IRB approval status: Not applicable.

Reprints not available from the authors.

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https://doi.org/10.1016/j.jaad.2020.02.021

Palm reading and water divining: A cross-sectional study of the accuracy of palmar hyperlinearity and transepidermal water loss to identify individuals with a filaggrin gene null mutation

To the Editor: Loss-of-function filaggrin (*FLG*) gene mutations are strongly associated with early-onset, severe, and persistent atopic dermatitis (AD) and impaired skin barrier function.[1] The impact of various environmental exposures[2,3] is greater in those with *FLG*-null mutations, and these mutations are likely to influence the effectiveness of primary and secondary prevention strategies for AD. Definitive genetic tests remain expensive. Although both trans-epidermal water loss (TEWL)[1] and palmar hyperlinearity (increased number of prominent palm lines)[4] have been associated with *FLG*-null mutation, the accuracy of these measures in identifying individuals with *FLG*-null mutations remains unclear.

Palmar line data, TEWL, and DNA were prospectively collected from probands and siblings during the 18-year follow-up of the Melbourne Atopy Cohort Study[5] (all had family history of allergic disease) from late 2009. The 5 most common *FLG*-null mutations in white populations were genotyped by using the Taqman platform (Roche Molecular Systems, Inc, CA, USA). TEWL was measured on the flexor forearm with a Tewameter T300 (Courage & Khazaka, Cologne, Germany). Palmar hyperlinearity was defined by the prominence and quantity of lines on the thenar eminence and was classified as normal, mild, or moderate/severe (Supplemental Figure 1; available via Mendeley at https://data.mendeley.com/datasets/7cbkrbpv3v/1). Palm lines were counted by using a standardized protocol (Supplemental Figure 2; available via Mendeley at https://data.mendeley.com/datasets/7cbkrbpv3v/1). Associations were assessed with logistic regression, with generalized estimation equations to account for clustering by family. Sensitivity and specificity were calculated, and receiver operator curves were developed using Stata, version 15 (StataCorp, College Station, TX). Potential interactions and no-linearity were assessed (see supplemental materials via Mendeley at https://data.mendeley.com/datasets/7cbkrbpv3v/1).

FLG-null mutations were detected in 12.2% (38/311) of participants. The average age was 18.4 years, 25.8% reported current AD symptoms (Table I), and 36.4% had evidence of hyperlinearity (Table II). Hyperlinearity was associated with increased

Table I. Distribution of age, sex, degree of palmar lines, number of vertical and horizontal lines, and current AD and TEWL in a cohort of 311 probands and siblings from 157 families

Variable	*FLG* null mutation carrier (n = 38)	*FLG* wild type (n = 273)
Mean age, y (SD)*	19.7 (4.3)	18.2 (3.4)
Sex, % female (n)*	47.4 (18)	50 (136)
Palmar hyperlinearity, % (n)		
None	19.4 (7)	69.5 (189)
Mild	55.6 (20)	28.3 (77)
Moderate/severe	25.0 (9)	2.2 (6)
Palmar lines, mean (SD)		
Vertical	12.6 (5.1)	8.9 (7.71)
Horizontal	16.7 (9.8)	9.3 (8.9)
Current AD, % (n)†	44.4 (16)	23.3 (61)
Mean TEWL, g/m^2/h, (SD)‡	7.2 (2.2)	6.5 (3.1)

AD, Atopic dermatitis; *SD*, standard deviation; *TEWL*, transepidermal water loss.
*Age and sex were missing for 1 participant.
†Data were missing on current AD for 13 participants; defined as either an episode of AD or medication for AD in the past 12 months.
‡TEWL data were missing for 8 participants.

Table II. Associations* between palmar linearity and TEWL and odds of *FLG*-null mutation adjusted for sex and current AD

Variable	Prevalence of *FLG* null mutations, % (n/N)	Unadjusted, OR (95% CI)	Adjusted,† aOR (95% CI)
Palmar linearity			
Normal	3.6 (7/196)	—	—
Mild	20.6 (20/97)	**6.0 (2.5-14.4)**	**6.6 (2.6-16.5)**
Moderate/severe	60 (9/15)	**29.3 (9.0-96.0)**	**45.7 (12.1-173)**
Any palmar linearity	25.9 (29/112)	**8.0 (3.4-18.6)**	**8.6 (3.6-20.9)**
TEWL per g/h/m^2	—	1.06 (0.95-1.18)	1.04 (0.93-1.16)‡
Per vertical line	—	**1.06 (1.02-1.11)**	**1.07 (1.02-1.11)**
Per horizontal line	—	**1.08 (1.04-1.13)**	**1.08 (1.04-1.13)**

AD, Atopic dermatitis; *aOR*, adjusted odds ratio; *CI*, confidence interval; *OR*, odds ratio; *TEWL*, transepidermal water loss.
*Adjusted for sex and current AD.
†Additionally adjusted for atmospheric temperature and humidity.
‡Associations with $P < .05$ are bolded.

prevalence of *FLG*-null mutation (Table II), with a sensitivity of 80.8% (95% confidence interval [CI], 63.9-91.0) and specificity of 69.5% (95% CI, 63.1-75.1) for detecting these mutations (positive predictive value, 23.1%; 95% CI, 15.9-32.2; negative predictive value, 96.4%; 95% CI, 92.0-98.4). Participants with both hyperlinear palms and current AD had the highest prevalence of *FLG*-null mutations (40.6%). TEWL was not associated with *FLG*-null mutations. Seven or more vertical lines identified 89.5% (95% CI, 76.7-95.9) of participants with *FLG*-null mutations (specificity, 50%; 95% CI, 42.9-56.9; PPV, 18.0%; 95% CI, 12.4-25.4; NPV, 96.6%; 95% CI, 91.3-98.4).

These results may not apply to individuals without a family history of allergic disease, older or younger individuals, or nonwhite individuals. Inclusion of a wider range of *FLG*-null mutations may have improved the observed sensitivity and specificity. Although TEWL was not associated with *FLG*-null mutations, we were not able to tightly control ambient temperature and humidity, both important determinants of TEWL, particularly when using an open chamber device. This may have led to null associations, so we cannot exclude the possibility that TEWL may predict *FLG*-null mutations.

Clinically graded palmar assessment and vertical palm line counting are very useful for identifying individuals who do not have *FLG* gene—null mutations (high specificity and negative predictive value). Although individuals with hyperlinearity have increased risk of FLG-null mutations, only approximately 20% will have such a mutation, making confirmatory genetic testing necessary. Future studies should assess these associations in neonates, where hyperlinearity may predict *FLG*-null mutations and development of AD. This simple assessment may help guide clinicians in counseling patients likely to carry an *FLG*-null mutation in terms of career choices and have therapeutic implications, such as avoidance of soap and routine use of emollients.

We thank the participants of the Melbourne Atopy Cohort Study (MACS). We acknowledge Dr David Hill, Dr Cliff Hosking, Dr John Thorburn, and Christine Axelrad for establishing the MACS and for leading the study up to 12 years. We also acknowledge contributions from the following investigators and assistants of the 18-year follow-up: Professor Catherine Bennett, Professor Lyle Gurrin, Dr Rida Khalafzai, Professor Sharon Goldfeld, Dr Chris Barton, Professor Vijaya Sundararajan, Professor Bircan Erbas, and Associate Professor Matthias Wjst.

Dr Allen was affiliated with the Murdoch Children's Research Institute at the time of this study.

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Drs Lodge and Dharmage contributed equally to this article.

Funding sources: The first 6 years of the Melbourne Atopy Cohort Study were funded (study formula and staff) by Nestec Ltd, a subsidiary of Nestle Australia. The National Health and Medical Research Council (NHMRC) of Australia funded the 18-year follow-up (GNT454856). Drs Dharmage, Lodge, Southey and Lowe are funded by the NHMRC.

Disclosure: Dr Abramson holds investigator-initiated grants from Pfizer and Boehringer Ingelheim for unrelated research and has undertaken an unrelated consultancy and received support for conference attendance from Sanofi. Drs Lowe, Lee, Orchard, King, Allen, Hui, Southey, Lodge, and Dharmage have no conflicts of interest to declare.

IRB approval status: Approved by the Human Research Ethics Committee of Royal Children's Hospital (reference number 28035).

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https://doi.org/10.1016/j.jaad.2020.01.083

Characteristics of postinflammatory hyper- and hypopigmentation in patients with psoriasis: A survey study

To the Editor: Although psoriasis is commonly associated with postinflammatory hyper- and hypopigmentation, their description remains limited. Postinflammatory hyperpigmentation appears to be more frequent than hypopigmentation.[1,2] Interestingly, a pattern of hyperpigmentation called lentiginous hyperpigmentation has been described in areas of previously affected skin after various topical or systemic treatments.[3,4] However, the literature remains speculative regarding the clinical factors associated with this phenomenon.

The aim of this monocentric study was to describe the prevalence of hyper- and hypopigmentation in patients with psoriasis and their association with their demographic and clinical features (see "Patients and Methods" in the Supplemental Appendix 1; available via Mendeley at https://doi.org/10.17632/r5dxjnn8fc.1). The study included 459 patients: 287 men and 172 women (Table I). The mean age was 49.9 years ($\sigma = 16.2$ years). The mean duration of psoriasis was 19.8 years ($\sigma = 18.2$). A total of 81.5% of patients had psoriasis vulgaris (Supplemental Appendix 2; available via Mendeley at https://doi.org/10.17632/r5dxjnn8fc.1). The prevalence of skin hyper- and hypopigmentation was 23.7%. Overall, 63 (13.7%) and 46 (10.0%) patients developed skin hyperpigmentation or hypopigmentation, respectively. Hyper- and hypopigmentation were observed only in areas previously affected by psoriasis. Hypopigmented lesions showed a homogeneous pattern with a sharp border and the presence of residual pigmentation confirmed by Wood's lamp examination (Fig 1, *A-D*). Two clinical patterns of hyperpigmentation were observed: (1) the lentiginous or nevus spilus–like pattern, characterized by the presence of multiple lentigines on a hyperpigmented background (Fig 1, *C*), and (2) a homogeneous pattern with well-defined borders (Fig 1, *D*). Hyperpigmentation was significantly associated with darker Fitzpatrick skin phototype (≥IV) (odds ratio [OR], 3.99; 95% confidence interval [CI], 1.60-10.00). In contrast, no significant association was found between hypopigmentation and skin phototype. Hypopigmentation was significantly observed with younger age (OR, 0.96; 95% CI, 0.93-0.99). No significant association was found between other clinical features including BMI, cardiovascular risk factors, and hyper- and hypopigmentation (Supplemental Appendix 2). Although univariate analyses showed no significant