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
**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 FLG 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). 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)) but hyperlinearity can also occur in FLG wild-type individuals (those with no FLG mutations).

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. The strongest and most highly significant effect of FLG null genotype on eczema risk is present in early-onset, persistent and severe disease associated with multiple other atopic conditions, including asthma and food allergy. 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.

The mechanisms by which FLG null genotype leads to palmoplantar hyperlinearity remain unknown.

2 | METHODS
This study was conducted using all available data from three pediatric eczema studies: the CLOTHES trial of silk clothing which recruited 300 children aged 1–5 years with moderate–severe atopic eczema; the BEEP study, which studied 1394 infants at high risk of atopic eczema based on family history, up to 2 years of age; 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. 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.

**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 and observational studies have reported differences in patient response to immunosuppressive treatment based on FLG genotype. 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.

**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. 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        | 1630 (62%)                        |
| **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*\(^b\)           |                   |                |                                   |
| Mean (SD)              | 10.1 (8.8)        | 0.7 (1.8)      | Not done                          |
| 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*\(^c\) |               |                |                                   |
| Mean (SD)              | 16.9 (5.1)        | 1.8 (3.8)      | Not done                          |
| Min, max               | 5, 28             | 0, 26          |                                   |
| n                      | 217               | 814            |                                   |
| *Nottingham Eczema Severity Score (NESS)*\(^d\) |               |                |                                   |
| 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.\(^23\)
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 (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
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. 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 2 Summary of FLG genotypes and HLP by study

| FLG genotype | Clothes (n = 217) | BEEP (n = 816) | UK-Irish case collection (n = 2623) |
|-------------|-----------------|----------------|-----------------------------------|
| +/+ (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) | - | - | 6 (0.5%) |

| Hyperlinear palms | Clothes (n = 217) | BEEP (n = 816) | UK-Irish case collection (n = 2623) |
|-----------------|-----------------|----------------|-----------------------------------|
| No | 127 (59%) | 632 (77%) | 1086 (41%) |
| Yes | 81 (37%) | 124 (15%) | 1142 (44%) |
| Unsure | 9 (4%) | 56 (7%) | 395 (15%) |
| Not assessed | - | - | - |

| Severity of hyperlinearity | Clothes (n = 217) | BEEP (n = 816) | UK-Irish case collection (n = 2623) |
|-----------------|-----------------|----------------|-----------------------------------|
| Normal | - | - | 76 (3%) |
| Mild | - | - | 489 (19%) |
| Marked | - | - | 296 (11%) |
| Not known | - | - | 263 (10%) |
| Missing | - | - | 18 (1%) |

| Pattern of hyperlinearity | Clothes (n = 217) | BEEP (n = 816) | UK-Irish case collection (n = 2623) |
|-----------------|-----------------|----------------|-----------------------------------|
| Vertical | - | - | 116 (4%) |
| Horizontal | - | - | 289 (11%) |
| Crosshatch | - | - | 433 (17%) |
| Not applicable | - | - | 41 (2%) |
| Unknown | - | - | 263 (10%) |

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

| CLOTHES study | Hyperlinear palms | Total |
|----------------|-----------------|-------|
| | No | Yes | Total |
| FLG genotype | +/+ | 104 | 34 | 138 |
| +/− or −/− | 23 | 47 | 70 |
| UK-Irish case collection | +/+ | 632 | 124 | 756 |
| +/− or −/− | 61 | 51 | 112 |
| | −/− | 263 (0.5%) | 41 (2%) |

| BEEP study | Hyperlinear palms | Total |
|----------------|-----------------|-------|
| | No | Yes | Total |
| FLG genotype | +/+ | 571 | 73 | 644 |
| +/− or −/− | 61 | 51 | 112 |
| | −/− | 263 (0.5%) | 41 (2%) |

| UK-Irish collection | Hyperlinear palms | Total |
|-----------------|-----------------|-------|
| | 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).

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

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. 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.
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

| FLG genotype | HLP pattern | '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.

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 accessed 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
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