Palmoplantar keratoderma as a clinical feature of pathogenic variants in the filaggrin gene

Clabbers, Julia M.K.; Bolling, Marieke C.; Burms, Charlotte; Vreeburg, Maaike; Lemmink, Henny H.; van den Akker, Peter C.; Steijlen, Peter M.; van Geel, Michel; Gostyński, Antoni H.

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LETTER TO THE EDITOR

Palmoplantar keratoderma as a clinical feature of pathogenic variants in the filaggrin gene

Pathogenic variants in the filaggrin (*FLG*) gene are known to cause ichthyosis vulgaris (IV) and predispose to atopic dermatitis (AD) with a semi-dominant inheritance pattern. IV is characterized by excessive scaling, xerosis, keratosis pilaris, hyperkeratosis and palmar hyperlinearity.[1] Hereditary palmoplantar keratoderma (hPPK) is a group of rare inherited disorders characterized by excessive thickening of the palmar and plantar epidermis. Currently, about 140 genes have been associated with various forms of hPPK, with 20 involved in isolated hPPK.[2,3] PPK in combination with ichthyosis is frequently seen.[1,4–6] To our knowledge, pathogenic variants in the *FLG* gene have not been described before as a cause of PPK and PPK has not been included in the list of *FLG*-related symptoms. In a Dutch cohort of about 200 patients diagnosed with PPK in two Centres of Expertise for Genodermatoses, Maastricht University Medical Centre+ (MUMC+) and University Medical Centre Groningen (UMCG), we identified 22 patients from different families with PPK, who had monoallelic or biallelic pathogenic *FLG* variants (Table 1). In 17/22 (77%), the genetic analysis comprised whole exome sequencing (WES)-based skin panels containing all known PPK genes, and no other pathogenic variants in these genes were identified. The study was done as a part of the KERATT project (Medical Ethical Committee of the MUMC+ 2020-2268). Ten patients were heterozygous (*FLG*−/+), six homozygous (*FLG*−/−) and six compound heterozygous (*FLG*−/−) for pathogenic *FLG* variants encompassing nonsense or frameshift mutations which introduced a preliminary stop codon. Two novel loss-of-function *FLG* variants were identified (c.10086del p.(His3365Ilefs*27) and c.5842G>T p.(Glu1948*)). Patients' age at diagnosis varied from 2 to 68 years (median 21 years) and was significantly lower in the *FLG*−/− group, 12 versus 33 years in FLG−/+ patients, $p = 0.04$. The clinical presentation was characterized by diffuse PPK (100%) with most patients showing palmoplantar erythema (82%), palmar hyperlinearity (91%), transgrediens (62%) and generalized xerosis cutis (100%) (Figure 1). The severity of the PPK was variable (41% mild, 45% moderate, 14% severe), and not significantly correlated with *FLG* status or age. AD was seen in 23% of patients, all of them being *FLG*−/−. The palmoplantar skin changes did not match the clinical presentation of hand/foot eczema, and the characteristic symptom of itch was missing.[7] The family history was positive for atopic diseases in 55%, PPK in 36% and other IV symptoms in 27%. The family history of PPK might be underreported due to the retrospective character of the study, variable clinical presentation and variable expression. The clinical presentation could further vary due to the semi-dominant inheritance pattern, (epi)genetics, environmental factors and dysbiosis of the skin microbiome. A limitation of this study is that in 23% cases, only the *FLG* gene was tested; however, the reason was the similarity of the phenotype to earlier tested patients. The fact that in 17/22 patients, variants in all currently known PPK genes were excluded, supports our theory that the detected *FLG* variants are indeed causing PPK. Nonetheless, a possible role of still undiscovered PPK genes cannot be excluded. However, the strong association with generalized xerosis cutis (100%) and hyperlinearity of palms (91%) underlines PPK as a possible sign of IV. AD was present in 5 of 22 cases, all of them having biallelic *FLG* variants, making it not a distinctive symptom in our cohort, but suggestive for being part of the *FLG* null phenotype. The reported carrier frequency of pathogenic *FLG* variants in the healthy population ranges from 4% to 9%.[4,8,9] We believe that the mild to moderate PPK in patients with *FLG* variants is underreported. Based on the presented cohort, we suggest screening of the *FLG* gene in case of a diffuse PPK, especially if it is accompanied by hyperlinearity, transgrediens, erythema and/or xerosis cutis. The presence of eczema or a history of atopy is not a prerequisite. We propose to add PPK to the list of symptoms associated with IV.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

TABLE 1 Characteristics of patients with PPK and mono- or biallelic pathogenic variants in FLG.

Patient ID	Age at diagnosis	Gender	Type of PPK	Severity of PPK	Erythema palms/soles	Transgrediens	Hyperlinearity palms/soles	Generalized xerosis cutis	Eczema	Family history[a]	Genetic testing[b]	Mutation(s)[c]
1	12	M	Diffuse	Mild	No	No	Doubtful	Yes	No	No	WES (PPK panel)	c.2282_2285del p.(Ser761Cysfs*36) heterozygous
2	5	M	Diffuse	Mild	No	No	Yes	Yes	No	No	WES (ichthyosis isolated panel)	c.2282_2285del p.(Ser761Cysfs*36); c.1501C>T p.(Arg501*) compound heterozygous
3	4	F	Diffuse	Mild	Yes	No	Yes	Yes	Yes	A	smMIP-NGS *FLG*	c.2282_2285del p.(Ser761Cysfs*36); c.1501C>T p.(Arg501*) compound heterozygous
4	10	M	Diffuse	Mild	Yes	No	Yes	Yes	No	A	smMIP-NGS *FLG*	c.2282_2285del p.(Ser761Cysfs*36); *c.10086del p.(His3365Ilefs*27)* compound heterozygous
5	17	F	Diffuse	Mild	Yes	No	Yes	Yes	Yes	A	Sanger sequencing + smMIP-NGS	c.63dup p.(Asp22Argfs*2); c.3551C>A p.(Ser1184*) compound heterozygous
6	53	F	Palms: punctata soles: diffuse	Mild	No	Yes	Yes	Yes	No	PPK	WES (skin panel) + Sanger sequencing	c.9085C>T p.(Gln3029*) heterozygous
7	61	F	Diffuse	Mild	Yes	Yes	Yes	Yes	No	A, IV, PPK	WES (skin panel)	c.2282_2285del p.(Ser761Cysfs*36) homozygous
8	35	M	Diffuse	Mild	Yes	No	Yes	Yes	No	A	smMIP-NGS *FLG*	*c.5842G≥T p.(Glu1948*)* heterozygous
9	18	M	Diffuse	Mild	Yes	Yes	Yes	Yes	No	PPK	WES (PPK panel)	c.2282_2285del p.(Ser761Cysfs*36) heterozygous
10	54	F	Diffuse	Moderate	No	No	Yes	Yes	No	A, IV, PPK	WES (skin panel)	c.1501C>T p.(Arg501*) heterozygous
11	6	M	Diffuse	Moderate	Yes	No	Yes	Yes	Yes	A, IV	WES (*FLG* only)	c.2282_2285del p.(Ser761Cysfs*36) homozygous
12	2	M	Diffuse	Moderate	Yes	No	Yes	Yes	No	PPK	WES (ichthyosis isolated panel)	c.2282_2285del p.(Ser761Cysfs*36); c.1501C>T p.(Arg501*) compound heterozygous

TABLE 1 (Continued)

Patient ID	Age at diagnosis	Gender	Type of PPK	Severity of PPK	Erythema palms/soles	Transgrediens	Hyperlinearity palms/soles	Generalized xerosis cutis	Eczema	Family history[a]	Genetic testing[b]	Mutation(s)[c]
13	21	F	Diffuse	Moderate	Yes	Yes	Yes	Yes	Yes	No	WES (ichthyosis isolated panel)	c.1501C>T p.(Arg501*) homozygous
14	14	F	Diffuse	Moderate	Yes	Yes	Yes	Yes	No	A	WES (skin panel) + smMIP-NGS	c.2282_2285del p.(Ser761Cysfs*36) homozygous
15	54	M	Diffuse	Moderate	Yes	Yes	Yes	Yes	No	PPK	WES (ichthyosis isolated panel)	c.2282_2285del p.(Ser761Cysfs*36) heterozygous
16	31	M	Diffuse	Moderate	Yes	Yes	Yes	Yes	No	IV	WES (PPK panel)	c.2282_2285del p.(Ser761Cysfs*36) heterozygous
17	18	F	Diffuse	Moderate	Yes	Yes	Yes	Yes	No	A	WES (skin panel) + Sanger sequencing	c.3321del p.(Gly1109Glufs*13) heterozygous
18	30	F	Diffuse	Moderate	Yes	Yes	Yes	yes	No	No	WES (skin panel)	c.3757G>T p.Glu1253* heterozygous
19	42	F	Diffuse	Moderate	Yes	Yes	Yes	Yes	Yes	A, IV, PPK	WES (skin panel)	c.1501C>T p.(Arg501*); c.2282_2285del p.(Ser761Cysfs*36) compound heterozygous
20	8	F	Diffuse	Severe	Yes	Yes	Yes	Yes	No	A, IV	WES (skin panel)	c.2282_2285del p.(Ser761Cysfs*36); c.2282_2285del p.(Ser761Cysfs*36) homozygous
21	55	M	Diffuse	Severe	Yes	Yes	Yes	Yes	No	A	WES (skin panel)	c.2282_2285del p.(Ser761Cysfs*36); c.2282_2285del p.(Ser761Cysfs*36) homozygous
22	68	M	Diffuse	Severe	Yes	Yes	Doubtful	Yes	No	PPK	WES (PPK panel)	c.2282_2285del p.(Ser761Cysfs*36) heterozygous
Summary	2–68 (median 21)	50% M 50% F	100% diffuse	41% mild 45% moderate 14% severe	82%	62%	91%	100%	23%	55% A 36% PPK 27% IV	77% WES 23% *FLG*	46% heterozygous 27% compound heterozygous 27% homozygous

Abbreviations: *FLG*, filaggrin; PPK, palmoplantar keratoderma; smMIP-NGS, single-molecule Molecular Inversion Probes – Next Generation Sequencing; WES, whole exome sequencing.

[a]Family history positive for: A, atopic constitution; IV, features of ichthyosis vulgaris; no, unremarkable family history; PPK, features of palmoplantar keratoderma.

[b]The WES-based skin panel consisted of 630 genes (Genome Diagnostics Nijmegen Maastricht, Skin disorders gene panel version DG3.3, https://www.radboudumc.nl/getmedia/fde4013f-640b-468b-b982-b614cf8218f4/SKINDISORDERS_DG330.aspx), the WES-based panels for PPK and ichthyosis contained 140 and 73 genes, respectively (Genome Diagnostics Groningen, PPK gene panel or ichthyosis gene panel, https://webshare.zenya.work/8yodxx6gk6p15j6d/Document.aspx?websharedocumentid=5e757178-20e6-40d3-bd75-ec6baf130478).

[c]Nomenclature based on *FLG* reference sequence NM_002016.1, new variants marked in italics.

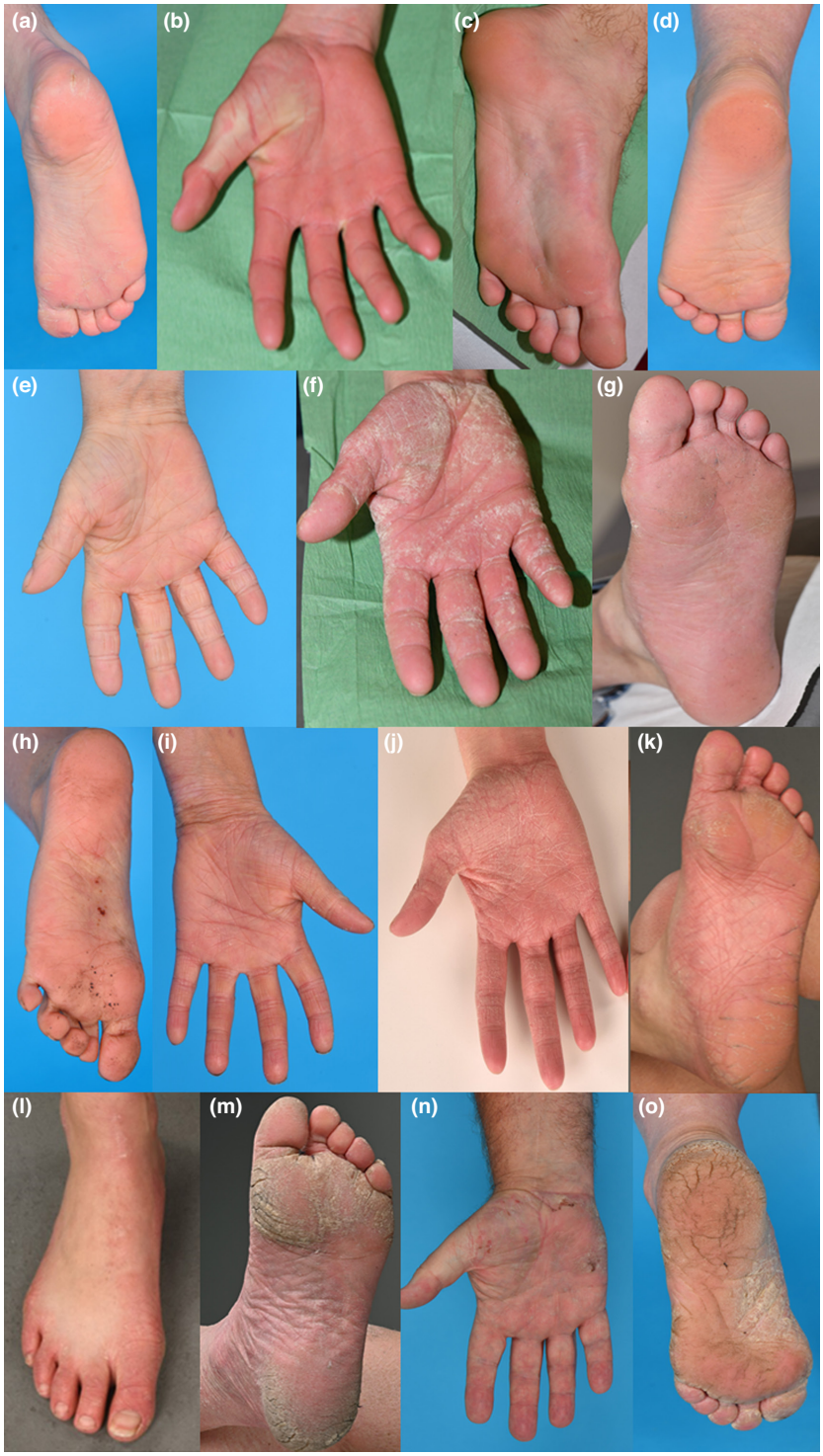

FIGURE 1 The clinical presentation of patients with palmoplantar keratoderma (PPK) due to mono- or biallelic pathogenic variants in *FLG*. (a–c) Mild forms of diffuse PPK with erythema (in b) and hyperlinearity (a = patient ID 1; b,c = patient ID 9). (d,e) Moderate diffuse PPK accompanied with hyperlinearity (patient ID 12). (f,g) Moderate presentation of PPK, more pronounced in the palms of the hands with erythema (patient ID 16). (h–l) Moderate diffuse PPK accompanied by erythema (in h-l), hyperlinearity (in h–k) and transgrediens (in i,l) (h,i = patient ID 11, j–l = patient ID 17). (m–o) Severe presentation of diffuse PPK with erythema (m = patient ID 21, n,o = patient ID 22).

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to the publication of their case details.

Julia M. K. Clabbers[1,2,3]
Marieke C. Bolling[4]
Charlotte Burms[1,2]
Maaike Vreeburg[5]
Henny H. Lemmink[6]
Peter C. van den Akker[6]
Peter M. Steijlen[1,2]
Michel van Geel[1,2,5]
Antoni H. Gostyński[1,2]

[1]*Department of Dermatology, Centre of Expertise for Genodermatoses, Maastricht University Medical Centre+, Maastricht, The Netherlands*
[2]*GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands*
[3]*Department of Dermatology, Haga Hospital, The Hague, The Netherlands*
[4]*Department of Dermatology, Centre of Expertise for Genodermatoses, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*
[5]*Department of Clinical Genetics, Centre of Expertise for Genodermatoses, Maastricht University Medical Centre+, Maastricht, The Netherlands*
[6]*Department of Genetics, Centre of Expertise for Genodermatoses, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*

Correspondence
Antoni Gostyński, Department of Dermatology, Maastricht University Medical Centre+, P. Debyelaan 25 6229HX Maastricht, The Netherlands.
Email: antoni.gostynski@mumc.nl

ORCID

Antoni H. Gostyński https://orcid.org/0000-0002-1091-2914

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