (1.4)	19 (1.0)	<.001
Surgery + adjuvant radiation	1514 (37.4)	715 (30.6)	431 (23.1)	<.001

*Case numbers represent the total volume from 2004 to 2015. Data are presented as number (%). The percentages represent valid percentages, excluding patients with missing information.

Marcus L. Elias, BS,[a] *W. Clark Lambert, MD, PhD,*[a,b] *and Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP Edin*[a,b]

From Dermatology[a] *and Pathology,*[b] *Rutgers New Jersey Medical School, Newark, New Jersey*

Funding sources: None.

Conflicts of interest: None disclosed.

Reprints not available from the authors.

Correspondence to: Robert A. Schwartz, MD, MPH, DSc (Hon), FRCP Edin, Professor and Head, Dermatology, Rutgers New Jersey Medical School, 185 S Orange Ave, Newark, NJ 07103

E-mail: roschwar@cal.berkeley.edu

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https://doi.org/10.1016/j.jaad.2019.05.027

Extending the phenotype of midface toddler excoriation syndrome (MiTES): Five new cases in three families with PR domain containing protein 12 (*PRDM12*) mutations

To the Editor: Midface toddler excoriation syndrome (MiTES) is a newly recognized autosomal recessive condition arising in the first year of life and characterized by deep, self-inflicted excoriations largely confined to the medial cheeks, nasal bridge, and central forehead. Eight patients, all children aged 11 years or younger, from 7 families have been reported, 6 from India and 2 from the United Kingdom and Ireland.[1,2] MiTES is associated with biallelic mutations in the gene PR domain containing protein 12 (*PRDM12*).[2]

We report 5 new patients from 3 families, including an affected adult. After informed consent, genomic DNA was isolated for targeted Sanger sequencing of

Table I. Midface toddler excoriation syndrome: summary of 5 new cases

Patient	Sex	Age when last seen	Affected relative	Parental consanguinity	Country of origin	Age of onset	Other features	Iron-deficiency anemia	*PRDM12* polyalanine expansion	*PRDM12* genotype	
										Mother's	Father's
1	Female	5 y	2 is sibling	No	India	6 mo	None	Yes	18/18	15/18	12/18
2	Male	3 y	1 is sibling		India	6 mo	None	Yes	18/18		
3	Male	18 mo	4 is uncle	Yes	India	7 mo	None	Yes	18/18	13/18	13/18
4	Male	26 y	3 is nephew	Yes	India	Early childhood	None		18/18		
5	Male	6 y	None	No	UK	10 mo	High pain threshold	No	18/18	13/18	13/18

No patient had neurologic abnormalities.
PRDM12, PR domain containing protein 12; *UK*, United Kingdom.

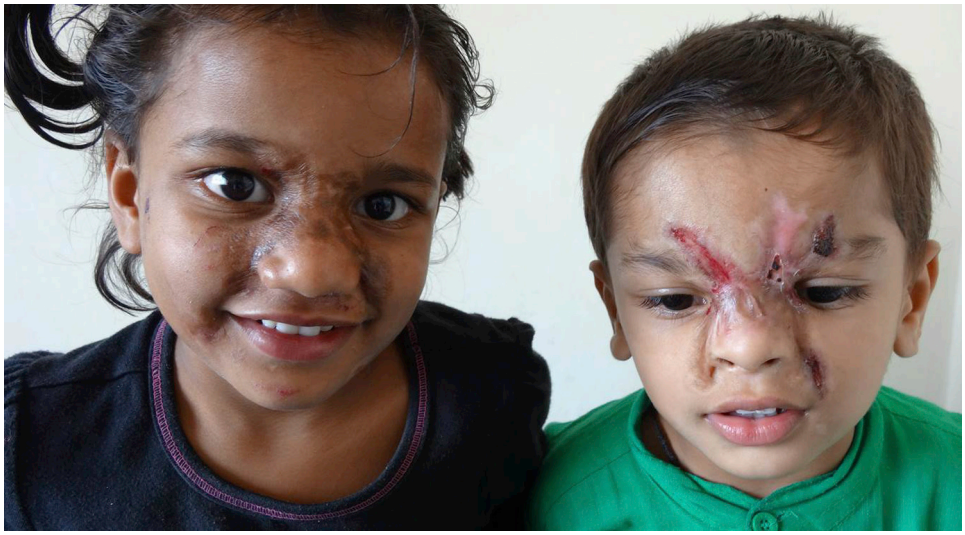

Fig 1. Midface toddler excoriation syndrome: typical midfacial lesions in siblings, patients 1 and 2.

all 5 *PRDM12* exons, conducted by a commercial laboratory (GENEWIZ, Takeley, United Kingdom). Sequencing products were analyzed as described previously.[2] Polymerase chain reaction conditions and primer sequences are available on request.

The clinical and molecular findings (Table I and Fig 1) are characteristic of this disorder. Patient 5 was initially diagnosed with bilateral congenital Frey syndrome (gustatory sweating), but the diagnosis was revised to MiTES as the phenotype became clearer with age. Patient 4, aged 26 years, reported itchy facial lesions until the age of 14, leaving postinflammatory pigmentation and scarring. No patient had neurologic abnormalities. All 5 affected individuals were homozygous for a polyalanine repeat expansion of 18 in *PRDM12*, for which all parents were heterozygous carriers.

PRDM12 located at 9q34 influences the development of sensory neurons into nociceptors. Biallelic mutations also cause hereditary sensory and autonomic neuropathy type 8 (HSAN8), characterized by widespread manifestations of pain insensitivity such as mutilated extremities.[3] MiTES patients lack generalized features of HSAN8, while a minority of patients with HSAN8 manifest MiTES-like facial excoriations. MiTES thus appears to represent a highly localized form of HSAN8, with similarities to trigeminal trophic syndrome in which midfacial excoriations result from a combination of neuropathic itch and unrestrained scratching due to lack of pain sensation. Neuropathic itch is a powerful trigger of impulsive and volitional scratching and occurs most frequently on the face.[4]

The polymorphic polyalanine tract in the final exon of *PRDM12* normally has 7 to 14 alanine repeats.[3] The genotype 15/18 in the unaffected mother of patients 1 and 2 prompted a careful examination and review of childhood photographs,

but she appeared healthy, with no evidence of MiTES, suggesting a normal upper limit of 15 repeats. All MiTES patients investigated to date were homozygous (18/18) or compound heterozygous (17/18). Two HSAN8 families had polyalanine tract expansion,[3] a Pakistani family homozygous for 19 repeats and an Irish family showing unusually mild disease, MiTES-type lesions, and homozygosity for 18 repeats. The evidence thus suggests that 17 or 18 repeats produces the localized MiTES phenotype, whereas 19 or more causes HSAN8. Polyalanine expansions are a known cause of genetic disease, previously described in 9 genes, 8 of which, like *PRDM12*, encode transcription factors associated with congenital syndromes.[5]

In summary, we have increased the number of reported cases of MiTES to 13, reported resolution of excoriations with persistent scarring in an adult, confirmed the cause as biallelic polyalanine expansions in *PRDM12* to 17 or 18 repeats, and revised the normal upper limit of repeats to 15.

We gratefully acknowledge the help of our clinical colleagues: Drs L. Taylor, E.T. Ooi, K. McWilliams, and the late Olivia Schofield at Edinburgh Royal Infirmary, and Drs D. Parsad and S. Dogra at Post Graduate Institute of Medical Education & Research, Chandigarh.

Arun C. Inamadar, FRCP,[a] Keshavmurthy Vinay, MRCP,[b] Bayanne Olabi, MRCP,[c] Nivedita Sarveswaran, MSc,[d] Anuradha Bishnoi, MD,[b] Christopher G. Woods, PhD,[d,e] and Celia Moss, FRCP[f,g]

From the Department of Dermatology, Shri BM Patil Medical College & Hospital, BLDE (Deemed to be University), Bijapur,[a] and Department of Dermatology, Post Graduate Institute of Medical Education & Research, Chandigarh,[b] India; the Department of Dermatology, Edinburgh Royal Infirmary,[c] the Cambridge Institute for Medical Research,[d] the Department of Medical Genetics, University of Cambridge,[e] Department of Dermatology, Birmingham Children's Hospital,[f] and College of Medical and Dental Sciences, University of Birmingham,[g] United Kingdom

Prior presentation: Patients 1 and 2 were presented by Prof Inamadar at the 31st Annual Society for Pediatric Dermatology Pre-AAD meeting, Washington, DC, February 28-March 1, 2019. Patient 5 was presented by Dr Olabi at the British Society for Paediatric Dermatology Annual Meeting, Glasgow, Scotland, November 9-10, 2018.

Funding: Supported by Biotechnology and Biological Sciences Research Council CASE studentship Ref BB/N504142/1 to Nivedita Sarveswaran and by National Institute of Health Biomedical Centre award to Cambridge 2017-2022, Integrated genomics theme, ref RG85443 to Dr Woods.

Conflicts of interest: None disclosed.

Reprint requests: Celia Moss, FRCP, Department of Dermatology, Birmingham Children's Hospital, Steelhouse Ln, Birmingham B4 6NH, UK

E-mail: celia.moss@nhs.net

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https://doi.org/10.1016/j.jaad.2019.05.036

Retrospective cohort study of anatomic localization of cutaneous squamous cell carcinomas in solid organ transplant recipients compared with immunocompetent patients

To the Editor: Solid organ transplant recipients (SOTRs) are at 65- to 250-fold increased risk of developing cutaneous squamous cell carcinoma (SCC). Their SCCs may behave more aggressively than SCCs in immunocompetent individuals.[1] As a potential reason for this observed difference in clinical outcomes, we asked whether the anatomic distribution of SCCs in SOTRs significantly differed compared with immunocompetent patients.

We conducted a retrospective cohort study of the anatomic location of primary SCCs in adult SOTRs and immunocompetent patients of the Yale Transplant Dermatology Clinic between January 1, 2008, and December 31, 2015. This study was approved by the Yale University Institutional Review Board. Data on age, sex, race, immunosuppression, and anatomic site of histopathologically confirmed SCCs sorted into 5 regions were collected.