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ORIGINAL ARTICLE

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Clinical examination for hyperlinear palms to determine filaggrin genotype: A diagnostic test accuracy study

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Abstract

Background: Palmar hyperlinearity is a feature of ichthyosis vulgaris, the monogenic skin disorder caused by *FLG* loss-of-function mutations.

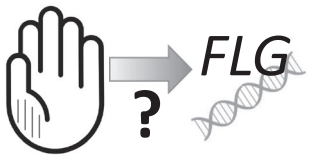
Objective: To investigate how well the presence or absence of hyperlinear palms (HLP) detect FLG genotype in children.

Methods: STARD criteria are used to report this diagnostic accuracy study. Phenotype and genotype data (four most prevalent FLG null mutations) were obtained from a total of 3656 children in three studies: the UK CLOTHES trial (children 1–5 years with moderate–severe atopic eczema); UK BEEP trial (2 year olds at high risk of developing atopic eczema); UK-Irish eczema case collection (0–16 year olds with atopic eczema). All participants included in analyses of HLP as the index test and FLG genotype as the reference were of white European ancestry.

Results: Thirty-two percent of participants (1159/3656) had FLG null mutation(s) and 37% (1347/3656) had HLP. In 13% (464/3656), HLP was recorded as 'unsure' or not recorded. The sensitivity and specificity of HLP for detecting FLG mutations in each of the studies was: 67% (95% CI 55–78%) and 75% (67–82%) in CLOTHES; 46% (36–55%) and 89% (86–91%) in BEEP; 72% (68–75%) and 60% (57–62%) in the UK-Irish case collection. Positive and negative likelihood ratios were: 2.73 (1.95–3.81) and 0.44 (0.31–0.62) in CLOTHES; 4.02 (2.99–5.40) and 0.61 (0.52–0.73) in BEEP; 1.79 (1.66–1.93) and 0.47 (0.42–0.53) in the UK-Irish collection.

Discussion: Trained observers were able to define palmar hyperlinearity in the majority (3191/3656, 87%) of cases. The presence of HLP is not a reliable sign to detect FLG mutations, but the absence of HLP excludes FLG null genotype with a reasonable degree of certainty.

KEYWORDS
atopic dermatitis, atopic eczema, filaggrin, hyperlinearity, keratosis pilaris, predictive



Can hyperlinear palms predict genotype?

GRAPHICAL ABSTRACT

Palmar hyperlinearity is associated with *FLG* loss-of-function mutations. This diagnostic test accuracy study used data previously collected as part of three paediatric cohorts, including a total of 3656 children. We aimed to investigate whether the presence or absence of hyperlinear palms (HLP) could be used to detect *FLG* genotype in children. Thirty-two percent of participants (1159/3656) had FLG null mutation(s) and 37% (1347/3656) had HLP. The presence of HLP was not a reliable clinical sign for the detection of F*LG* mutations.

1 | INTRODUCTION

Palmoplantar hyperlinearity, keratosis pilaris and ichthyosis are features of ichthyosis vulgaris (MIM #146700) caused by loss-of-function (null) mutations in the gene encoding filaggrin (*FLG*).[1] *FLG* null mutations are semi-dominant, meaning individuals with one mutation have a mild phenotype and individuals with two null mutations have more severe ichthyosis. Palmar hyperlinearity was the clinical feature most strongly associated with *FLG* null genotype in a population-based study of children aged 7–9 years (heterozygote odds ratio 19.3 (95% confidence interval 11.7–31.7))[2] but hyperlinearity can also occur in *FLG* wild-type individuals (those with no *FLG* mutations).[2]

In addition to causing the monogenic dry skin condition of ichthyosis vulgaris, *FLG* null mutations also increase risk of the common complex trait atopic eczema.[3] The strongest and most highly significant effect of *FLG* null genotype on eczema risk is present in early-onset, persistent and severe disease[4] associated with multiple other atopic conditions, including asthma and food allergy.[5-7] *FLG* haploinsufficiency is believed to contribute to the pathophysiology of atopic disease by multiple mechanisms in the biochemical, physical and microbial components of skin barrier formation and function.[8] The mechanisms by which *FLG* null genotype leads to palmoplantar hyperlinearity remain unknown.

Key Messages

- Examination for palmar hyperlinearity is not a sensitive or specific way to detect filaggrin mutations
- However, the absence of HLP can be used to exclude *FLG* haploinsufficiency with reasonable certainty
- This study focused on people of white European ethnicity; other ethnic groups require further work

Filaggrin deficiency has been targeted therapeutically using emollients containing filaggrin's constituent amino acids[9] and observational studies have reported differences in patient response to immunosuppressive treatment based on *FLG* genotype.[10] Knowledge of an eczema patient's *FLG* genotype could therefore be used for current and future personalized medicine strategies, but genotyping is not yet available in routine clinical practice.

We sought to test the hypothesis that examination for the clinical feature of hyperlinear palms (HLP) can be used as a proxy for *FLG* null genotype (having one or two loss-of-function mutations) in children with eczema or at high risk of atopic eczema.

2 | METHODS

This study was conducted using all available data from three paediatric eczema studies: the CLOTHES trial of silk clothing which recruited 300 children aged 1–5 years with moderate–severe atopic eczema[11]; the BEEP study, which studied 1394 infants at high risk of atopic eczema based on family history, up to 2 years of age[12]; and a UK-Irish case collection which recruited 4053 children aged 0–16 years with doctor-diagnosed atopic eczema from secondary and tertiary care in the Republic of Ireland, Scotland, England and Northern Ireland.[5,13,14] The presence or absence of HLP or 'unsure' was recorded by research nurses in the CLOTHES and BEEP studies and medical doctors in the UK-Irish case collection. Research nurses received training in the observation of HLP using clinical photographs of the palmar aspects of children's hands, including paediatric ichthyosis vulgaris cases. The teaching material is shown

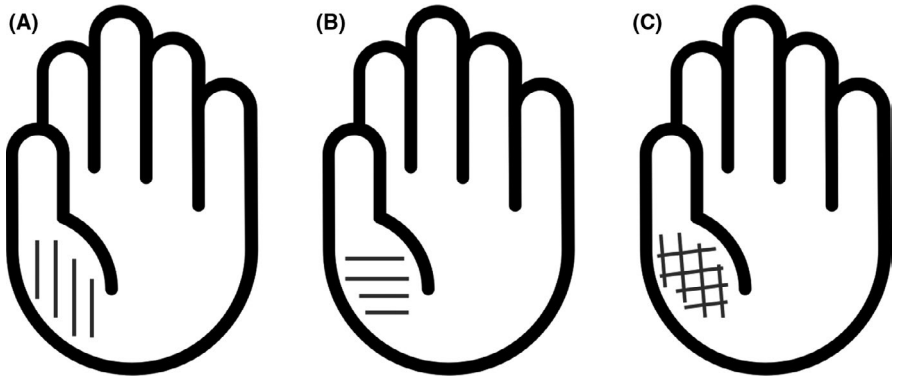


FIGURE 1 Patterns of palmer hyperlinearity recorded in the UK-Irish case collection. Clinical appearance of Vertical (A), Horizontal (B) and Crosshatch (C) HLP patterns as previously reported by Brown et al.[2] CC Hand by HeadsOfBirds from the Noun Project

in the Supplementary material. Severity and patterns[2] (Figure 1) of hyperlinearity were recorded in the UK-Irish case collection only. The clinicians and trained observers recording HLP were unaware of the participants' genotypes and similarly the laboratory staff carrying out genetic analysis did not have access to the phenotypic data.

Individuals had been genotyped for the four most prevalent *FLG* null mutations (R501X, 2282del4, R2447X and S3247X) as part of the previous studies.[5,11-14] Individuals with one or two *FLG* null mutations (heterozygotes, homozygotes and compound heterozygotes) were considered as one group for this analysis, to be compared with the group of individuals with *FLG* wild-type genotype (having no mutations). Characteristics of the study participants are shown in Table 1. Individuals of white European ethnicity were selected because of knowledge about the prevalent *FLG* mutations in this population group.[15] All the participants in this study (or their parents or guardians) had given written informed consent as part of the original study consent process for their data and DNA from blood or saliva to be used for future research.[1,11,12]

The utility of HLP (assessed as yes or no) as a proxy for *FLG* null genotype was reviewed using cross-tabulation and investigated by calculation of sensitivity, specificity, likelihood ratios, diagnostic odds ratios, positive and negative predictive values for each study and presented with 95% confidence intervals. For the BEEP study, this was repeated for the subset of children with eczema at 24 months old. The cases where HLP were assessed as unsure were included in a sensitivity analysis as no HLP. We have reported this diagnostic accuracy study, in which the presence/absence of HLP is the index test and *FLG* genotype is the reference standard, using STARD criteria.[16] These analyses were not pre-specified in the original study protocols.

TABLE 1 Characteristics of children included in the *FLG* and HLP analysis

	Clothes (*n* = 217)	**BEEP (*n* = 816)**	**UK-Irish case collection (*n* = 2623)**
Age in years			
Mean (SD)	4.9 [3.6]	Randomized just after birth; HLP assessed up to 2 years	4.0 [4.1]
Min, max	1, 15		0.5, 18
Sex			
Male	124 (57%)	432 (53%)	1630 (62%)
Female	93 (43%)	384 (47%)	992 (38%)
Missing data	-	-	1
Eczema at 24 months[a]			
no	-217 (100%)	627 (77%)	-2623 (100%)
yes		189 (23%)	
Eczema severity scores			
EASI [b]	***EASI assessed at recruitment*** [b]	***EASI assessed at24 months of age***[b]	***Not done***
Mean (SD)	10.1 (8.8)	0.7 (1.8)	
Median (IQR)	6.8 (4–13.6)	0 (0 to 0.6)	
Min, max	1, 46	0, 20.5	
n	217	812	
Patient Orientated Eczema Measure[c]	***At recruitment***	***At 24 months of age***	***Not done***
Mean (SD)	16.9 (5.1)	1.8 (3.8)	
Min, max	5, 28	0, 26	
n	217	814	
Nottingham Eczema Severity Score (NESS) [d]	***At recruitment***	***Not done***	***At recruitment***
Mean (SD)	13 (1.6)		11 (2.8)
Min, max	9, 15		3, 15
n	217		2613

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]Diagnosed using UK Working Party criteria.[20]

[b]Eczema Area and Severity Index.[21]

[c]POEM.[22]

[d]Nottingham Eczema Severity Score.[23]

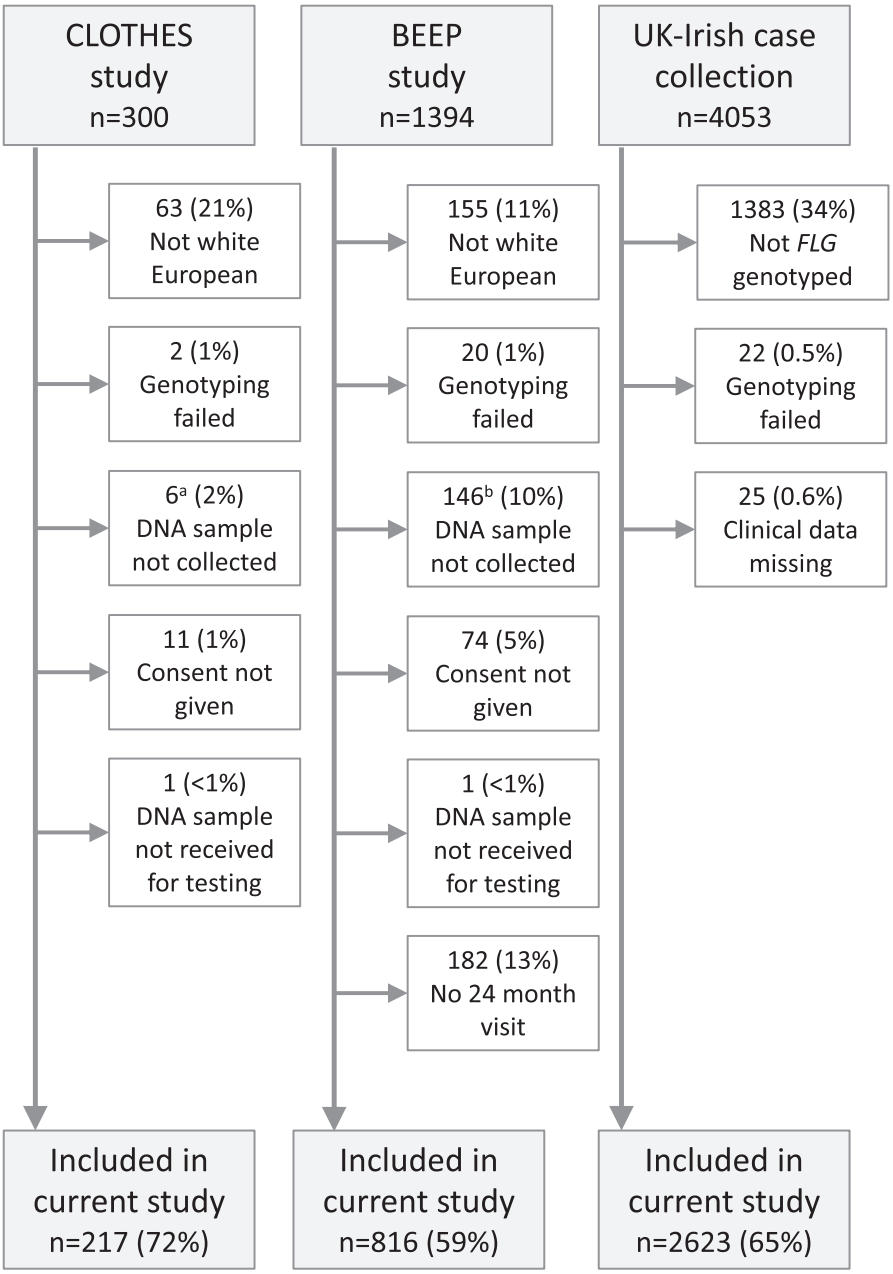


FIGURE 2 Flow diagram showing recruitment, exclusions and reasons for missing data. [a]Child too distressed, child declined, parents changed their minds, participant did not attend any follow-up visits and consent withdrawn from clinical trial. [b]Either visit not done face to face or sample not collected at visit and either the kit was not left or the parents did not return sample

3 | RESULTS

Phenotype and genotype data were available for a total of 3656 children of white European ethnicity, including 217 from the CLOTHES study, 2623 from the UK-Irish case collection and 816 from the BEEP study (Figure 2). The prevalence of *FLG* null mutations varied from 15% (125/816) in BEEP to 37% (960/2623) in the UK-Irish eczema case collection (Table 2). The prevalence of HLP varied from 15% (124/816) in BEEP to 44% (1142/2623) in the UK-Irish collection (Table 2). HLP was recorded as 'unsure' or not recorded in 13% of the total combined study population, but 15% in the UK-Irish collection (395/2623) (Table 2).

Cross-tabulation of *FLG* genotype by HLP in Table 3 shows that HLP are observed in children with and without *FLG* null mutations in each of the three studies. Table 4 shows the sensitivity, specificity, likelihood ratios, diagnostic odds ratio and predictive values of HLP for *FLG* genotype in each study. Results varied according to the context. Participants in the CLOTHES study and UK-Irish case collection have established atopic eczema (moderate–severe in CLOTHES; mild, moderate and severe in the UK-Irish collection). In these studies, the sensitivity and specificity of HLP for *FLG* null genotype are estimated to be 67% and 72% sensitivity, 75% and 60% specificity respectively (Table 4). In contrast, in the BEEP study, which comprised young children at high risk for atopic eczema, the sensitivity of HLP was only ~46% but the specificity was ~89%. Similar sensitivity and specificity were observed in BEEP in the subset of children who had developed eczema by 24 months of age. Figure 3 displays the sensitivity and specificity for each study.

The positive likelihood ratios in Table 4 compare the probability that HLP is present in a child with *FLG* null genotype compared to

TABLE 2 Summary of *FLG* genotypes and HLP by study

	Clothes ($n = 217$)	BEEP ($n = 816$)	UK-Irish case collection ($n = 2623$)
FLG genotype			
+/+ (no mutations)	143 (66%)	691 (85%)	1663 (63%)
+/− (one *FLG* null mutation)	51 (24%)	122 (15%)	733 (28%)
−/− (two *FLG* null mutations)	23 (11%)	3 (<0.5%)	221 (8%)
+/− or −/− (unsure)[a]	-	-	6 (<0.5%)
At least one *FLG* null mutation	74 (34%)	125 (15%)	960 (37%)
Hyperlinear palms			
No	127 (59%)	632 (77%)	1086 (41%)
Yes	81 (37%)	124 (15%)	1142 (44%)
Unsure	9 (4%)	56 (7%)	395 (15%)
Not assessed	-	4 (<0.5%)	-
Severity of hyperlinearity[b]	*Not done*	*Not done*	
Normal	-	-	76 (3%)
Mild	-	-	489 (19%)
Marked	-	-	296 (11%)
Not known	-	-	263 (10%)
Missing	-	-	18 (1%)
Pattern of hyperlinearity[b,c]	*Not done*	*Not done*	
'Vertical'	-	-	116 (4%)
'Horizontal'	-	-	289 (11%)
'Crosshatch'	-	-	433 (17%)
Not applicable	-	-	41 (2%)
Unknown	-	-	263 (10%)

[a]Incomplete genotype results but included in this study because the results are sufficient to define 'At least one *FLG* null mutation'.

[b]Severity and pattern summarized for children assessed as having hyperlinear palms in the UK-Irish case collection.

[c]Patterns are shown in Supplementary Material, as previously reported.[2]

TABLE 3 Cross-tabulation of *FLG* genotype and HLP by study

CLOTHES study	Hyperlinear palms: No	Yes	Total
FLG genotype			
+/+	104	34	138
+/− or −/−	23	47	70
	127	81	208
BEEP study	**Hyperlinear palms**		
—all children	**No**	**Yes**	**Total**
FLG genotype			
+/+	571	73	644
+/− or −/−	61	51	112
	632	124	756
BEEP study	**Hyperlinear palms**		**Total**
—children with atopic eczema [a]	No	Yes	
FLG genotype			
+/+	115	20	135
+/− or −/−	20	19	39
	135	39	174
	Hyperlinear palms		
UK-Irish collection	**No**	**Yes**	**Total**
FLG genotype			
+/+	864	578	1442
+/− or −/−	222	564	786
	1086	1142	2228

Note: +/+ indicates no mutations (*FLG* wild-type genotype); +/− or −/− indicates an individual with at least one mutation (*FLG* heterozygous, homozygous or compound heterozygous for null mutations).

[a]diagnosis based on UK working party criteria at 24 months of age.

the probability of HLP in a child without *FLG* null genotype. Positive likelihood ratios can be used to assess how good HLP is as a potential test for identifying *FLG* mutations. In these three studies the positive likelihood ratios show that HLP are around twice as likely in children with a *FLG* null mutation compared to children who do not have a mutation.

The positive predictive value of HLP is determined in part by the prevalence of *FLG* null genotype. In the BEEP study population, where ~15% have *FLG* null mutations, the positive predictive value is only 41% (95% CI 32–50%) whilst in CLOTHES, where 34% have *FLG* null mutations, the positive predictive value is 58% (47–69%). In all three studies the negative predictive values were estimated to be ≥80%.

Additional sensitivity analysis was carried out to investigate the effect of including children for whom HLP were recorded as 'unsure' (Tables S1 and S2). Estimates of sensitivity were smaller when children for whom HLP were recorded as 'unsure' were included. Other estimates of diagnostic performance were similar to the analysis including HLP assessed as no/yes.

Severity and patterns of hyperlinearity were recorded in the UK-Irish case collection only. Of those with HLP, 489/1142 (43%) had mild hyperlinearity and 296 (26%) had marked HLP (Table 5). The most prevalent pattern was 'crosshatch' (Table 6, Figure 1C) as previously reported.[2] The percentage of children with *FLG* null mutations increased with HLP severity, however, severity was not classified for 281 of the 1142 children assessed as having hyperlinear palms which, therefore, limits interpretation of a possible correlation between *FLG* genotype and HLP severity.

TABLE 4 Diagnostic test accuracy of HLP for detecting *FLG* genotype by study

	CLOTHES	BEEP *all children*	BEEP *children with atopic eczema*[a]	UK-Irish case collection
Prevalence of FLG null mutation	70/208 (34%)	112/756 (15%)	39/174 (22%)	786/2228 (35%)
Sensitivity	67% (55% to 78%)	46% (36% to 55%)	49% (32% to 65%)	72% (68% to 75%)
Specificity	75% (67% to 82%)	89% (86% to 91%)	85% (78% to 91%)	60% (57% to 62%)
Positive likelihood ratio	2.73 (1.95 to 3.81)	4.02 (2.99 to 5.4)	3.29 (1.96 to 5.51)	1.79 (1.66 to 1.93)
Negative likelihood ratio	0.44 (0.31 to 0.62)	0.61 (0.52 to 0.73)	0.60 (0.44 to 0.82)	0.47 (0.42 to 0.53)
Diagnostic odds ratio	6.25 (3.33 to 11.72)	6.54 (4.2 to 10.19)	5.46 (2.51 to 11.93)	3.8 (3.15 to 4.58)
Positive predictive value	58% (47% to 69%)	41% (32% to 50%)	49% (32% to 65%)	49% (46% to 52%)
Negative predictive value	82% (74% to 88%)	90% (88% to 93%)	85% (78% to 91%)	80% (77% to 82%)

Note: 95% confidence intervals are shown in parentheses; note positive and negative predictive values depend on the prevalence of *FLG* null mutations. Children whose HLP status could not be determined were excluded from analysis.

[a]diagnosis based on UK working party criteria at 24 months of age.

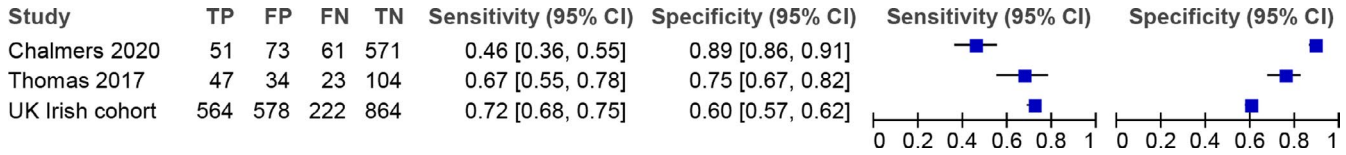


FIGURE 3 Forest plot showing sensitivity and specificity of HLP for detecting FLG status. CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive

TABLE 5 Relationship between severity of HLP and *FLG* genotype. (a) HLP severity and *FLG* genotype in all children (children assessed as not having hyperlinear palms are included in the normal category)

	HLP severity					
FLG genotype	Normal (*n* = 1162, 52%)	Mild (*n* = 489, 22%)	Marked (*n* = 296, 13%)	Not known (*n* = 263, 12%)	Missing (*n* = 18, 1%)	Total (*n* = 2228)
+/+	921 (79%)	303 (62%)	77 (26%)	136 (52%)	5 (28%)	1442 (65%)
+/− or −/−	241 (21%)	186 (38%)	219 (74%)	127 (48%)	13 (72%)	786 (35%)

Note: Data shown are for children in the UK-Irish case collection only. +/+ indicates no mutations (*FLG* wild-type genotype); +/− or −/− indicates an individual with at least one mutation (*FLG* heterozygous, homozygous or compound heterozygous for null mutations).

4 | DISCUSSION

4.1 | Main findings

This analysis brings together three of the largest clinical studies in which HLP have been reported. Screening was performed for the four most common *FLG* null mutations in the study populations using well-established methodology.[15,17] The presence or absence of HLP was recorded in 87% of children, indicating a degree of confidence in the trained observers. However, in the context of these paediatric studies HLP was not a reliable clinical sign for the detection of *FLG* null genotype. In contrast, our data show that the absence of HLP can be used to exclude *FLG* mutations with a reasonable degree of certainty (negative predictive value 80–90%).

The prevalence of *FLG* null mutations detected in these three studies was in keeping with a high-risk population in the BEEP study (15%) and in children with a range of atopic eczema severities in the CLOTHES study and UK-Irish case collection (34–35%). The prevalence of *FLG* null mutations affects the utility of HLP as a diagnostic test to some extent, as reflected in the positive and negative predictive values. It is important to note that if these findings are applied to an unselected population in which *FLG* mutation prevalence is lower (e.g. Northern Europe where *FLG* mutations are seen in <9% of people) the positive predictive value of HLP is likely to be <41%.

4.2 | Strengths and limitations

A strength of this work is the opportunity to compare findings from three paediatric studies carried out for different purposes, giving complementary insights. Data from the pilot study conducted in

TABLE 6 Relationship between pattern of HLP and *FLG* genotype

	HLP pattern					
FLG genotype	'Vertical' ($n = 116$, 10%)	'Horizontal' ($n = 289$, 25%)	'Crosshatch' ($n = 433$, 38%)	NA ($n = 41$, 4%)	Not known ($n = 263$, 23%)	Total ($n = 1142$)
+/+	60 (52%)	179 (62%)	179 (41%)	22 (54%)	138 (52%)	578 (51%)
+/− or −/−	56 (48%)	110 (38%)	254 (59%)	19 (46%)	125 (48%)	564 (49%)

Note: Data shown are for children determined as having HLP in the UK-Irish case collection only. +/+ indicates no mutations (*FLG* wild-type genotype); +/− or −/− indicates an individual with at least one mutation (*FLG* heterozygous, homozygous or compound heterozygous for null mutations); NA were individuals with HLP for whom a pattern was not recorded.

preparation for BEEP[18] were not included in our analysis because infants in the BEEP pilot were followed up to 6 months of age, and at this stage of development it is very difficult to distinguish palmoplantar hyperlinearity from physiological wrinkling of the neonatal palmar skin. This young age at recruitment may also have contributed to the higher proportion recorded as 'unsure' in the UK-Irish case collection.

Involvement of palmar skin is not common in infant eczema cohorts and the presence or absence of palmar eczema was not specifically recorded; since eczema can cause a wrinkled appearance to the skin this is a minor potential confounding factor. A further important limitation is the restriction to participants of white European ethnicity. This was necessary to ascertain *FLG* null status by screening the four mutations which are most prevalent in the white European population and further work is required in populations of other ethnicities. More detailed *FLG* analysis, for example, using optimized methods of next-generation sequencing to fully sequence the gene,[19] might be useful to ascertain the full burden of *FLG* null mutations and this might improve predictive value. However, it would also preclude current routine clinical use.

Additional limitations include the selection criteria required by recruitment to these clinical studies, meaning each is not an unselected population. Furthermore, not all children recruited to these studies were able to be included, where consent was not given for a saliva sample, genotyping failed or not genotyped. These missing data meant the participants were excluded. However, the three studies provide new information on the value of HLP in the key populations in which the sign is most likely to be used: in those at high risk of developing eczema and in those who already have eczema. Given that clinical trial participants for new eczema treatments are likely to be recruited from dermatology clinics, the external validity of the data from CLOTHES and the UK-Irish cohort is strong. Observers were allowed to record palmar hyperlinearity as 'unsure' or 'unknown' to optimize the reliability of any that were recorded present or absent, but the inter-observer variability in the observation of HLP has not been tested and this represents another potential limitation. Severe HLP are most highly predictive of *FLG* null genotype (74% of children with severe HLP in the UK-Irish case collection had one/more *FLG* null mutations) but the assessment of severity and patterns of HLP each included substantial proportions of missing data (Tables 5 and 6) which limit the interpretation of these associations.

4.3 | Clinical implications

Genetic analysis is likely to increase in availability in the future, but the use of bedside genetic testing is not yet available in routine clinical practice. The ability to use HLP as a proxy for *FLG* genotype appears an attractive opportunity to utilize genetic knowledge without costly DNA analysis. However, our data show that HLP on clinical examination is not a useful surrogate for detecting *FLG* null mutations. Conversely the absence of HLP can be used to exclude *FLG* haploinsufficiency with reasonable certainty. These studies were limited to people of white European ethnicity and further work is needed to study people of other ethnicities.

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CONFLICT OF INTEREST

The funding bodies have had no influence over study design, conduct, analysis or reporting of this study.

AUTHOR CONTRIBUTIONS

LEB, SJB, HCW conceptualized the study and planned the investigations; LEB, RHH, KST, JRC, ADI, SJB contributed to data curation; LEB conducted the formal analysis; KST, JRC, ADI, HCW, SJB acquired funding; methodology was defined by LEB, HCW and SJB; the manuscript original draft was written by LEB and SJB; review and editing was carried out by LEB, ADI, HCW and SJB; all authors reviewed and approved the manuscript.

ETHICAL STATEMENT

The CLOTHES study was approved by the Health Research Authority East Midlands–Nottingham 1 Research Ethics Committee, UK (13/EM/0255), and parents/guardians gave written informed consent (children gave assent as appropriate). The BEEP trial was approved by the West Midlands Ethics Committee, UK (14/WM/0162). The UK-Irish case collection was approved by

the Research Ethics Committee of Our Lady's Children's Hospital Crumlin, Dublin, Ireland (SAC/68/06), the West Glasgow Ethics Committee 1, Scotland, UK (08/S0703/62) and St John's Hospital /Adelaide and Meath NCH Research Ethics Committee, Dublin, Ireland (2006/25/13).

DATA AVAILABILITY STATEMENT

Data are available through collaboration with the source study authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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