MULTIMODAL ASPECTS OF RARE INHERITED SKIN DISEASES

PhD thesis outlines

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1. Introduction

Genodermatoses are rare inherited skin disorders with diverse phenotypes, ranging from limited cutaneous involvement to severe multisystemic disease. Diagnosis is often challenging due to their rarity, clinical and genetic variability. Non-invasive tools, such as dermoscopy, are increasingly valuable for facilitating the early diagnosis and for monitoring treatment response. Dermoscopy enables recognition of characteristic morphologic features *in vivo*. To promote accurate application, consistency, and comparability of dermoscopic terminology, the use of standardized terminologies is recommended.

Darier disease (DD) is a rare genodermatosis caused by mutations of the *ATP2A2* gene, which leads to the impairment of the epidermal barrier, therefore, predisposing to superinfections.

The human skin microbiome is a diverse group of microorganisms that plays a vital role in maintaining skin homeostasis, protecting against pathogens, and modulating immune function. Dysbiosis, as a result of an imbalance among the different skin microbiotas, has been implicated in the onset and exacerbation of various dermatologic conditions.

One of the differential diagnoses of DD is Hailey-Hailey disease (HHD). The two disorders often called as skin fragility syndromes and share similarities in prevalence, gender distribution, symptoms, treatment approaches, and health-related quality of life impact. Intense, chronic pain

combined with mobility restrictions, recurrent superinfections, and unpleasant odor can contribute to disability or reduced work capacity and the impairment of intra-and interpersonal relationships. Therefore, both conditions can have a significant impact on patients' quality of life.

The EQ-5D-5L is widely used for HRQoL assessment and QALY estimation. However, its five core dimensions may not capture all aspects of some conditions. Additional bolt-ons, such as skin-irritation and self-confidence, can improve the content validity of the EQ-5D-5L in dermatoses, such as psoriasis, atopic dermatitis and chronic urticaria.

2. Objectives

Study I.

This study aimed to investigate the dermoscopic features of various genodermatoses by conducting a systematic review and comparing the results to our own findings. We also aimed to examine whether the existing standardized dermoscopic terminologies are applicable for describing lesions in genodermatoses.

Study II.

The aim of the study was to investigate the clinical and genetic aspects of patients with DD. In the major part of our work, we aimed to determine the skin microbiome composition in two predilectional sites, such as the chest

and the back in DD patients and in healthy individuals. We aimed to investigate whether there are region-specific alterations between the analysed regions. the bacterial We also aimed to explore the microbial composition of the inner epidermal skin layers in DD patients.

Study III.

The aim of this study was to investigate the content validity- specifically relevance, comprehensiveness, and comprehensibility- of the EQ-5D-5L and the skin irritation and self-confidence bolt-ons among patients with DD and HHD. We aimed to explore how DD and HHD can affect patients' lives. We also sought to assess whether the EQ-5D-5L and the two bolt-ons is comprehensible for patients with DD and HHD, and identified which dimensions are relevant for these patient groups. We also aimed to assess whether there is any conceptual overlap between the EQ-5D-5L and the two bolt-ons. Finally, we also aimed to evaluate whether the EQ-5D-5L and the two bolt-ons are comprehensive for use in DD and HHD.

3. Methods

Study I.

1.

The systematic review followed the PRISMA 2020 Statement and was registered on PROSPERO (CRD42023452448). Literature searches were conducted in PubMed, Embase, and Cochrane (CENTRAL)

databases. Eligible publications included original articles, case reports, short communications, correspondences, and letters on the dermoscopic features of DD, HHD, and other genodermatoses (e.g., Dowling–Degos disease, palmoplantar keratoderma, various ichthyoses, pseudoxanthoma elasticum, tuberous sclerosis complex, neurofibromatosis type 1, Fabry disease, basal cell nevus syndrome, Noonan syndrome with multiple lentigines, CYLD cutaneous syndrome, monilethrix). Two independent authors performed study selection and data extraction (EndNote X9, Excel), and quality was assessed using the JBI Critical Appraisal tool for case reports and case series.

2.

In the descriptive part, patients with a genodermatosis were enrolled at the Department of Dermatology, Semmelweis University, between September 2020 and January 2023. Exclusion criteria included other skin diseases potentially affecting dermoscopic features. Demographics were recorded, and all patients underwent clinical examination and imaging. Clinically relevant lesions were selected for dermoscopic images. All authors evaluated images using standardized terminologies by *Kittler et al.* and *Errichetti et al*. Onychoscopic and trichoscopic findings were referenced from case reports and reviews. Findings were compared with literature data.

Study II.

1.

Participants were enrolled at the Department of Dermatology between February 2022 and May 2023. Inclusion criteria for patients were a histopathologically confirmed diagnosis of DD, age ≥18, active skin lesions, and symmetrical non-lesional areas. Controls were excluded for any skin infections or chronic skin conditions. All participants were excluded if they had used systemic antibiotics or immunosuppressives in the past three months, or topical antibiotics/antiseptics within three days prior to sampling.

2.

For genetic analysis, peripheral blood samples were collected from DD patients. Sanger sequencing of the *ATP2A2* gene was performed. Variants were evaluated with MutationTaster and classified according to ACMG guidelines.

3.

Bacterial DNA was extracted, and the V3–V4 region of the bacterial 16S rRNA gene was amplified with tagged primers. Purified PCR products were pooled and sequenced. Negative controls for extraction and PCR were included to detect reagent contamination. All samples underwent independent extraction and sequencing twice. Raw sequencing data were analyzed using the CosmosID

Metagenomics Cloud platform. Although *Propionibacterium* and *Cutibacterium* are taxonomically unified, they are presented separately in Study II results according to the CosmosID output.

4.

For the statistical analysis, the Wilcoxon rank sum test for Shannon alpha diversity and PERMANOVA for Jaccard PCoA of beta diversity were performed with the CosmosID statistical software.

Study III.

1.

Semi-structured interviews were conducted with patients diagnosed with DD or HHD. All interviews were conducted by the first author using a topic guide based on previous studies in psoriasis and atopic dermatitis. Interviews had three parts: (1) explanation of study objectives and patients' personal observations on health and HRQoL; (2) completion of the Hungarian version of the EQ-5D-5L and EQ VAS with a think-aloud protocol; (3) completion of the Hungarian version of the EQ-5D-5L with skin irritation and self-confidence bolt-ons (7 dimensions, no EQ-VAS). Patients were encouraged to comment on dimensions' relevance, overlaps, missing concepts, response levels, wording, and recall period. Finally, sociodemographic and clinical data were collected via a short questionnaire.

2.

Interviews were anonymous, audio-recorded, and transcribed verbatim. Thematic analysis followed a multi-stage inductive approach, such as initial coding by the primary author, development of categories/subcategories, and review by two senior authors. Data were organized in an Excel with patient quotations (original Hungarian and English translation).

4. Results

S*tudy I.*

1.

Systematic search identified 471 articles, of which 74 eligible studies were selected through title, abstract, and full-text screening, and nine additional studies were identified through citation searching.

2.

A total of 119 patients with 20 different genodermatoses, such as basal cell nevus syndrome, CYLD cutaneous syndrome, DD, Dowling-Degos disease, erythrokeratodermia variabilis et progressiva, Fabry disease, HHD, ichthyoses (congenital ichthyosiform erythroderma, Harlequin ichthyosis, ichthyosis vulgaris, pleomorphic ichthyosis, lamellar ichthyosis, pleomorphic ichthyosis, X-linked recessive ichthyosis), neurofibromatosis type I, Noonan syndrome with multiple lentigines, monilethrix, palmoplantar keratodermas

(punctate, diffuse epidermolytic), and tuberous sclerosis complex were enrolled.

3.

The standardized dermoscopic terminology by *Kittler et al.* were applied in Fabry disease, neurofibromatosis type I, basal cell nevus syndrome, Noonan syndrome with multiple lentigines, and CLYD cutaneous syndrome.

The standardized dermoscopic terminology by *Errichetti et al.* were applied in congenital ichthyosiform erythroderma, Harlequin ichthyosis, ichthyosis vulgaris, pleomorphic ichthyosis, lamellar ichthyosis, pleomorphic ichthyosis, X-linked recessive ichthyosis, DD, HHD, erythrokeratodermia variabilis et progressiva, Dowling-Degos disease, pseudoxanthoma elasticum, palmoplantar keratodermas, and tuberous sclerosis complex. Onychoscopic and trichoscopic findings were based on case reports and reviews.

Study II.

1.

Genetic analysis of DD patients revealed the presence of a heterozygous pathogenic or likely pathogenic variant of the *ATP2A2* gene in 5 patients. In one case, we identified a novel variant that was confirmed with Nci I enzyme restriction digestion.

2.

In the skin microbiome analysis, statistically significant difference in microbial alpha diversity between lesional and non-lesional DD cohorts was found by Shannon analysis with Wilcoxon rank sum testing at the species level ($p \leq 0.01$). We found significant differences among all groups of different localizations based on the principal coordinate analysis of Jaccard beta diversity (biopsy: non-lesional, biopsy:control, lesional:non-lesional; lesional: control: $p \leq 0.001$; non-lesional:control: $p \leq 0.004$).

3.

The bacterial composition altered in lesional, non-lesional and healthy skin samples. At the phylum level, the relative abundance of *Actinobacteria* was significantly lower in DD patients compared to controls ($p \leq .0.008$). No significant difference was observed between lesional and non-lesional sites. Conversely, *Firmicutes* phylum significantly increased in lesional sites compared to both non-lesional sites and controls ($p \leq 0.002$ and $p \leq 0.0001$, respectively). No significant increase was found between non-lesional and control samples. At the genus level, the *Staphylococcus* genus was significantly higher in lesional sites than in non-lesional and control sites, while no significant difference was observed between DD patients' non-lesional sites and healthy controls ($p \leq 0.0001$, $p \leq 0.0001$, $p \leq 0.187$, respectively). In contrast, the relative abundance of *Propionibacterium* and *Cutibacterium*

genera was significantly lower in lesional sites compared to non-lesional sites and controls ($p \leq 0.005$ and $p \leq 0.006$, $p \leq 0.0001$ and $p \leq 0.0001$). A significant decrease was detected in non-lesional sites relative to healthy controls in both genera ($p \leq 0.002$ and $p \leq 0.002$). The *Pseudomonas* genus was more abundant in lesional areas and continuously decreased toward non-lesional and healthy control areas, however, no significant differences were detected.

In lesional sites, the most frequent species was *S. aureus*, followed by *S. epidermidis*. The relative abundance of various *Staphylococcus* species, including *S. aureus, S. epidermidis, S. hominis, S. equorum,* and *S. haemolyticus,* was significantly higher in lesional sites compared to non-lesional sites and to controls ($p \leq 0.0001$, $p \leq 0.0001$, $p \leq 0.002$, $p \leq 0.001$, $p \leq 0.005$, $p \leq 0.004$, $p \leq 0.0001$, $p \leq 0.0001$, $p \leq 0.001$, $p \leq 0.0001$, $p \leq 0.0001$, $p \leq 0.0001$). Except for *S. aureus* and for *S. haemolyticus,* significant differences were found between non-lesional sites and controls ($p \leq .0.0001$, $p \leq 0.011$, respectively). In contrast, control samples were dominated by *Propionibacterium acnes (P. acnes)* and *Cutibacterium acnes subspecies defendens (C. acnes subsp. def.)*. The relative abundance of these two bacteria was significantly lower in DD patients compared to healthy individuals ($p \leq 0.0001$, $p \leq 0.0001$, respectively). Interestingly, significant reductions of the amounts of these species were also observed between lesional and non-lesional sites in DD patients ($p \leq 0.004$,

$p \leq 0.006$, respectively). Overall, we found a negative correlation between the relative abundance of *S. aureus, S. epidermidis, S. hominis, S. sciuri, and S. equorum* and the abundance of *P. acnes* and *C. acnes subsp. def.*

4.

In healthy controls, *Propionibacterium* predominated in both sites (chest and back), with higher abundance on the chest (33.29%) than on the back (14.94%). The control chest was also enriched in *Staphylococcus* (12.86%) and *Corynebacterium* (10.86%), compared to the back (3.03% and 4.55%, respectively). *Cutibacterium* accounted for 8.02% on the chest and 3.63% on the back. In DD patients, *Staphylococcus* dominated all sites (lesional chest: 53.25%, lesional back: 50.81%, non-lesional chest: 13.39%, non-lesional back: 8.74%), followed by *Corynebacterium* (lesional chest: 9.64%, lesional back: 9.01%, non-lesional chest: 12.66%, non-lesional back: 6.71%.)

5.

In biopsy samples, we detected a notable increase in *Staphylococcus* abundance (69.73%) compared to superficial lesional swab samples (50.06%). In contrast, the amounts of *Propionibacterium* and *Cutibacterium* were below the reliable detection threshold of the program.

Study III.

1.

Most patients found the EQ-5D-5L easy to complete, comprehensible and relevant to their disease. The majority of the patients mentioned multiple HRQol areas related to the EQ-5D-5L and the two bolt-ons, such as pain (93%), various forms of skin irritation (i.e. itching (47%), tightness and burning sensation (53%), mobility (73%), work-related problems (67%) or difficulties with self-confidence or self-esteem (40%) before completing both questionnaires.

2.

In the EQ-5D-5L, 40% of patients rated all dimensions equally relevant; 27% prioritised usual activities, followed by mobility, self-care, and pain/discomfort (20% each). With the two bolt-ons, self-confidence was most relevant (33%), followed by skin irritation (20%); 33% rated all seven dimensions equally relevant. Only one patient (6%) identified a least relevant dimension (self-care).

3.

Two patients (13%) noted conceptual overlap between usual activities and self-care core dimensions, and one between pain/discomfort and skin irritation bolt-on.

4.

All participants found the EQ-5D-5L with bolt-ons comprehensive, though 6 missing concepts were identified after the EQ-5D-5L by four patients (27%), and 12 missing concepts were identified after the bolt-ons by six patients (40%). The most frequent of them was financial impact (27%), followed by sexual life (13%). Each of the following aspects was mentioned only once, by different patients: work challenges, the importance of education for non-physical work, employers' tolerance, social/relationship difficulties, special care/diet, seasonal fluctuations, and disease-related limitations beyond usual activities. One patient noted the absence of a self-esteem dimension, linked to self-confidence. All preferred the version with bolt-ons.

5.

Most respondents (100%) were satisfied with the five-level scale. Two (13%) suggested reducing it to four or three levels for certain dimensions (mobility, self-care, skin irritation). Some felt that terms like "no problem" and "unable to" did not reflect their condition; one (6%) noted unclear differences between levels, and another recommended examples to define mild or severe pain.

5. Conclusions

Study I.

1. We were the first to carry out a systematic review of dermoscopic findings in 15 genodermatoses, such as basal cell nevus syndrome, CYLD cutaneous syndrome, DD, Dowling-Degos disease, Fabry disease, HHD, some ichthyoses (annular epidermolytic ichthyosis, lamellar ichthyosis, ichthyosis vulgaris, X-linked recessive ichthyosis), neurofibromatosis type I, Noonan syndomre with multiple lentigines, monilethrix, palmoplantar keratoderma and tuberous sclerosis complex.

2. We expanded the literature on dermoscopic analysis of 20 specific genodermatoses, including basal cell nevus syndrome, CYLD cutaneous syndrome, DD, Dowling-Degos disease, erythrokeratodermia variabilis et progressiva, Fabry disease, HHD, some ichthyoses (congenital ichthyosiform erythroderma, Harlequin ichthyosis, ichthyosis vulgaris, pleomorphic ichthyosis, lamellar ichthyosis, pleomorphic ichthyosis, X-linked recessive ichthyosis), neurofibromatosis type I, Noonan syndrome with multiple lentigines, monilethrix, palmoplantar keratodermas (punctate, diffuse epidermolytic), and tuberous sclerosis complex.

3. We were the first to report the dermoscopic findings in diffuse epidermolytic palmoplantar keratoderma, erythrokeratodermia variabilis et progressiva, and certain autosomal recessive congenital ichthyoses, such as

congenital ichthyosiform erythroderma, pleomorphic ichthyosis and Harlequin ichthyosis.

4. Standardized dermoscopic terminology by *Kittler et al.* was applicable for the evaluation of skin lesions in Fabry disease, neurofibromatosis type I, basal cell nevus syndrome, Noonan syndrome with multiple lentigines and CLYD cutaneous syndrome.

5. Expanded dermoscopic terminology on general dermatology by *Errichetti et al.* was applicable for the evaluation of skin lesions in congenital ichthyosiform erythroderma, Harlequin ichthyosis, ichthyosis vulgaris, pleomorphic ichthyosis, lamellar ichthyosis, pleomorphic ichthyosis, X-linked recessive ichthyosis, DD, HHD, erythrokeratodermia variabilis et progressiva, Dowling-Degos disease, pseudoxanthoma elasticum, palmoplantar keratodermas and tuberous sclerosis complex.

Study II.

1. We expanded the existing literature and provided novel insights by conducting a comprehensive analysis of the clinical characteristics of enrolled DD patients and identifying a previously unreported pathogenic variant of the ATP2A2 gene, c.1858G>T, (p.Val62330Phe).

2. This is the first study to investigate the bacterial composition of both superficial and deeper epidermal layers of the chest and back skin in DD patients, compared to healthy individuals.

3. The skin microbiome of DD patients in lesional chest and lesional back areas differed from that of non-lesional skin areas; moreover, non-lesional chest and back sites were different compared to controls.
4. Significant differences in alpha and beta diversity of DD patients' lesional and non-lesional skin were observed.
5. We were the first to identify a significant decrease in the amount of *C. acnes subsp. def.* in patients with DD compared to healthy individuals.
6. Negative correlation between various Staphylococcus species (e.g., *S. aureus, S. epidermidis*) and between *P. acnes* and *C. acnes subs. def.* were observed comparing lesional, non-lesional, and control samples.
7. Region-specific alterations by the two examined predilectional regions could be observed in DD patients and in healthy individuals.
8. A marked increase in *Staphylococcus* abundance, along with a significant decrease in *Propionibacterium* and *Cutibacterium* abundance, was detected in the inner epidermal layers of lesional skin compared to the superficial layers.

Study III.
1. This is the first study investigating the content validity of the EQ-5D-5L and two additional bolt-on dimensions (skin irritation and self-confidence) in two rare inherited skin diseases, DD and HHD.

2. Most patients considered both the EQ-5D-5L and the two bolt-ons comprehensible and relevant to their skin diseases.
3. Some missing concepts were identified, but only two (financial impact and sex life) were identified by more than one patient.
4. There is only very limited conceptual overlap between the skin irritation bolt-on and the pain/discomfort dimension.
5. There is no actionable evidence indicating gaps in the content validity (relevance, comprehensibility and comprehensiveness) of the EQ-5D-5L with skin irritation and self-confidence bolt-ons in DD and HHD.

6. Publications

Publications directly related to this thesis

(Σ IF: 11)

Plázár D, Meznerics FA, Pálla S, Anker P, Farkas K, Bánvölgyi A, Kiss N, Medvecz M. Dermoscopic Patterns of Genodermatoses: A Comprehensive Analysis. Biomedicines. 2023 Oct 6;11(10):2717. doi: 10.3390/biomedicines11102717. PMID: 37893091; PMCID: PMC10604867.
IF: 3,9

Plázár D, Metyovinyi Z, Kiss N, Bánvölgyi A, Makra N, Dunai Z, Mayer B, Holló P, Medvecz M, Ostorházi E. Microbial imbalance in Darier disease: Dominance of

various staphylococcal species and absence of Cutibacteria. Sci Rep. 2024 Oct 14;14(1):24039. doi: 10.1038/s41598-024-74936-x. PMID: 39402279; PMCID: PMC11473830.
IF: 3,8

Plázár D, Metyovinyi Z, Medvecz M, Rencz F. Qualitative evidence on EQ-5D-5L skin irritation and self-confidence bolt-ons in Darier's disease and Hailey-Hailey disease. Qual Life Res. 2024 Dec 20. doi: 10.1007/s11136-024-03871-1. PMID: 39704914.
IF:3,3

Publications not directly related to this thesis

Plázár D, Joura MI, Kiss N, Medvecz M. Dermatoskopie von Genodermatosen [Dermoscopy of genodermatoses]. Dermatologie (Heidelb). 2023 Apr;74(4):256-261. German. doi: 10.1007/s00105-023-05124-7. Epub 2023 Mar 7. PMID: 36882583; PMCID: PMC10050017.
IF: 0,8

Plázár D, Medvecz M, Preisz K, Sárdy M, Becker K. Autoimmun hólyagos bőrbetegségek ritka formái. [Rare forms of autoimmune blistering diseases.]
Bőrgyógyászati és Venerológiai Szemle. (2021): 217-228. Hungarian
IF: -