SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

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MULTIMODAL ASPECTS OF RARE INHERITED SKIN DISEASES

PhD thesis

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List of Abbreviations

AD	atopic dermatitis
ARCI	autosomal recessive congenital ichthyoses
CALMS	café-au-lait macules
DD	Darier disease
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
GERD	Gastroesophageal reflux disease
HHD	Hailey-Hailey disease
HRQoL	health-related quality of life
HSV	herpes simplex virus
IL-	interleukin-
PCoA	Principal Coordinates Analysis
PDT	photodynamic therapy
QALY	quality-adjusted life years
SERCA	sarco/endoplasmic reticulum calcium ATPase
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNF-α	tumor necrosis factor alpha
UV	ultra violet
VAS	Visual Analogue Scale

1. Introduction

1.1. Genodermatoses in general

Genodermatoses are a clinically and genetically heterogeneous group of inherited skin disorders, most of which are classified as rare diseases by the European Union, affecting fewer than 1 in 2,000 individuals in the general population. These chronic conditions exhibit a broad spectrum of cutaneous and extracutaneous manifestations, which can significantly impact overall health and quality of life [1, 2]. The pathogenesis of genodermatoses commonly involves mutations in genes encoding structural proteins, signal transduction molecules, tumor suppressors, metabolic enzymes, or components of cell adhesion mechanisms [2].

Inherited skin fragility syndromes, such as Darier disease (DD) and Hailey-Hailey disease (HHD), are characterized by defective keratinocyte adhesion, resulting in a structurally weakened epidermis and increased susceptibility to blistering and erosions [3]. Inherited disorders of cornification comprise a wide range of conditions, e.g., ichthyoses, palmoplantar keratodermas, Dowling-Degos syndrome, and erythrokeratodermia variabilis et progressiva, which are marked by abnormal keratinization. These defects in the formation or maintenance of the stratum corneum manifest clinically as hyperkeratosis or scaling [4-7]. In other conditions, skin appendages may be affected, as in monilethrix, whereas in some disorders, such as Noonan syndrome with multiple lentigines, the predominant manifestation is a pigmentation abnormality [8, 9]. Neurocutaneous syndromes (e.g., neurofibromatosis type I, tuberous sclerosis complex, and basal cell nevus syndrome), as well as skin adnexal tumor syndromes like CYLD cutaneous syndrome, are typically caused by mutations in tumor suppressor genes. These conditions are associated with an increased risk of benign and malignant tumor development due to impaired regulation of cell growth [10-13]. The systemic nature of genodermatoses is further exemplified by Mendelian connective tissue disorders (such as pseudoxanthoma elasticum) and lysosomal storage disorders (such as Fabry disease), which frequently present with cardiovascular or neurological manifestations in addition to cutaneous findings [14, 15]. A recently developed multistep diagnostic algorithm for inherited skin diseases emphasizes the integration of phenotypic features, clinical data, mode of inheritance, target protein function, and genetic variants in the diagnostic process. Accurate diagnosis relies on a comprehensive approach that includes clinical

history, detailed family history, thorough phenotypic assessment, histopathological examination, and molecular genetic testing [2].

1.1.1. Focusing on Darier disease, a rare skin fragility syndrome with dyskeratosis

DD (follicular dyskeratosis, ORPHA:218, OMIM #124200) is a rare, autosomal dominantly inherited acantholytic skin disorder characterized by impaired adhesion of epidermal keratinocytes that presents distinct challenges for clinicians [3, 16]. It was first described in 1889 independently by two dermatologists, *Ferdinand-Jean Darier* and *James C. White,* which is why the disease is often referred to as Darier-White disease [3].

1.1.1.1. Epidemiology

The global prevalence of DD is estimated at 1: 30,000–1: 100,000, and it typically manifests during adolescence or early adulthood. Pediatric cases are quite rare [16, 17].

1.1.1.2. Pathomechanism

The disease is caused by pathogenic variants of the *ATP2A2* gene which encodes a calcium pump in the endoplasmic reticulum called sarco/endoplasmic reticulum calcium ATPase (SERCA2) that showcases high penetrance but variable expressivity [18-20]. Impaired pump function leads to alterant desmosomal disintegration and weak cohesion between keratinocytes, that attributed to acantholysis and anoikosis [21]. Moreover, decreased calcium stores in the endoplasmic reticulum may trigger a cellular stress response, which is considered to result in dyskeratotic, apoptotic cells (*corps ronds*) observed in histology [22]. Supporting this theory, UV radiation and heat can act as triggers that exacerbate the stress response, potentially leading to disease flare-ups [23]. Recent studies also suggest that mutations in the *ATP2A2* gene may compromise immune function, especially affecting the B-cell compartment, as SERCA2 is crucial for B-cell maturation. In addition, several recent studies report an increased expression of IL- 17-signaling- related cytokines in the lesional skin and increased amount of Th17 cells in both the circulation and skin of DD patients [24, 25].

1.1.1.3. Clinical features

DD is characterized by reddish brown hyperkeratotic papules or plaques predominantly in the seborrheic areas such as the face, chest, and back (Figure 1). Symptoms may vary from mild to severe. A recent study of 76 patients from 34 families systematically classified the clinical manifestations of the disease into 'classical' and 'non-classical' lesion types [26].

Classical lesions- present in all patients- are the hallmark features of DD and include keratotic papules, acral pits, wart-like lesions on the skin and mucosa, and characteristic nail abnormalities, such as longitudinal erythronychia, leukonychia, ridging, splitting, and V-shaped notches at the nail edge (Figure 5, parts a and c). Skin lesions often merge into larger plaques on the trunk and may form macerated, hypertrophic growths in the intertriginous areas. Palmoplantar involvement typically manifests as palmar papules with central pits and yellowish-brown hyperkeratotic papules. Flat, wart-like papules on the dorsal hands and feet- sometimes referred to as acrokeratosis verruciformis of Hopf, an allelic variant of DD- are also observed [27]. Oral mucosal involvement- which is more common in severe disease- includes cobblestone-like papules, leukokeratosis, gingival hyperplasia, and macroglossia. Ocular involvement and complications, such as blepharitis, dry eye, and corneal changes are also reported [26].

Non-classical lesions, which may coexist with the classical phenotype, are less common- observed in about one-third of patients- and include acral keratoderma, leucodermic (hypopigmented) macules, giant comedones, keloid-like vegetations, and acral hemorrhagic blisters. Additional rare variants comprise bullous forms (with vesicles and blisters triggered by sweating, stress, or fever), comedonal forms (predominantly facial comedones), and guttate leukoderma (confetti-like hypopigmented macules, especially in patients with darker skin) [26].

Patients frequently report pruritus, burning sensation, and pain, with involvement of intertriginous areas often leading to malodor and social isolation [25]. In addition DD patients have an increased risk of developing skin cancers [28].

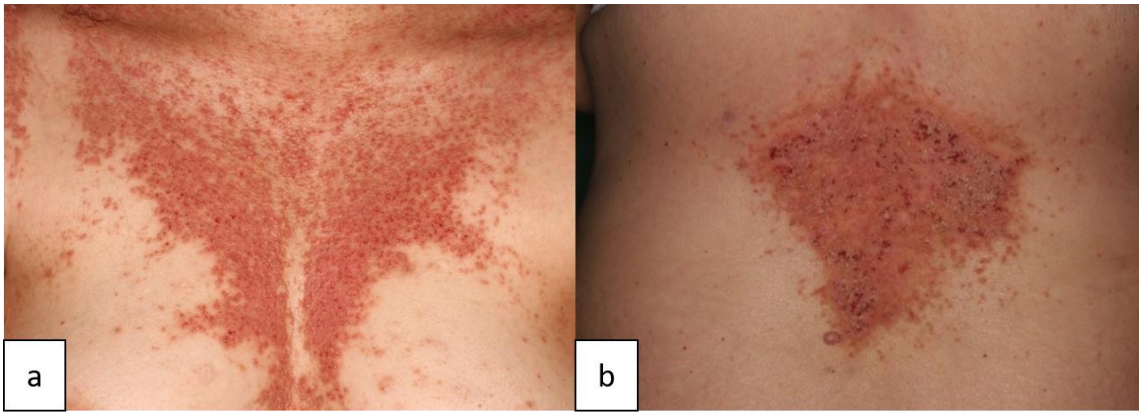

Figure 1. Classical lesions in Darier disease. Erythematous hyperkeratotic papules and plaques in two predilectional sites, such as the chest (part a) and back (part b) (*Semmelweis University, Department of Dermatology, Venereology and Dermatooncology*).

1.1.1.3.1. Segmental Darier disease

In linear or segmental forms of the disease, lesions align with Blaschko's lines, indicating genetic mosaicism, most commonly type 1 segmental mosaicism. This variant results from heterozygosity due to a postzygotic *de novo* mutation. However, type 2 segmental mosaicism has also been observed when a second postzygotic mutation arises in a patient already carrying a prezygotic mutation. It is characterized by homozygosity or hemizygosity within the affected segment, while heterozygosity is maintained in the surrounding areas [3, 25, 29].

1.1.1.4. Trigger factors

Heat, humidity, sweating, friction, mechanical trauma, physical and emotional stress, UV radiation or sunlight exposure, hormonal changes (e.g., menstruation, pregnancy), and infections are known as trigger factors [25, 30]. Certain medications, such as lithium carbonate may worsen symptoms in DD, according to several case reports [31-33].

1.1.1.5. Darier disease, as a multisystemic condition

DD is associated with higher risk of certain neuropsychiatric comorbidities including mood disorders (e.g. major depression disorder, bipolar disorder), and increased incidence of distinct neurodegenerative disorders (e.g. Parkinson disease, vascular

dementia), schizophrenia, and epilepsy compared to the general population [17, 31, 32, 34-38]. In recent years, the disease has been increasingly recognized as a multisystemic disorder that may affect multiple organs as SERCA2 is expressed in the brain, heart, kidneys, salivary glands, and other organs beyond the skin, explaining various potential extracutaneous involvements [39].

1.1.1.6. Diagnosis

Diagnosis is primarily established through a comprehensive evaluation of family history, clinical manifestations, and characteristic histopathological findings [3]. Additionally, dermoscopy may serve as a valuable non-invasive diagnostic adjunct [40-46]. Molecular genetic testing is critical for confirming the diagnosis, guiding management and genetic counseling [18, 47-49].

1.1.1.6.1. Histopathology

Histopathological analysis shows hyper-or parakeratosis, acantholytic dyskeratotic cells, *ronds corps* cells and suprabasal cleft, respectively (Figure 2) [3].

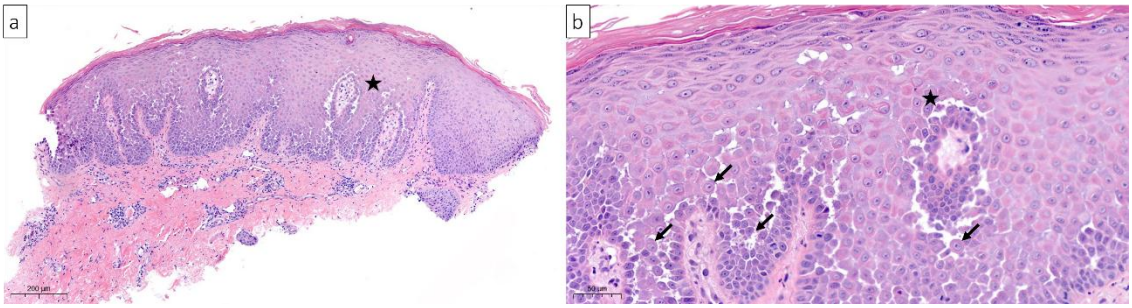

Figure 2. Histopathological features of Darier disease in a H&E-stained histological lesional skin section (magnification 9,6 and 32,7, respectively). Mild hyperkeratosis, chronic dermal inflammation, suprabasal clefting (stars) and single acantholytic *'corps ronds'* cells (arrows) (*Semmelweis University, Department of Dermatology, Venereology and Dermatooncology*).

1.1.1.6.2. Molecular genetic analysis

In recent years, over 300 pathogenic variants of the *ATP2A2* gene have been reported, including missense, nonsense, splice-site, and frameshift mutations [50, 51]. Sanger sequencing remains the gold standard for identifying pathogenic variants. [51, 52].

1.1.1.6.3. Classical dermoscopic features

The dermoscopic characteristics of DD were first reported by *Vázquez-López et al.* in 2004 [53]. In subsequent years, more detailed descriptions of the dermoscopic patterns have been published [42-46, 54]. The most common dermoscopic features representing hyperkeratosis and dyskeratosis are the centrally located polygonal, roundish or star-shaped yellowish-brownish areas surrounded by a whitish halo, which correlates histologically with acanthosis (Figure 3, parts b and d). These findings could be seen in nearly all of the cases [40, 43, 44, 46, 55]. Comedo-like openings (pseudocomedones) with keratin plugs reflecting follicular hyperkeratosis may also be seen as a central structure [53]. Pinkish homogenous structureless areas indicating underlying chronic inflammation, linear or dotted vessels and whitish scales are also frequent (Figure 1, part f) [40, 43, 44, 46, 55]. Dermoscopy of the nails may reveal reddish/white longitudinal nail bands with a V-shaped nick at the free margin (Figure 3, parts b and d) [40].

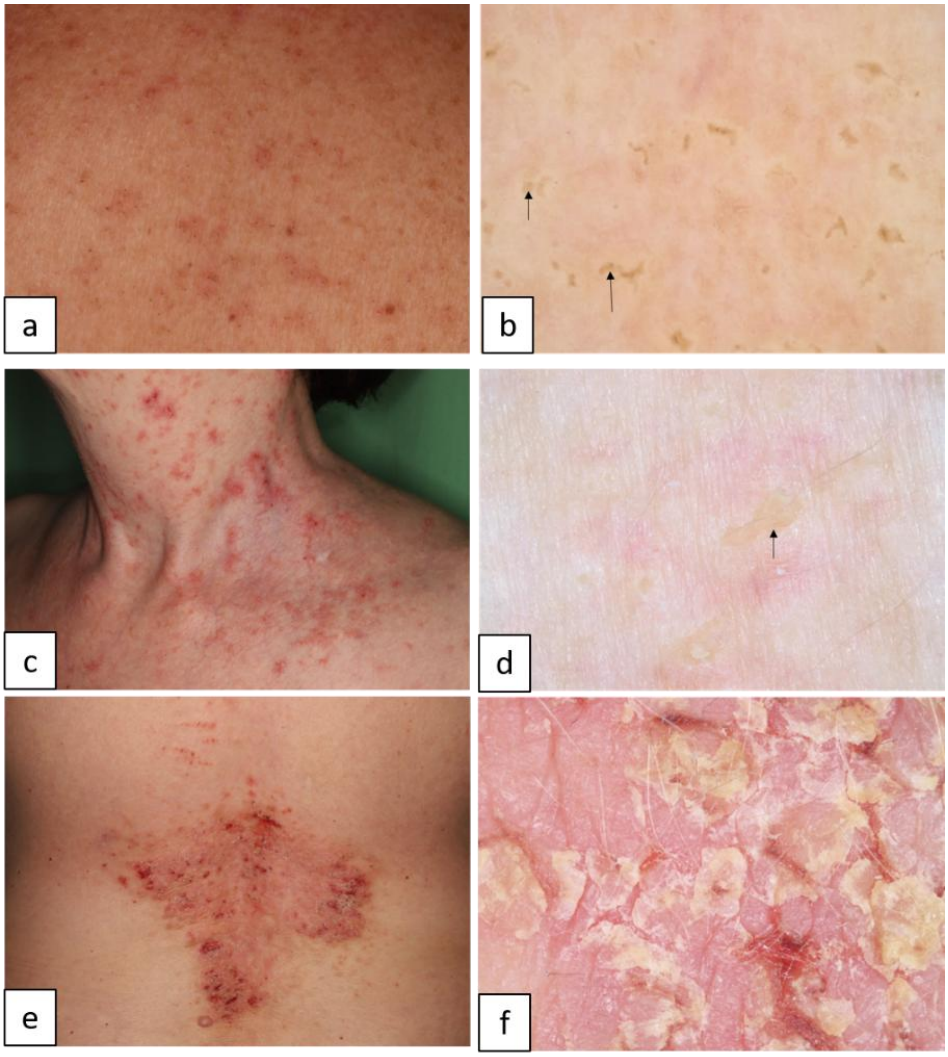

Figure 3. Clinical and dermoscopic features in Darier disease. Erythematous hyperkeratotic papules and plaques on the back (a) and on the neck (c). Dermoscopy shows (b, d, arrows) polygonal yellow/brown areas surrounded by white halo. Severe plaque-type lesion on the lumbosacral region (e). Dermoscopy reveals erythematous structureless areas with yellow/white scales (f) [56].

1.1.1.6.3.1. Dermoscopic variants

In severe cases, parallel pink-reddish furrows or whitish-pinkish areas and whitish-yellowish scales may give rise to a “tire tread-like” or “cracked riverbed-like” appearance (Figure 1, part f) [40]. In darker skin phototypes (Fitzpatrick IV–VI), the dermoscopic appearance may be dominated by hyperkeratotic brown polygonal plugs, which can conceal the typical white halo and vascular structures. Robust hyperkeratosis in long-standing untreated cases may mask acanthosis, mimicking verrucous disorders [42].

1.1.1.7. Management of Darier disease

DD is a debilitating, chronic condition with recurrent flares. Management remains challenging due to the disease's chronic course, frequent relapses, and variable response to therapy. Therapy is often individualized due to the lack of randomized clinical studies or standardized guidelines, and often requires a combination of different therapeutic options [25].

1.1.1.7.1. General recommendations

The primary goal is to first identify the various aspects of the disease- cutaneous, mucosal and maybe extracutaneous involvement- in order to evaluate its impact on patients' quality of life and daily functioning [3, 25]. Management is generally symptomatic, aiming to reduce symptoms and prevent complications (e.g., superinfections). Patient education on trigger avoidance and proper self-care is essential. Severe and complex cases require a multidisciplinary care involving professionals of other fields, such as psychologists, psychiatrists, internalists, intensive care physicians, infectologists, etc [25, 26].

1.1.1.7.2. Treatment

Current treatment strategies are primarily guided by disease severity, extent and patient-specific factors with options categorized into topical and procedural interventions for localized disease, systemic agents for more extensive involvement, and emerging biologic therapies for refractory cases [25].

1.1.1.7.2.1. First-line therapy

In mild cases, topical treatments are recommended as first-line therapy. Emollients containing urea or glycerin are used to reduce hyperkeratosis, while topical antiseptics such as chlorhexidine or octenidine, as well as topical antibiotics or antifungals can help to prevent or manage secondary infections. During acute inflammatory flares, topical corticosteroids- typically of moderate to high potency- are often employed; however, prolonged use of potent steroids, especially in intertriginous areas, should be avoided due to the risk of skin atrophy [3, 25]. For long-term management, topical calcineurin inhibitors are preferred over corticosteroids [25, 57]. Infectious exacerbations may require a short course of appropriate oral antibiotics, although there are no established

guidelines for long-term antibiotic use in DD [58]. If herpes simplex virus infection occurs, prompt initiation of oral or intravenous antiviral therapy (e.g., acyclovir) is essential [25]. For chronic, severe, or refractory cases, oral retinoids such as acitretin and isotretinoin are considered the cornerstone of treatment. These agents effectively reduce hyperkeratosis and malodor but require careful monitoring due to potential adverse effects, including mucocutaneous dryness, skin fragility, hepatotoxicity, ophthalmological complications, pancreatitis, and skeletal changes. Intermittent dosing may be considered to minimize side effects. Typical regimens include acitretin at 0.25–0.5 mg/kg/day or isotretinoin at 0.5 mg/kg/day. Oral alitretinoin is an alternative retinoid that may be particularly suitable for women of childbearing potential [25, 59].

1.1.1.7.2.2. Second-line therapy

Alternative therapeutic options include topical retinoids and vitamin D analogs such as calcipotriol and tacalcitol are reported to be effective, though some individuals may experience local irritation [60]. Other topical agents, such as 5-fluorouracil cream, diclofenac 3% gel, and topical agents containing vitamin A (retinyl palmitate), vitamin E, and urea, have shown benefit in isolated case reports [25, 61, 62]. Botulinum toxin injections have been reported as an effective intervention for intertriginous DD [63]. Physical ablative therapies-including dermabrasion, CO_2 laser, Er: YAG laser, pulsed dye laser, and diode laser-are considered for selected patients with localized, recalcitrant lesions, while large-scale surgical excision or allograft skin may be reserved for extensive, eroded areas [25, 64, 65]. Photodynamic therapy (PDT), including both conventional and daylight modalities, as well as Aminolevulinic Acid- PDT (ALA-PDT) combined with ablative fractional Er:YAG laser, has also yielded positive outcomes in some cases [25]. Opioid antagonist naltrexone showed benefit in a subset of patients with mild to moderate DD [66]. Other reports describe successful use of doxycycline monotherapy, oral magnesium, and oral vitamin A in severe phenotypes, with magnesium chloride-calcium carbonate notably effective in a pregnant patient [67-70]. The combination of naltrexone with isotretinoin, intravenous low-dose immunoglobulins for refractory disease, and the oral JAK inhibitor baricitinib have been documented in single case reports. [71-73]. Apremilast, a phosphodiesterase 4 inhibitor, has also been reported as beneficial in individual patients [74, 75]. In therapy refractory cases, monoclonal

antibodies targeting the IL-23/IL-17 (e.g. secukinumab and guselkumab) may be promising. Additionally, IL-4/IL-13 inhibitors (e.g., dupilumab, tralokinumab) have shown success in single DD cases [24, 76]. However, evidence regarding the long-term efficacy of these treatments remains limited [25].

1.1.1.8. Differential diagnosis

Differential diagnosis includes acne vulgaris, seborrhoeic dermatitis, transient acantholytic dermatosis (Grover's disease), pemphigus vegetans, Dowling- Degos disease or Galli Galli disease and HHD [25].

1.1.2. Hailey-Hailey disease, a blistering skin fragility syndrome

HHD (benign chronic familial pemphigus, ORPHA:2841, OMIM #169600) was first defined by two brothers, Howard and Hugh Hailey in 1939. This autosomal dominant disease is caused by mutations in the *ATP2C1* gene encoding the human secretory-pathway Ca^{2+}/Mn^{2+}-ATPase isoform 1 (hSPCA1) in the Golgi apparatus. Similar to DD, the disease is characterized by insufficient keratinocyte adhesion, as the hSPCA1 pump has a crucial role in transporting Ca^{2+} and Mn^{2+} into the Golgi lumen, ensuring the maintenance of normal intracellular Ca^{2+}/Mn^{2+} levels. Prevalence of HHD is close to DD, approximately 1: 50,000 [3, 58].

1.1.2.1. Clinical features

HHD can be recognized by papulovesicles and blisters that may coalesce and rupture, leading to erythematous plaques with erosions, fissures, and painful ‘rhagades’ (Figure 4, part a). Predilection sites include the intertriginous areas, such as the axillae, inguinal, genital, and perianal areas and the neck. In women, the submammary region may also be affected. Lesions can also appear on the trunk [3]. Burning sensations, pruritus, severe pain, and odor are common. Lesions often heal with hypo- or hyperpigmentation [77]. Longitudinal leukonychia is seen in about half of patients (Figure 5, parts e). Mucous membranes remain unaffected [30].

1.1.2.2. Diagnosis

Diagnostic procces is similar to DD and is previously demonstrated in *Chapter 1.1.1.6.* Histopathological examination demonstrates suprabasal and intraepidermal clefting. The acantholysis is more extensive than in DD, sometimes involving the whole thickness of the epidermis resulting a ’dilapidated brick wall’ appearance [3].

1.1.2.2.1. Dermoscopic features

Pink-whitish or pink-yellowish homogeneous structureless areas, and white clouds separated by parallel pink furrows representing acantholysis and epidermal cleavage can be observed in all cases (Figure 4, part b) [45, 78-80]. Polymorphous vessels including branched, glomerular, coiled, and linear-loop forms may be distributed randomly or parallel to furrows. The ‘crumpled fabric’ pattern resembles an irregular pattern of raised, whitish folds, seen in 75% of cases. [45]. Secondary to vesicle rupture, erosions and crusts often accompanied by dotted vessels can be detected. In chronic cases, white scales may present, typically at the periphery of erosions [81].

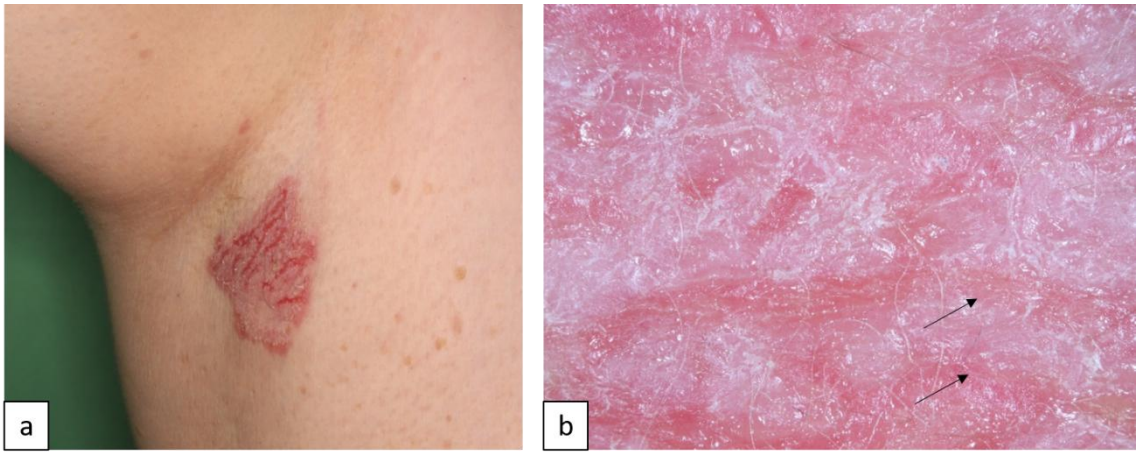

Figure 4. Hailey–Hailey disease. Erythematous plaques, erosions and fissures in the axillary region (a). Dermoscopy shows white structureless areas separated by parallel lines and erosions (b, arrows) [56].

In some cases, onychoscopy shows white longitudinal streaks representing longitudinal leukonychia [82, 83]. These findings may similar to nail changes in DD (Figure 5).

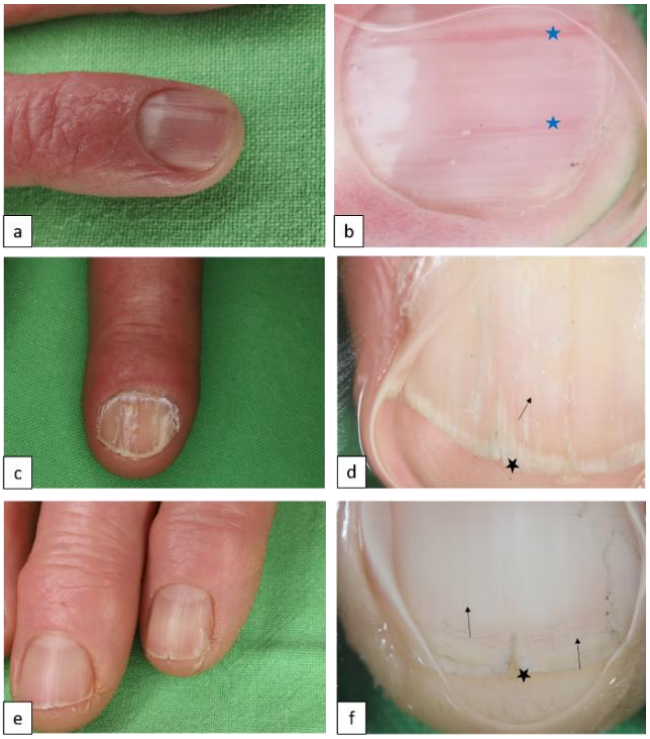

Figure 5. Nail findings in two distinct acantholytic skin fragility syndromes (a, c, e). Onychoscopy reveals red (b, blue stars) and white longitudinal bands (d, f, arrows) and a V-shaped nick (d, f, black stars) in Darier disease (a, b, c, d) and in Hailey-Hailey disease (e, f) [56].

1.1.2.3. Management of Hailey-Hailey disease

General recommendations are similar that in DD *(Chapters 1.1.1.7. and 1.1.1.7.2.).* Loose clothing and weight control are key factors in order to minimize friction in the intertiginosus areas. First-line therapies include topical antiseptics (e.g. chlorhexidine,-octenidine) to reduce the bacterial colonization [3]. Topical corticosteroids (moderate-to-high potency) are recommended for acute flares, while topical calcineurin inhibitors, such as tacrolimus and pimecrolimus are advised in long-term management, especially in skin folds [84]. In cases of secondary superinfections, oral antibiotics or oral antiviral treatment may be needed. Botulinum Toxin Type A may serve as an effective adjuvant therapy by decreasing hydrosis in the flexural areas, therefore helps to prevent bacterial colonization [84, 85]. Second line treatments include oral antibiotics, such as doxycycline or oral retinoids (e.g. acitretin, isotretinoine) [86-88]. For severe flares, cyclosporine for short-term use may be efficient [89, 90]. In therapy-refractory cases, CO_2 or Er:YAG laser, PDT, radiotherapy (electron beam), methotrexate, dapsone, or thalidomide may

suitable treatment options [91-95]. In recent years, several case reports and series have been published on biologics and small molecule inhibitors, such as the IL-4/IL-13 inhibitor dupilumab, JAK inhibitors (upadacitinib, abrocitinib), the PDE-4 inhibitor apremilast, and tumor necrosis factor-α inhibitors, such as adalimumab and etanercept, which have shown potential effects [96]. There are also some emerging options in this field, as low-dose naltrexone reduces inflammation, whereas oral anticholinergics (glycopyrrolate) control sweating [97, 98]. Additionally, surgical excision/dermabrasion are viable treatment options for localized, hypertrophic plaques [84]. Glucagon-Like-Peptide-1 (GLP-1) agonists, such as liraglutide, may be an effective adjunct treatments due to their potential anti-inflammatory and weight-loss effects [99].

1.1.3. Complications in Darier disease and Hailey-Hailey disease

Secondary superinfections, such as *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*), and herpes viruses (HSV), are common and can provoke exacerbations or dissemination of lesions in DD or HHD [3, 77, 100]. Intense, chronic pain combined with mobility restrictions, recurrent superinfections, pruritus and unpleasant odor can contribute to disability or reduced work capacity [3, 101]. Besides to physical symptoms, as may be seen in other chronic skin conditions, interpersonal relationships, self-esteem and self-perception may be significantly impaired [101, 102]. Therefore, both conditions have a significant impact on patients' quality of life [101-105].

1.2. Dermoscopy, as a noninvasive diagnostic tool in genodermatoses

1.2.1. Dermoscopy in general

Dermoscopy, also known as epiluminescence microscopy is a fast, non-invasive technique for facilitating the diagnostic process and monitoring treatment responses in various skin conditions. It was primarily developed for pigmented lesions, however, its use has expanded for non-pigmented lesions, various inflammatory conditions, granulomatous and infectious skin diseases [106, 107].

1.2.2. Standardized dermoscopic terminology

To promote accurate application, consistency, and comparability of dermoscopic terminology, *Kittler et al*. established standardized terms in 2015, as the result of the third

consensus conference of the International Society of Dermoscopy. Both descriptive and metaphorical terminologies are accepted to describe dermoscopic features, however, the introduction of new metaphorical terms is generally discouraged [107]. As these terms were primarily developed for skin tumors, *Errichetti et al*. sought to establish dermoscopic terminology and fundamental parameters applicable in general dermatology, including non-neoplastic skin conditions [106, 108]. Five basic dermoscopic parameters, such as vessels, scales, follicular findings, other structures and specific clues should be considered in the identification of inflammatory, infiltrative and infectious dermatoses [106].

1.2.3. The use of dermoscopy in genodermatoses

Several case reports, brief reports are published describing characteristic dermoscopic findings in various genodermatoses (e.g. ichthyoses, acantholytic skin fragility syndromes, neurocutaneous syndromes, pseudoxanthoma elasticum). However, large-scale studies and the consistent application of standardized terminology have not yet become widespread [109-113].

1.2.4. Clinical applications of dermoscopy in Darier disease and Hailey-Hailey disease

Dermoscopy may help to differentiate DD from other dermatoses, for example acne vulgaris, seborrheic dermatitis, especially in atypical or mild cases or early stage of the disease. While DD demonstrates pseudocomedones, acne vulgaris is characterized by papules, pustules and comedones with varying degrees of erythema [114]. Sebborheic dermatitis represents twisted red loops and comma vessels [115]. It also helps distinguishing DD from HHD due to the lack of pink furrows and crumbled fabric patterns, instead showing star-like yellow structures with white halos [45]. HHD can be differentiate from pustular psoriasis and infectious intertrigo due to the presence of white clouds and characteristic vascular patterns which are missing in pustular psoriasis and intertrigo [78]. Beyond the initial diagnosis, dermoscopy can also provide objective assessment of treatment response [46]. While histopathology remains essential for definitive diagnosis, dermoscopy serves as a valuable adjunctive tool that can facilitate earlier recognition and more precise clinical management of both DD and HHD.

1.3. The human skin microbiome in general

The human skin microbiome plays a vital role in maintaining skin homeostasis, protecting against pathogens, and modulating immune function [116]. Environmental conditions, age, sex, and hormones and anatomical site all influence the composition of the skin microbiome. This variation reflects the skin's division into three major environments including sebaceous (oily), moist and dry. Furthermore, skin appendages, such as sweat glands, hair follicles and sebaceous glands may have an impact by influencing the local environment. Sebaceous areas, such as the face, chest, and back, are mainly colonized by *Cutibacterium* species (formerly *Propionibacterium*), *Staphylococcus* bacteria and Malassezia yeasts. Sebaceous glands produce a hydrophobic lipid-rich sebum, which acts as a 'mantle' and provides an antibacterial surface for hair and skin Moist skin sites include intertriginal folds, ligament of elbow, knee, and groin, are dominated by Staphylococci, Corynebacteria and beta-Proteobacteria. Sweat glands and sweat in moist areas are important factors in inhibiting the colonization of certain microorganisms, as sweat contains free fatty acids and antimicrobial peptides. Dry sites (volar forearm and palms) are largely colonized by Cutibacteria and Corynebacteria, and additionally contain Micrococci, *Enhydrobacter* species and Streptococci [116].

1.3.1. The role of the skin microbiome in various dermatoses

Dysbiosis, as a result of an imbalance among the different microbiotas may lead to the onset or progression of various skin disorders. According to recent studies, relevant changes in the cutaneous microbiota have been found in several chronic dermatoses, such as psoriasis, atopic dermatitis, acne, hidradenitis suppurativa, that may have an impact on the pathogenesis and course of these diseases [117-122].

1.4. Health-related quality of life in genodermatoses

The term Health-Related Quality of Life (HRQoL) describes how individuals perceive their physical and mental well-being, capturing the effects of diseases and health conditions on daily living. HRQoL in genodermatoses is generally impaired due to both physical symptoms and psychological burden [123-125]. The negative impact of several diseases extends beyond the skin, affecting emotional well-being, social functioning,

daily activities, and professional life. Depression and anxiety are common in this population due to pain, impaired mobility, and social stigma [126, 127].

Tools used to assess HRQoL in dermatology can be grouped into three main types [128]. Generic HRQoL instruments are designed for use across all populations, whether healthy or ill, enabling comparisons between dermatologic and non-dermatologic conditions as well as with the general population. Some of these tools also support the calculation of health utilities and Quality-Adjusted Life Years (QALYs) for cost-effectiveness evaluations [129, 130]. Skin-specific instruments focus on measuring HRQoL in the context of any skin condition related to a particular disease (e.g. itching or burning sensation in skin diseases), while disease-specific instruments are tailored to evaluate issues unique to a particular dermatologic disease [131]. Compared to generic tools, skin-specific and disease-specific instruments tend to be more sensitive in detecting HRQoL changes in patients with skin disorders. Utilizing validated tools for both disease severity and HRQoL is essential for delivering personalized and effective care, as well as for ensuring the efficient use of healthcare resources.

1.4.1. EQ-5D

The EQ-5D is the most commonly used instrument for assessing HRQoL, with over 10,000 studies utilizing it over the past three decades, and, moreover, has preferred for estimating QALYs in pharmacoeconomic evaluations in nearly 30 countries [132]. However, its five core dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) may not fully capture HRQoL in some conditions. To address this, additional 'bolt-on' dimensions- such as cognition, sleep, vision, and breathing- have been introduced to enhance its validity [133-135]. In dermatology, two extra bolt-ons (skin irritation- itching and self-confidence) were developed for psoriasis patients in the EQ-5D-5L, demonstrating good validity and responsiveness [136-138]. Recent research suggest these bolt-ons are also applicable in other dermatological conditions (e.g., atopic dermatitis, chronic urticaria) and systemic diseases associated with itching, such as chronic kidney disease [139-142].

2. Objectives

2.1. Study I.: To investigate the dermoscopic features of various genodermatoses by conducting a systematic review and comparing its results to our own findings.

- Are the existing standardized dermoscopic terminologies applicable for describing lesions in genodermatoses?

2.2. Study II.

II/1. To investigate the clinical and genetical aspects of DD patients.

II/2. To investigate the skin microbiome of two predilectional areas, such as the chest and back in DD patients and in healthy individuals.

- Does skin microbiome in DD patients differ from healthy individuals?
- Is there any change in the bacterial composition in simultaneously collected samples from lesional and symmetrical non-lesional skin areas in DD patients?
- Are there any region specific alterations between the two analyzed regions in DD patients and in healthy individuals?
- What is the bacterial composition of the inner epidermal skin layers in DD patients?

2.3. Study III.: To investigate the content validity (relevance, comprehensiveness and comprehensibility) of the EQ-5D-5L and skin irritation and self-confidence bolt-ons among patients with DD and HHD.

- How can DD and HHD affect patients' lives?
- Is the EQ-5D-5L comprehensible in DD and HHD?
- Which dimensions of the EQ-5D-5L and the two bolt-ons are relevant in DD and HHD?
- Is there any conceptual overlap between the EQ-5D-5L and the two bolt-ons?
- Is the EQ-5D-5L and the two bolt-ons comprehensive in DD and HHD?

3. Methods

3.1. Methods of study I.

3.1.1. Systematic review

Our systematic review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement [143]. The review protocol was registered on PROSPERO (No. CRD42023452448). A literature search was performed in Pubmed, Embase and Cochrane (CENTRAL) databases to identify eligible records. The search key detailed in our previous work was applied [56]. The search process had no language or other restrictions. We included original articles, case reports, short communications, correspondences, and letters discussing the dermoscopic characteristics of skin lesions in DD, HHD, Dowling-Degos disease, palmoplantar keratoderma, various ichthyoses, such as ichthyosis vulgaris, X-linked recessive ichthyosis, autosomal recessive inherited lamellar ichthyosis, annular epidermolytic ichthyosis pseudoxanthoma elasticum, tuberous sclerosis complex, neurofibromatosis type 1, Fabry disease, basal cell nevus syndrome, Noonan syndrome with multiple lentigines, CYLD cutaneous syndrome and monilethrix. Non English articles were excluded. Two independent authors conducted the selection and data extraction using EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) and Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA). The quality assessment was conducted using the JBI Critical Appraisal tool for case reports and case series [144].

3.1.2. Descriptive study

Patients with previously established diagnosis of a genodermatosis were enrolled in this study at the Department of Dermatology, Venereology, and Dermatooncology, Semmelweis University, between September 2020 and January 2023. Exclusion criteria were diagnoses of other skin diseases (e.g., skin infections) that may interfere with dermoscopic features. Demographic data, such as age, gender, and the type of genodermatosis were documented. All patients underwent detailed clinical examinations. Clinical and dermoscopic images were captured. For dermoscopic analysis, clinically relevant skin lesions were selected. Dermoscopy was performed using Illuco IDS-1100C (Illuco Corporation Ltd., Gunpo, Republic of Korea) and Heine dermatophot (10-fold magnification, Heine Optotechnik GMBH & CO. KG., Gilching, Germany) with an

optional polarized light source. All authors evaluated the dermoscopic images. Standardized terminologies and processes suggested by *Kittler et al.* and *Errichetti et al.* were used, with the exception of neurofibromas, where the terms used by *Duman et al.* were applied. Onychoscopic and trichoscopic findings were based on case reports and reviews. Comparison of our own findings to those reported in the literature was carried out.

3.2. Methods of study II.

3.2.1. Clinical characteristics of the study population

Participants were enrolled at the Department of Dermatology, Venereology, and Dermatooncology, Semmelweis University, from February 2022 to May 2023. Eligible individuals met the following criteria: a histopathological diagnosis of DD, age 18 or older, the presence of active skin lesions, and symmetrical non-lesional skin areas. For the control group, exclusion criteria included any skin infections (regardless of location) and chronic skin conditions. Additionally, participants from all groups were excluded if they had taken antibiotics or immunosuppressive drugs within the past three months or had used topical antibiotics or antiseptics within three days prior to sample collection. The clinicopathological characteristics of the patients are summarized in Table 1.

Table 1. Clinical characteristics of Darier disease patients included in study II [116]**.**

Patient N°	*Sex*	*Age (years)*	*Age at onset (years)*	*Affected areas*	*Therapy*	*Comorbid conditions*	*Localization of biopsy sample*
1	M	55	11	ears, neck, chest, back	topical*, oral acitretine	hepatomegaly, hiatal hernia, GERD	chest
2	F	61	18	neck, chest, back	topical*,	cataracta	chest
3	F	51	6	whole body	oral acitretine	sclerosis multiplex	chest
4	F	65	25	neck, chest, back	topical*	fibromyalgia, tinnitus, depressive disorder	chest
5	F	65	14	ears, back, legs	topical*, oral isotretionine	hyperprolactinaemia, depressive disorder	chest
6	F	42	32	axilla, inguina, chest, back	topical,* oral acitretine	-	chest
7	F	42	31	chest	topical*, oral acitretine	panic disorder, coeliac disease	chest
8	F	35	8	whole body	topical* and topical retinoids	depressive disorder	chest

M-male; F-female; GERD-Gastroesophageal reflux disease; * includes topical corticosteroids and antiseptics

3.2.2. Sample collection

For genetic tests, peripheral blood samples were collected from DD patients in Vacuette K3EDTA tubes (Greiner Bio One, Kremsmünster, Austria).

For the microbiome analysis, both skin biopsies and swab samples were taken from DD patients, while only swab samples were taken from healthy controls. A 4-mm punch biopsy of a lesional chest was performed in DD patients (Table 1). Skin swabs were collected from two predilection sites (chest and lower back, both lesional and symmetric non-lesional skin areas from DD patients and corresponding sites from controls). In DD, lesional skin referred to erythematous skin with typical hyperkeratotic papules and plaques, while non-lesional skin referred the unaffected skin areas in a symmetric or the same body region least 5 cm away from a well-defined lesional skin area. A 2-ml DNA/RNA Shield™ Collection Tube w/Swab (Zymo Research Corp. Irvine, CA, USA) was used for each skin swab.

3.2.3. Genetic Analysis of the ATP2A2 gene

Sanger sequencing was performed on the exons and adjacent intron regions of the *ATP2A2* gene (RefSeq: NG_007097.2, mRNA: NM_170665.4, var b) following a previously established method (Racz et al., 2004, https://doi.org/10.1111/j.0906-6705.2004.00118.x). Detected *ATP2A2* variants were assessed using MutationTaster and classified as pathogenic or likely pathogenic based on ACMG guidelines, utilizing data from MutationTaster and ClinVar.

3.2.4. DNA isolation and sequencing for skin microbiome analysis

DNA isolation was performed using the ZymoBIOMICS DNA Miniprep Kit (Zymo research, USA). DNA concentration was measured with a Quibit 2.1. Fluorometer and the Uubit dsDNA HS Assay Kit (Thermo Fisher Scientific, USA). The extracted DNA was stored at −80°C until PCR amplification. The V3-V4 region of the bacterial 16S rRNA gene was amplified using tagged primers specific to the given region. DNA purification post-PCR followed the Illumina protocol, and tagged libraries were analyzed with an Agilent 2100 Bioanalyzer (Agilent Technologies, Germany). Equimolar concentrations of tagged PCR products were pooled and sequenced on an Illumina MiSeq platform using a MiSeq Reagent Kit v3 (600 cycles PE). Negative controls for extraction

and PCR were included to detect reagent contamination. To ensure reproducibility, all samples underwent independent extraction and sequencing twice. For analysis, raw sequencing data from Illumina BaseSpace were uploaded to the CosmosID Bioinformatics Platform (CosmosID Metagenomics Cloud). Additionally, genomic DNA

for genetic analyses was isolated from peripheral blood leukocytes using the Roche MagNA Pure Compact Nucleic Acid Isolation Kit I and the Roche MagNA Pure Compact LC System (Roche Diagnostics, Germany). Although novel nomenclatures classify *Propionibacterium* and *Cutibacterium* as the same genus, in the result section of study II, we present them separately as they were distinguished in the software we used (CosmosID Metagenomics Cloud).

3.2.5. Statistical analysis

Statistical significance between cohorts were evaluated using the Wilcoxon rank sum test for Shannon alpha diversity and PERMANOVA for Jaccard PCoA of beta diversity. These analyses were performed with the CosmosID statistical support application.

3.3. Methods of study III.

3.3.1. Participants, study design

This study adhered to the Standards for Reporting Qualitative Research (SRQR) recommendations [145]. Semi-structured qualitative interviews were conducted with patients previously diagnosed with DD or HHD. The two patient groups share similarities in prevalence, gender distribution, patient experience, symptoms, treatment, and HRQoL impairment, making them suitable for being considered together in this study. The demographic and clinical characteristics of the patients are presented in Table 2.

Table 2. Demographic and clinical characteristics of patients included in study III [146].

Characteristics of the population		Median (range) or n (%)
Age (years)		48 (35-77)
Gender	Female	12 (80%)
	Male	3 (20%)
Education	Secondary without certificate	5 (33%)
	Secondary	7 (47%)
	College/university	3 (20%)
Employment	Employment full-time	5 (33%)
	Retired	3 (20%)
	Disability pensioner	3 (20%)
	Employed part-time	1 (7%)
	Unemployed	1 (7%)
	Homemaker/housewife	1 (7%)
	Others	1 (7%)
Disease duration (years)		19 (4-47)
Age at onset (years)		30 (6-50)
Comorbidities [a]	None	2 (13%)
	Obesity	6 (40%)
	Anxiety	6 (40%)
	Cardiovascular diseases	4 (40%)
	Depression	3 (20%)
	Neurological conditions	3 (20%)
	Diabetes	2 (20%)
	Cancer	1 (7%)
	Atopic dermatitis	1 (7%)
	Asthma	1 (7%)
	Allergies	1 (7%)
	Gastroesophageal reflux disease	1 (7%)
	Diverticulosis	1 (7%)
	Thyroid disease	1 (7%)
	Arthritis	1 (7%)
Number of body regions affected	1-2	4 (27%)
	3-4	2 (13%)
	>5	9 (60%)
Current therapy [a]	Only topical therapy (antiseptics, corticosteroids)	4 (27%)
	Oral corticosteroids	4 (27%)
	Oral retinoids	6 (40%)
	Laser therapy	4 (27%)
	Disease-modifying therapy	1 (7%)
EQ VAS (0-100) [b]		81.5 (25-98)
Self-reported severity VAS (0-10) [c]		6 (2-8)

a: multiple responses possible, b: 0 = the worst health you can imagine, 100= the best health you can imagine, c: 0 = not at all severe, 10 = extremely severe

3.3.2. Interviews

All interviews were conducted by the first author. A topic guide was developed by the research team, based on two similar studies with psoriasis and atopic dermatitis patients in Hungary [138, 139]. The interview was divided into three parts. In the first part, the study's objectives and procedure were explained, and patients were asked to share their personal observations on their diseases, particularly focusing on the most important aspects related to health and HRQoL. In the second part, participants completed the EQ-5D-5L descriptive system, followed by the EQ VAS, using a concurrent think-aloud protocol to explore the cognitive processes behind their responses rather than just gathering precise answers [147, 148]. In order to investigate the three areas of content validity (relevance, comprehensiveness, comprehensibility), exploratory questions were applied, as recommended by the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) standards [149].

In the third part, patients completed the EQ-5D-5L together with the two bolt-ons (i.e. a total of 7 dimensions). No EQ VAS was filled in afterward.

Throughout the second and third parts, patients were encouraged to share their thoughts on the meaning and relevance of the dimensions, potential overlaps between concepts, missing concepts related to HRQoL, appropriateness of the response levels, wording, and recall period, and to compare the standard EQ-5D-5L with the version extended by two additional bolt-ons. At the end of the interview, patients filled out a short questionnaire about their sociodemographic and clinical background.

3.3.3. Measures

The official Hungarian version of each questionnaire was applied. The EQ-5D-5L includes a descriptive system and a vertical visual analogue scale (EQ VAS), ranging from 0 (representing ‘the worst health you can imagine’) to 100 (representing ‘the best health you can imagine’) [150, 151]. The descriptive system has five HRQoL dimensions, such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five response levels for each: no problem, slight problems, moderate problems, severe problems, and extreme problems/unable to. Two previously developed bolt-ons- skin irritation (related to itching) and self-confidence- were also applied [136]. The recall period for all dimensions, including the bolt-ons, is the day of completion (‘today’).

3.3.4. Qualitative data analysis

The interviews were conducted anonymously, and the audio recordings were transcribed verbatim. A thematic analysis was carried out through a multi-stage process [152]. First, the primary author reviewed all transcripts, identifying initial themes through an inductive process. Categories and subcategories were then developed to define the emerging themes. The coding process involved three researchers with one primary coder. The codes were reviewed by a senior author, and disagreements were resolved through discussion with another senior author. A data extraction matrix was created in Microsoft Excel 2016 to report categories, subcategories, and related patient quotations with interview IDs. English translations of the most significant quotes were also performed.

3.4. Ethical statements

Studies were carried out in the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University. All protocols for Studies I, II, and III were approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (Study I: No. 135/2023 SE RKEB, Study II: No. 278/2021 SE RKEB, Study III: No. 220/2022 SE RKEB). All three studies adhered to the ethical guidelines of the Institutional National Research Committee, the 1964 Declaration of Helsinki, and its subsequent revisions. All participants provided written informed consent for sample collection, analysis, and research purposes.

4. Results

4.1. Results of study I.

4.1.1. Systematic review of dermoscopic findings in genodermatoses

Systematic search provided a total of 471 articles; 74 eligible studies by title, abstract and full-text selection [4, 9, 14, 15, 29, 40-42, 44, 54, 78-83, 110-113, 153-206], and nine additional studies by citation searching [43, 53, 109, 207-212] were identified. Figure 6 shows the selection process (PRISMA). The characteristics of the included study are detailed in our original publication [56]. Table 3 provides a summary of the dermoscopic findings by each genodermatoses from the literature included in this study.

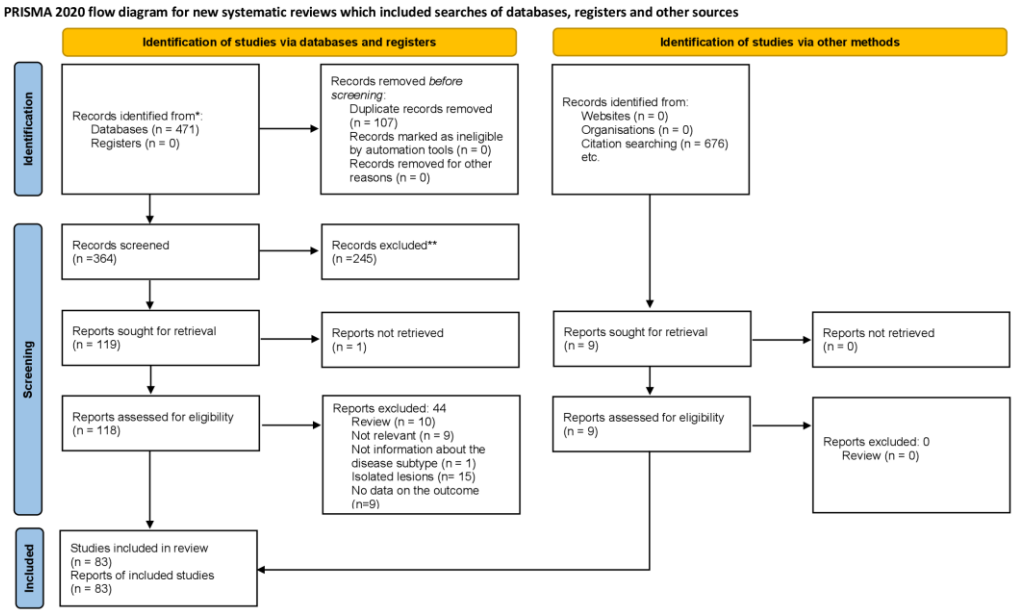

Figure 6. PRISMA Flow Diagram of the screening and selection process [56].

Table 3. Dermoscopic findings of various genodermatoses included in study I. [56].

Genodermatosis	Dermoscopic findings described in the literature
Ichthyosis vulgaris	-prominence of linear dermatoglyphic patterning, raised or ragged keratinocyte borders, background erythema, and presence of dull sheen [193] -criss-cross pattern of fine white scale [211, 213]
X-linked recessive ichthyosis	rhomboid/mosaic pattern of brown structures with space in between [213]
ARCI- lamellar ichthyosis	-multiple large keratotic plugs in the cristae cutis, sulci cutis were highly accentuated [214]

	-quadrilateral brownish structures with fine white scale arranged in lamellar pattern [213]
Annular epidermolytic ichthyosis	white scales and diffuse, punctate hemorrhages [112]
Dowling-Degos disease	-multiple hyperpigmented brownish spots with a regular [215] or reticular pattern [164] characterized by a coarse grid of brown lines over a diffuse, light brown background, follicular plugging and inclusion cysts [4] -brownish projections around a hypopigmented center [208] -brown pigmentation in Chinese letter pattern/irregular star shape, central brown follicular plugs and comedones [216] -verrucous papules and plaques [209]
Palmoplantar keratoderma	scales and pigmentation, thickened yellow stripes stratum corneum with punctate bleeding [202]
Darier disease	-variable vascular structures (red dots, red lines, or erythema), dilated openings with raised or flat borders and central brown or yellowish hyperkeratotic plugs [53] -polygonal, starlike, or roundish-oval-shaped yellowish/brownish areas of various sizes surrounded by a thin whitish halo [29, 40, 43, 217-220] or structureless areas [156] -pinkish homogeneous structureless area or background, whitish scales or crusts, dotted and/or linear vessels [217, 218, 221] -polygonal structureless white and yellowish areas [218] -irregular linear parallel furrows “cracked riverbed-like” appearance [40]
Hailey-Hailey disease	-irregular whitish areas were separated by pink furrows (crumpled fabric or cloud pattern) [78, 222], irregular combination of white and pink areas (cloud or iceberg pattern) [223, 224] -polymorphous vessels predominantly in peripheral distribution, pink-whitish or pink-yellowish background, scales, erosions [81]-red to brown linear ulcers with sharp angulated margins along with whitish macerated edges, pinkish-white background, peripheral arborizing telangiectasia [225] -diffuse white structureless areas and linear/linear-parallel erosions (tire-like appearance) [226]
Pseudoxanthoma elasticum	-multiple irregular, yellowish areas alternating with prominent superficial linear vessels. Yellowish areas may coalesce to form parallel strands [227, 228] -distinct coalescing and reticulated yellow-white clods on a light purplish-red background [167, 229, 230] giving a cobblestone appearance [229] -yellow to ivory white non-follicular globules, the arrangement of dots, linear, broad, narrow mesh network, lines and plaques on a pink or purplish-red background [231] and reticulated vessels [232] -yellowish-orange area with reddish and whitish areas [233] -yellowish-white structures coalescing into linear streaks, interspersed with erythema, exaggerated pigment network [234] -yellowish brown structureless areas or background, semicircular, curved/serpiginous yellowish-brown lines, linear, dotted or hairpin vessels, keratotic plugs [235-237] -unspecific pattern of irregular pigmentation with a predominant yellowish-orange color alternating with reddish and whitish areas, microulcerations [238]
Fabry disease	

angiokeratoma	dark purple or red glomerular/ lacunar/ dotted/ linear-irregular vascular structures with or without a whitish veil [239]
Neurofibromatosis type 1	
neurofibroma	pink-red homogeneous areas, peripheral pigment network, fissures, scar-like white areas in "star burst appearance"[226], peripheral pigmented network, fingerprint-like structures, peripheral halo of brown pigmentation, fissures, vessels [240]
café-au-lait macule	a homogenous brown pigmentation with perifollicular halo (face), reticular patterned brown pigmentation (neck) [241]
Tuberous sclerosis complex	
adenoma sebaceum (angiofibroma)	-multiple yellowish white globules or dots of varying length on brownish, reddish-brown or pinkish-gray background [242-244] -dots of brown pigmentation [243] - bluish-white lacunae, red dots and white globules [245]
ash leaf macule	white patch with irregular feathery border [213]
shagreen patch	yellowish globules, brownish background [213]
Basal cell nevus syndrome	
acral pits	-flesh-colored or pinkish, irregular-shaped, depressed lesions containing red globules in parallel lines [177, 181, 198, 246, 247] -blue structures and microarborizing vessels (more frequently seen in childhood) [247]
basal cell carcinoma	absence of pigment network, maple-leaf-like structures, arborizing vessels, blue-grey ovoid nests, blue-grey globules and dots, concentric structures, spoke-wheel structures and ulceration [177, 178, 181, 198, 246-249]
CYLD cutaneous syndrome	
trichoepithelioma	arborizing vessels, multiple milia-like cysts and rosettes, whitish background [183, 191, 201, 250]
cylindroma and spiradenoma	-background pink coloration with ill-defined arborizing vessels and ill-defined blue structures [171, 210] -white globules at the center [210] -absence of pigment network, white-ivory background, polymorphous vessels [197]
Noonan syndrome with multiple lentigines ***lentigines***	pigment network, black dots or brown globules, branched streaks [251]
café noir spot (melanocytic nevi or lentigo simplex)	-pigment network, black dots and dark globules [169] -branched streaks forming hyphae-like structures, light brown globules [251]

4.1.2. Descriptive study of dermoscopic findings in various genodermatoses

4.1.2.1. Sample characteristics

A total of 119 patients with 20 different genodermatoses were enrolled. The number of patients, analyzed areas or lesions and the affected areas for each disease are summarized in Table 4.

Table 4. Characteristics of the descriptive study part of study I [56].

	Number of patients	Number of analyzed areas or lesions	Affected areas
Dowling-Degos disease	1	3 areas	chest, back, axillae
Erythrokeratodermia variabilis et progressiva	2	6 areas	trunk, extremities
Monilethrix	2	15 trichoscopic fields of views	hair shaft
Noonan syndrome with multiple lentigines	3	154 lentigines 5 café noir spots	extremities, hands, trunk
CYLD cutaneous syndrome	3	12 trichoepitheliomas	scalp, faceshoulder
Fabry disease	3	37 angiokeratomas	neck, trunk, legs
Tuberous sclerosis complex	6	16 areas of adenoma sebaceum, 4 ash leaf macules, 2 Shagreen patches	face, trunk, thighs
Pseudoxanthoma elasticum	7	14 areas	neck, axillae, fossa cubita
Darier disease	8	25 areas, 7 nail findings	chest, back, neck, calf
Hailey-Hailey disease	14	38 areas 5 nail findings	axillae, submammae, inguinae
Palmoplantar keratodermas	12	24 areas	palms, soles
Basal cell nevus syndrome	11	8 palmar pits, 11 basal cell carcinomas	palms, soles, face, trunk
Neurofibromatosis type 1	20	45 neurofibromas, 14 CALMS	trunk, extremities
Ichthyoses	27	59 areas	face, neck, trunk, extremities, palms

CALMS- cafe au lait macules

Tables 5 and 6 summarize the dermoscopic analysis following the terminology of *Errichetti et al.* and *Kittler at al*., while Table 7 includes onychoscopic and trichoscopic findings. Both descriptive and metaphoric terminologies were applied. Metaphoric terms are printed in bold and italics [56].

Table 5. Dermoscopic findings of genodermatoses included in the descriptive part of study I, following the standardized dermoscopic terminology of *Kittler et al.* [56].

Genodermatosis/ skin manifestations	**Dermoscopic findings**
Fabry disease	
angiokeratoma	-combination of reddish and purplish dots and globules and yellowish structureless areas covered by a ***whitish veil***; globules are divided by yellow reticular lines (45.95%) -various size of dark blue and purplish dots and globules with ***whitish veil***. Smaller dots and globules may be grouped (54.05%)
Neurofibromatosis type 1	
café-au-lait macules	structureless (homogenous) pigmentation with perifollicular hypopigmentation (73.33%) or reticular pattern of brown pigmentation (26.67%)
neurofibromas	pink-red structureless areas (100%), ***scar-like areas*** (97.8%), fissures (68.8%), ***fingerprint-like structures*** (80%), peripheral pigment network (37.8%), peripheral halo of brown pigmentation (57.8%)
Basal nevoid cell syndrome	
basal cell carcinoma	absence of pigment network (100%, ***maple-leaf like structures*** (63,64%), ***arborizing vessels*** (100%), ***blue-grey ovoid nests*** (81.82%), ***concentric structures*** (54.55%), ***spoke-wheel structures*** (45.45%) and ulceration (45.45%)
acral pits	flesh-coloured (36.36%) or pinkish areas (63.64%) containing red dots in parallel lines (100%)
Noonan syndrome with multiple lentigines	
lentigines	-1 to 3 mm in size, light brown to brown in colour -homogenous light brown pigmentation -symmetric brown follicular pigmentation ***(pseudonetwork)*** (100%)
café noir spots	-symmetric, in certain areas irregular brown follicular pigmentation ***(pseudonetwork)*** (100%) -brown pigmentation in a ***cobblestone-like pattern*** (brownish polygonal large clods) (20%)
CYLD cutaneous syndrome	
trichoepithelioma	***milia-like cysts***, pinkish-whitish background***, arborizing vessels*** (100%)

Standardized metaphoric terms are in bold and italics

Table 6. Dermoscopic findings of genodermatoses included in the descriptive part of study I, following the standardized dermoscopic terminology of *Errichetti et al.* [56].

Genodermatosis	Dermoscopic findings				
	Vessels	**Scales**	**Follicular findings**	**Other structures**	**Specific clues**
Ichthyosis vulgaris	-	fine white scales in criss-cross pattern (100%)	-	-	-
X-linked recessive ichthyosis	-	brown structures in rhomboid or mosaic with space in between (100%)	-	-	-
Autosomal recessive congenital ichthyoses (ARCI)					
Lamellar ichthyosis	dotted (50%)	quadrilateral brown structures with fine white scale around arranged in lamellar pattern (100%)	-	-	-
Congenital ichthyosiform erythroderma	dotted (100%)	diffuse white scales sometimes in rhomboid pattern (100%)	-	parallel white lines (100%)	erythema
Pleomorphic ichthyosis	-	fine white scales in criss-cross pattern (100%)	-	-	-
Harlequin ichthyosis	dotted (100%)	yellow white scales in parallel pattern (100%)	-	-	excessive erythema
Dowling-Degos disease	dotted, linear curved (100%)	-	follicular plugs (100%)	yellow/ brown structureless areas (100%) white globules (100%)	-
Palmoplantar keratodermas					
Punctate	dotted (100%)	white (100%)	-	oval yellow areas, white lines (100%), brown dots (50%)	hyperkeratosis, fissures (100%)
Diffuse epidermolytic	erythematous edge: dotted (50%)	white (100%)	-	orange and yellow structureless areas, parallel or angulated white lines (100%), brown dots (12.5%)	hyperkeratosis, fissures, erythematous edge (100%)
Erythrokeratodermia variabilis et progressiva	dotted (100%)	fine white scales (100%) in rhomboid (25%) or criss-cross pattern (25%)	-	brown thick lines and structureless areas (100%) hyperkeratotic white globules (50%)	erythematous lines
Darier disease					
hyperkeratotic papules and plaques	dotted (48%), linear (48%)	yellowish scales/ crusts (72%)	-	parallel, perpendicular and angulated lines (64%)	polygonal yellow/ brown areas with whitish halo (100%) erosions (64%) erythema (100%)
pseudocomedones	-	-	follicular plugs (100%)	-	polygonal yellow/ brown areas with whitish halo (100%)

Hailey-Hailey disease	dotted (68.42%) linear (52.63%)	white/yellow (50.00%)	-	white structureless areas (100%)	fissures, erosions (89.47%) livid parallel, perpendicular or unspecifically arranged lines (89.47%)
Pseudoxanthoma elasticum	superficial linear (33.3%), reticulated (55.56%) or dotted (11.11%)	-	-	yellow/white globules (100%) that may coalesce into parallel (22.22%) or linear lines (22.22%), broad (11.11%) or narrow meshwork (22.22%) light purple (55.56%) or brown (44.44%) structureless areas	mild erythema (66.67%)
Tuberous sclerosis complex ***adenoma sebaceum (angiofibroma)***	linear, linear curved (46.15%)	-	-	yellow/ white dots and globules, white structureless areas (100%), central brown dots surrounded by white circles (53.85%)	-
ash leaf macules	linear, linear curved (50%)	-	-	white structureless areas with feathery irregular border (50%), white globules coalescing into reticulated lines (50%)	-
shagreen patch	linear, linear curved, linear with branches (50%)	-	-	white/light yellow structureless areas (100%)	-

Table 7. Trichoscopic and onychoscopic findings of genodermatoses included in the descriptive part of study I [56].

Genodermatosis	**Trichoscopic or onychoscopic findings**	**Our findings**
Monilethrix	regular constrictions of the shaft with elliptical nodes separated by internodes [170, 186, 252], regularly bent ribbon sign [157, 187, 188, 192, 242] or beaded appearance [162, 204] rosary beads with nodes and constrictions [253]	100% (2 patients)
Darier disease	reddish/white longitudinal nail bands with a V-shaped nick at the free margin [40]	87.5% (7 patients)
Hailey-Hailey disease	longitudinal white bands [82, 83]	35.71% (5 patients)
Tuberous sclerosis complex *subungual red comets*	tortuous or corkscrew-like vessels with a narrow proximal tail and a dilated distal head, surrounded by a whitish halo, parallel binary tortuous capillaries [254, 255]	0% (0 patients)

4.2. Results of study II.

4.2.1. Sample characteristics

Study II included a total of 8 DD patients (female: male ratio 7:1, mean age 51.63 ±11.49) and 6 matched healthy controls (female: male ratio: 5:1, mean age 52.8± 7.06). Clinical diagnosis was confirmed by histological and/or molecular genetic verification. For microbiome analysis, a total of 49 samples (biopsies and skin swabs) were obtained from lesional and non-lesional skin sites of DD patients and from controls.

4.2.2. ATP2A2 gene analysis

Genetic analyses revealed the presence of a heterozygous pathogenic or likely pathogenic variant of the *ATP2A2* gene in 5 patients (*Patient 1, 2, 3, 6 and 8).* In the case of *Patient 3*, we identified a novel variant that was confirmed with Nci I enzyme restriction digestion. The genetical analysis of *Patient 5* was already published in a previous study [49]. In two cases *(Patient 4 and 7)* we could not identify any pathogenic or likely pathogenic mutation (Table 8).

Table 8. Genetic analysis of Darier disease patients included study II [116].

Patient N°	*Heterozygous pathogenic or likely pathogenic variants of the ATP2A2 gene (RefSeq Gene: NG_007097.2, RefSeq mRNA: NM_170665.4, var b)*	*Reference*
1	c.1288-6A>G	Nakamura et al. 2016. [37]
2	c.118+1G>A	Jacobsen et al. 1999. [36]
3	c.1858G>T, p.Val62330Phe*	**this study**
4	not identified**	
5	c.558dup, p.(Val187Cysfs*6) published as (c.558insT)	Racz et al. 2006. [49]
6	c.1043T>C, p.(Ile348Thr)	Wang et al. 2011. [21]
7	not identified**	
8	c.2098A>G, p.(Thr700Ala)	Liang et al. 2014. [47]

* novel variant confirmed with Nci I restriction digestion; ** no pathogenic or likely pathogenic variant was identified using Sanger sequencing of the *ATP2A2* exons and the boundary intron regions

4.2.3. Microbial alpha and beta diversity of skin biopsy and swab samples

Statistically significant difference in microbial alpha diversity between lesional (both biopsy and swabs) and non-lesional DD cohorts was found by Shannon analysis with Wilcoxon rank sum testing at species level (Figure 7, part a). The median alpha diversity was lowest in the biopsy samples, showed a significant increase in lesional swabs, and

further increased significantly in non-lesional regions. In the healthy control group, the median alpha diversity was nearly similar to that of the non-lesional sites; however, the high variability within the healthy group prevented the detection of a significant difference compared to the other groups. Figure 7, part b and Table 9 illustrate significant differences among all groups of different localizations based on the principal coordinate analysis of Jaccard beta diversity.

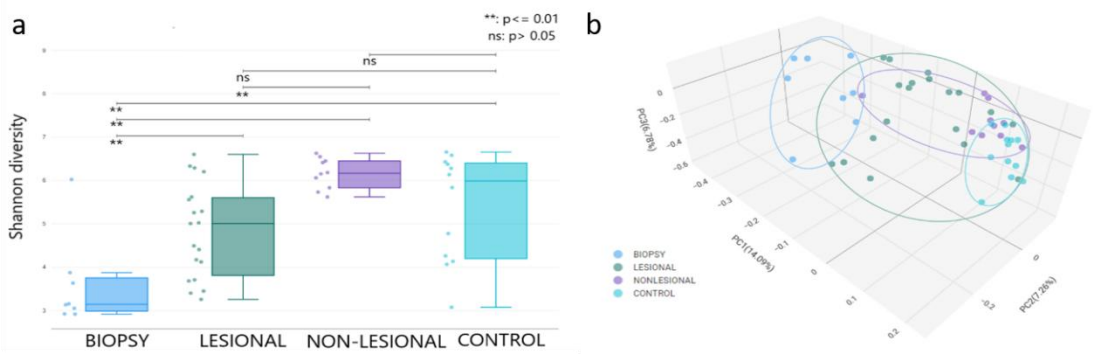

Figure 7. Comparison of Shannon alpha diversity (a) and Jaccard beta diversity Principal Coordinate Analysis (PCoA) (b) across different samples (skin biopsy, lesional and non-lesional swab) from Darier disease patients and from controls (swab samples). Error bars represent standard deviation [116].

Table 9. PERMANOVA analysis of Jaccard beta diversity Principal Coordinate Analysis (PCoA). Number of included samples (lesional biopsy samples and lesional, non-lesional and control swabs), permutations and a normalized *p*-value for each cohort combination [116].

Cohorts	Sample Size (n)	Permutations (n)	*P*-value
Biopsy <-> Lesional	27	999	0.140
Biopsy <-> Non-lesional	18	999	0.001
Biopsy <-> Control	20	999	0.001
Lesional <-> Non-lesional	29	999	0.001
Lesional <-> Control	31	999	0.001
Non-lesional <-> Control	22	999	0.004

4.2.4. Microbiome composition at phylum and genus level

The bacterial composition altered in lesional, non-lesional and healthy skin samples. At phylum level, the relative abundance of *Actinobacteria* was significantly lower in DD patients compared to controls. In DD patients, we detected significant decrease in biopsy samples compared lesional swab samples. 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. Significant increase could be observed in biopsy samples relative to lesional swab samples. No significant increase was found between non-lesional and control samples. At genus level, *Staphylococcus* genus accounted for more than 50% of the total amount of bacteria in DD patients' lesional sites. However, in healthy individuals, the most frequent genus was *Propionibacterium* (24.12%), which represented for only 1.48% of the total in lesional and 4.56% of the total in non-lesional sites. Furthermore, the genus *Cutibacterium* accounted 5.82% of the total amount of bacteria in healthy controls, compared to 1.05% in non-lesional and 0.34% in lesional sites in DD patients. In biopsy samples, the amounts of these two bacteria were below the reliable detection threshold of the program. These findings indicated that *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. In contrast, the *Propionibacterium* and *Cutibacterium* genera were significantly lower in lesional sites compared to non-lesional sites and controls. A significant decrease was detected in non-lesional sites relative to healthy controls in both genera. The heatmap in Figure 8 part c clearly shows sharp boundaries indicating differences in the abundance of the 10 most frequently occurring genera between symptomatic (biopsy and lesional swabs) and asymptomatic (non-lesional DD swab and healthy control swab) skin sites. *Pseudomonas* genus was more abundant in lesional areas- particularly in biopsy samples-, and continuously decreased toward non-lesional and healthy control areas, however no significant differences was detected. We observed the opposite trend for the *Finegoldia* genus, although no significant differences were found either.

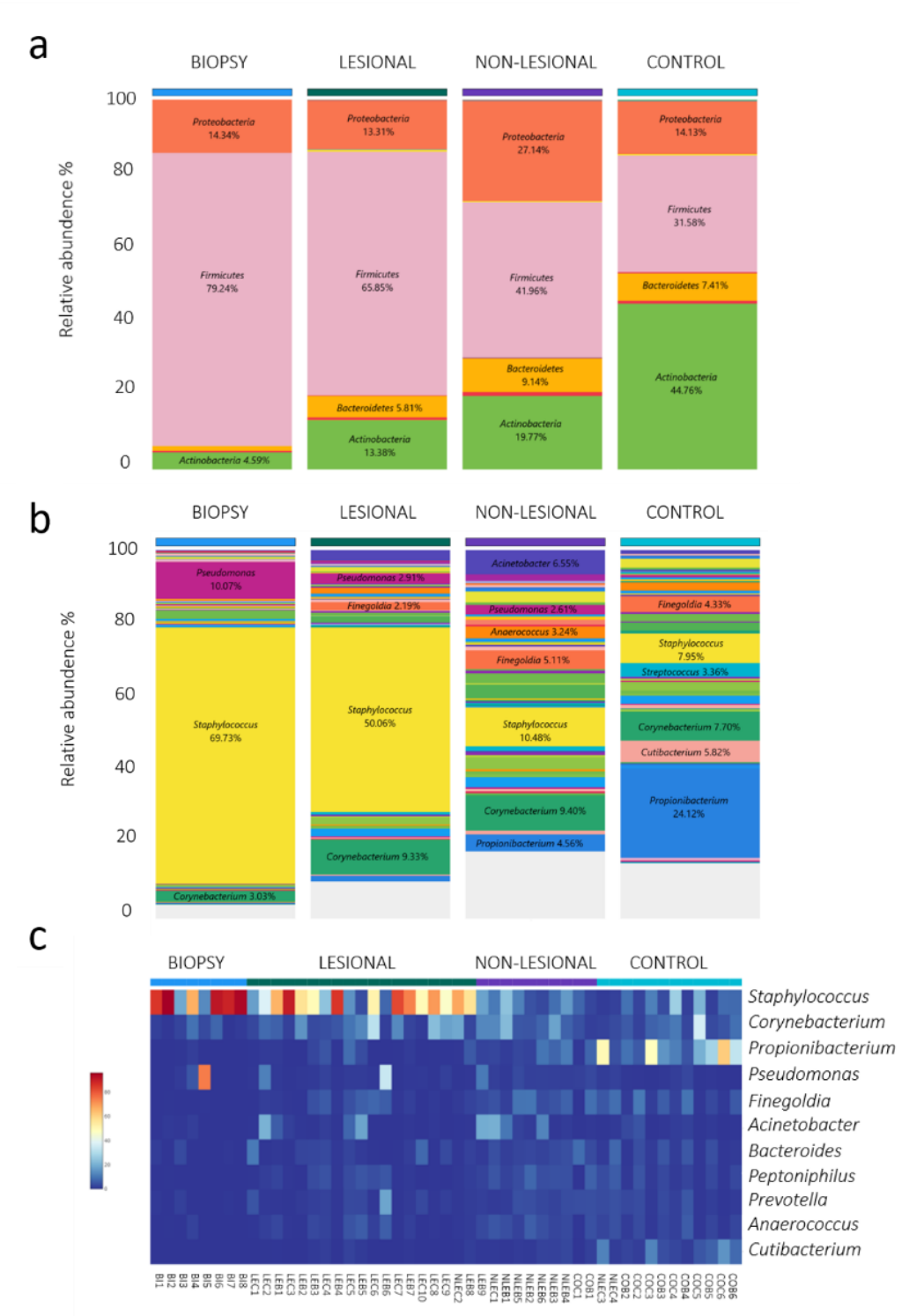

Figure 8. Visualization of skin microbiome composition in Darier disease patients and controls at the phylum (a) and genus (b) levels using stacked bar plots, and at the genus level using a heatmap (c) [116].

4.2.5. Microbiome composition at species level

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. Except for *S. aureus* and for *S. haemolyticus*, no significant differences were found between non-lesional sites and controls. 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. Interestlingly, significant reductions of the amounts of these species were observed also between lesional and non-lesional sites in DD patients. 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*. (Figure 9).

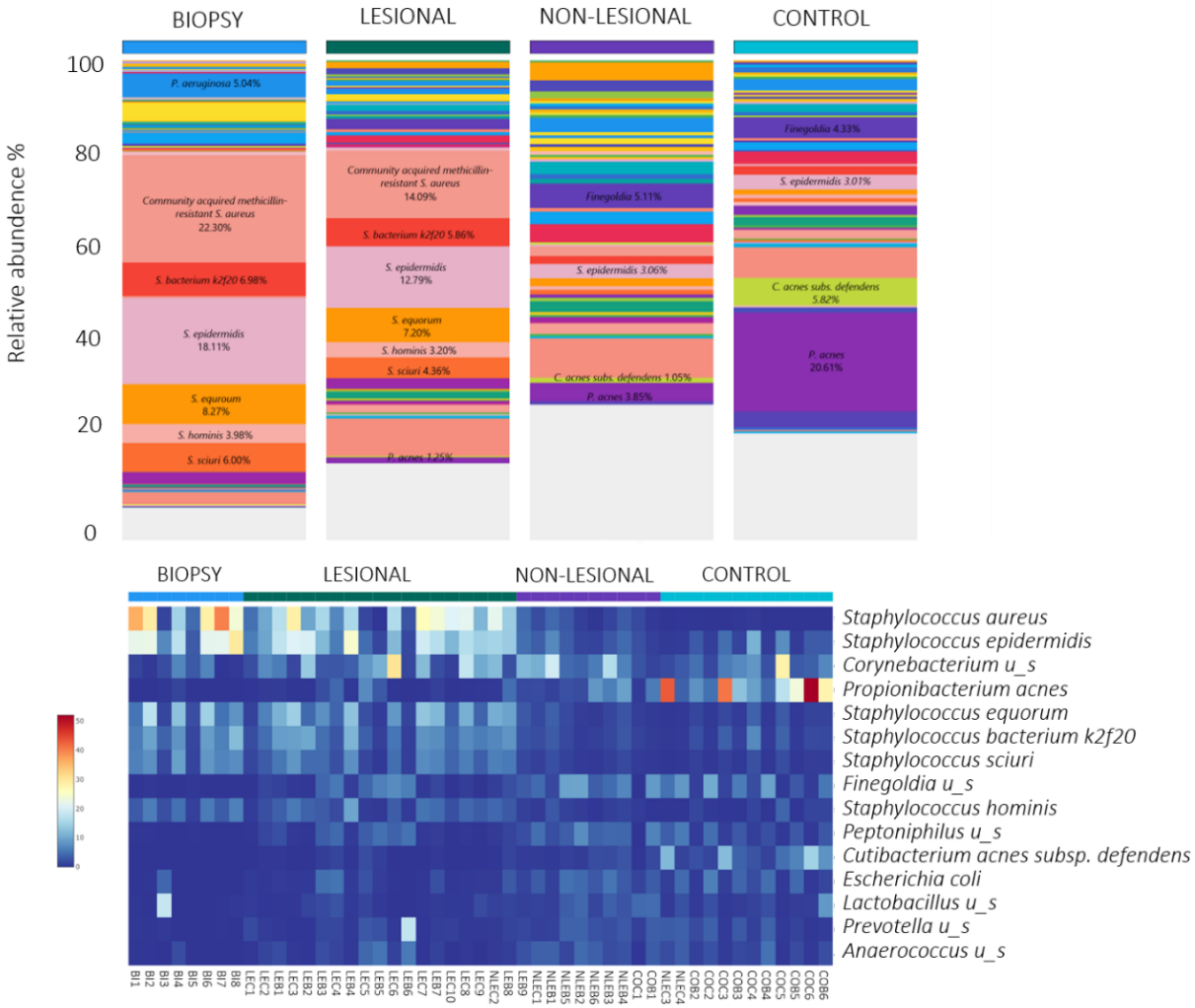

Figure 9. Microbiome composition at the species level. Negative correlation between various *Staphylococcus* species and between *Propionibacterium acnes* and *Cutibacterium acnes subspecies defendens* was observed comparing lesional, non-lesional and control samples [116].

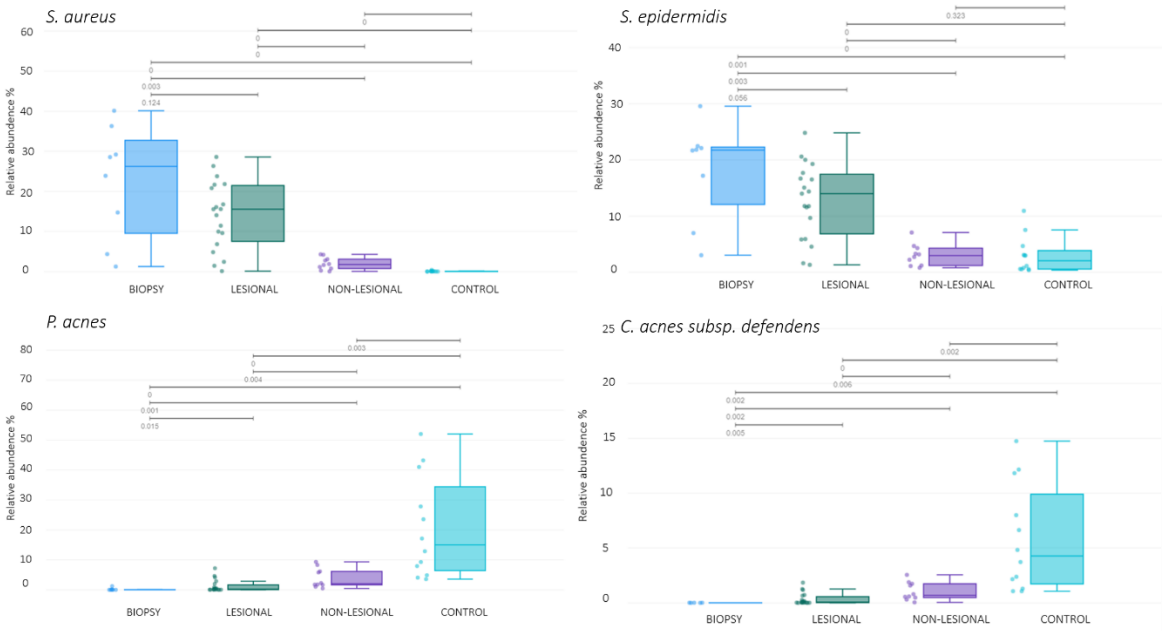

Figure 10. Significant differences in the relative abundance of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes* and *Cutibacterium acnes subspecies defendens*. Error bars represent in standard deviation [116].

Table 10. Variations in the most significant bacterial changes at the phylum, genus, and species levels [116].

	B-DD Median (IQR)	L-DD Median (IQR)	NL-DD Median (IQR)	C Median (IQR)	***P*-values**			
					B-DD: L-DD	L-DD: NL-DD	L-DD: C	NL-DD: C
Phylum								
Actinobacteria	3.01 (5.26)	12.22 (14.38)	19.16 (11.32)	39.92 (48.29)	0.006	0.054	0	0.008
Firmicutes	92.74 (26.06)	70.87 (21.18)	42.09 (8.11)	33.41 (25.3)	0.038	0.002	0	0.075
Genus								
Staphylococcus	87.40 (50.43)	51.75 (42.26)	9.57 (11.75)	5.58 (8.66)	0.056	0	0	0.187
Propionibacterium	0.02 (0.01)	0.22 (2.03)	2.55 (5.14)	17.43 (33.03)	0.015	0.005	0	0.002
Cutibacterium	0.01 (0.01)	0.07 (0.03)	0.69 (1.26)	4.27 (8.18)	0.005	0.006	0	0.002
Species								
S.aureus	26.23 (23.23)	15.55 (13.92)	1.76 (2.32)	0.02 (0.07)	0.124	0	0	0
S. epidermidis	21.75 (10.22)	13.99 (10.59)	2.96 (3.09)	2.06 (3.31)	0.056	0	0	0.323
S. hominis	4.04 (3.33)	3.14 (2,3)	0.65 (0.61)	0.21 (1.11)	0.243	0.002	0.001	0.356
S. equorum	6.00 (10.20)	7.73 (7.39)	1.45 (1.92)	0.75 (1.18)	0.595	0.001	0	0.166
S. haemolyticus	0.03 (0.12)	0.09 (0.02)	0.01 (0.02)	0.003 (0.004)	0.856	0.005	0	0.011
P. acnes	0.02 (0.07)	0.18 (1.6)	2.03 (4.49)	15.00 (28.99)	0.015	0.004	0	0.003
C. acnes subsp. defendens	0.01 (0.01)	0.07 (0.04)	0.69 (1.25)	4.27 (8.18)	0.005	0.006	0	0.002

B-DD: biopsy, Darier disease; L-DD: lesional swab, Darier disease; NL-DD: non-lesional swab, Darier disease; C: control swab

4.2.6. Region specific alterations of the skin microbiome in Darier disease

Both the chest and back areas are considered sebaceous regions; however, the distribution of several bacteria differed across the different anatomical locations (Table 11). In healthy individuals, *Propionibacterium* genus dominated both regions, however, its relative abundance was twice as high on the chest (33.29%) as on the back (14.94%). In the control chest, the second most abundant genus was *Staphylococcus* (12.86%), whereas it ranked only tenth in the control back (3.03%). *Corynebacterium* was the third most common genus in both locations; however, its relative abundance was 10.86% in the control chest and 4.55% in the control back. The genus *Cutibacterium* represented 8.02% in the chest and 3.63% in the back of the total amount of bacteria in healthy controls. In DD patients, regardless of whether the sample was taken from a lesional or non-lesional area, *Staphylococcus* genus dominated (lesional chest: 53.25%, lesional back: 50.81%,

non-lesional chest: 13.39%, non-lesional back: 8.74%), followed by Corynebacteria (lesional chest: 9.64%, lesional back: 9.01%, non-lesional chest: 12.66%, non-lesional back: 6.71%).

Table 11. The 10 most abundant bacterial genera from two predilectional sites of Darier disease patients and healthy individuals (swab samples) [116].

LESIONAL CHEST		NON-LESIONAL CHEST		CONTROL CHEST	
Genus	%	Genus	%	Genus	%
Staphylococcus	53.25	*Staphylococcus*	13.39	*Propionibacterium*	33.29
Corynebacterium	9.64	*Corynebacterium*	12.66	*Staphylococcus*	12.86
Acinetobacter	2.67	*Acinetobacter*	7.44	*Corynebacterium*	10.86
Bacteroides	2.61	*Propionibacterium*	5.18	*Cutibacterium*	8.02
Finegoldia	1.94	*Finegoldia*	4.32	*Streptococcus*	4.59
Pseudomonas	1.71	*Pseudomonas*	3.26	*Finegoldia*	1.63
Prevotella	1.30	*Peptoniphilus*	3.54	*Prevotella*	1.42
Propionibacterium	1.26	*Anaerococcus*	3.43	*Micrococcus*	1.09
Peptoniphilus	1.23	*Xanthomonas*	2.74	*Peptoniphilus*	0.98
Escherichia	1.06	*Escherichia*	2.54	*Anaerococcus*	0.97
LESIONAL BACK		NON-LESIONAL BACK		CONTROL BACK	
Genus	%	Genus	%	Genus	%
Staphylococcus	50.81	*Staphylococcus*	8.74	*Propionibacterium*	14.94
Corynebacterium	9.01	*Corynebacterium*	6.71	*Finegoldia*	7.03
Pseudomonas	4.35	*Acinetobacter*	5.94	*Corynebacterium*	4.55
Prevotella	2.89	*Finegoldia*	5.57	*Bacteroides*	4.23
Acinetobacter	2.74	*Propionibacterium*	4.68	*Escherichia*	4.09
Finegoldia	2.25	*Peptoniphilus*	3.85	*Cutibacterium*	3.63
Anaerococcus	2.19	*Bacteroides*	3.82	*Peptoniphilus*	3.48
Peptoniphilus	1.84	*Anaerococcus*	3.27	*Anaerococcus*	3.41
Bacteroides	1.23	*Escherichia*	3.2	*Lactobacillus*	3.32
Escherichia	1.05	*Prevotella*	2.99	*Staphylococcus*	3.03

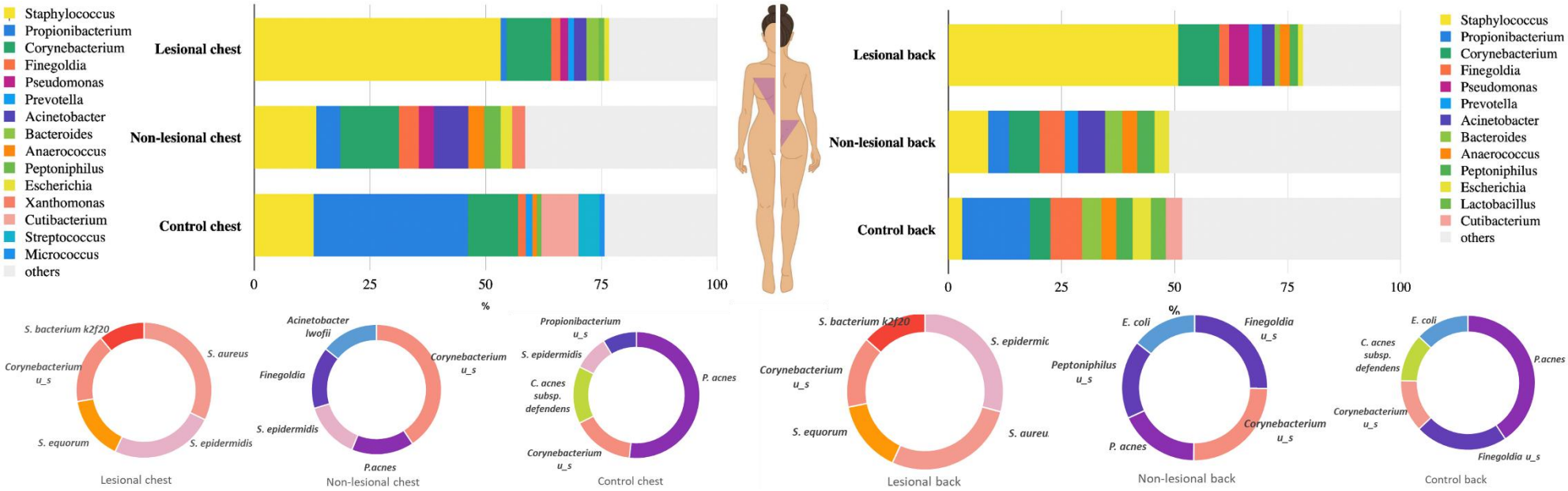

Figure 11. The 15 most abundant bacterial genera and the 5 most abundant species in the skin microbiome of swab samples from Darier disease patients and controls are presented. Darier disease patients showed a significant reduction in the genera *Propionibacterium* and *Cutibacterium*, alongside a massive colonization of the genus *Staphylococcus* in two predilection sites (chest and back) [116].

4.3. Results of study III.

4.3.1. Sample characteristics

A total of 25 (13 DD and 12 HHD) patients were invited to participate in study III. Nine of them withdrew, and one did not attend, leaving a final sample of 15 participants (8 DD and 7 HHD, 80% female, age range 35 to 77 years). The mean interview duration was 48 minutes. The sample represented a wide range of age groups and education levels, exhibiting diverse clinical characteristics (Table 2). All but one interviews were conducted in person, while one interview performed via online video-interviewing. In one case, a DD patient who used a wheelchair and had recently been diagnosed with multiple sclerosis, preferred to attend the in-person interview with her husband present.

4.3.2. Common symptoms of Darier disease and Hailey-Hailey disease and their impacts on patients' lives

Table 12 summarizes patients' thoughts on how their disease impacts various aspects of their lives, with a total of 46 different aspects identified. These were grouped into five main categories: (1) triggers, (2) physical symptoms, (3) impact on mental health and social, (4) everyday difficulties, and (5) healthcare-related issues. The most commonly reported symptom was pain (93%, n=14), followed by issues such as leaking, bleeding, and superinfection linked to the skin lesions (60%, n=9). Over half of the patients (53%, n=8) expressed concerns about their appearance, feelings of shame, or misconceptions about the disease (e.g., being perceived as contagious or caused by poor hygiene). Issues with self-esteem and self-confidence were reported by 40% of participants (n=6). Many patients described difficulties with daily activities, mobility, work, and sleep. Forty percent (n=6) mentioned challenges with dressing, while others (33%, n=5) had issues finding clothing to cover their skin lesions or with personal hygiene.

Table 12. Key life aspects affected by Darier disease and Hailey-Hailey disease [146]**.**

Main categories	Subcategory	n	%	
Triggers	Seasonal fluctuations	8	53	P10 (HHD): It's much harder during the summer months, I suppose because of the heat and sweating.
	Sun exposure	5	33	P8 (DD): Well, when I was eight years old, I had a rash on my forehead on the beach, and we thought it was a sun allergy.
	Stress	5	33	P2 (DD): So when I'm a bit more stressed, it completely exacerbates the symptoms.
	Onset in childhood	5	33	P15 (DD): According to my parents, I was five years old when my disease started.
	Period-related	3	33	P10 (HHD): A week before menstruation, my skin starts to feel tense.
Physical symptoms	**Pain**	**14**	**93**	P02 (HHD): It is so painful sometimes that I could cry.
	Superinfection, prolonged wound healing	9	60	P15 (DD): Since 2005, my skin in the groin has been constantly sore, and the problem is not just that, but it also gets infected and warts appear.
	Skin bleeding and leaking	9	60	P4 (DD): It's uncomfortable when it [skin lesion] comes out in the groin area, and then it's leaking.
	Skin irritation (e.g. tightness, burning sensation)	**8**	**53**	P06 (DD): My skin feels tight and burns.
	Appearance	8	53	P02 (DD): It feels bad that until I was a teenager, I never had a pimple, my skin was so clear and beautiful. And then I have to face the fact that I have an ugly skin like this.
	Itching	**7**	**47**	P07 (HHD): Well, it burns, it itches, it prevents me from moving.
	Odor	4	27	P11 (DD): This inflammation I have now, which is accompanied by such an unpleasant odor, is particularly uncomfortable for me.
	Facial symptoms	3	20	P02 (DD): I was in eighth grade when it [the disease] started on my face.
Impact on mental health and social life	Adaptation	11	73	P13 (HHD): I have reluctantly dealt my illness.
	Shame	8	53	P03 (HHD): I clench my armpits and walk in that way so that no one can see it [the symptoms] P04 (DD): The feeling of shame will always be there in a me.
	Others' misconceptions about the illness	8	53	P11 (DD): It happened once on a public transport, when I didn't even notice that skin lesions were visible, a pregnant woman asked me if it was chickenpox. P02 (HHD): Sometimes people think that I have burned myself.
	Mental health problems	6	40	P01 (HHD): It has definitely affected me emotionally, it is terrible, not knowing what this is and why I am not getting better.
	Self-esteem or self-confidence problems	**6**	**40**	P10 (HHD): I don't see anything else on myself but ugliness, and this affects things like my anxiety, self-esteem, and emotional balance, so basically everything.
	Romantic relationship problems, break up/divorce	5	33	P06 (DD): When Darier breaks out, I can become very self-conscious, then I'm afraid of being in a relationship.
	Social network, support from friends, family, and colleagues	5	33	P01 (HHD): My family gives me a lot of mental strength... they keep me going, I try to be better for them.
	Social relationship problems	5	33	P07 (HHD): I find it much harder to handle interactions at home during flare-ups; my mood changes are extremely difficult for the people around me.
	Anxiety	**4**	**27**	P14 (HDD): The lesions in my armpit make my anxious.
	Fear of heredity	3	20	P07 (HHD): I'm afraid because it is a 50% risk for even my two children got it [the disease].
Everyday difficulties	**Mobility issues**	**11**	**73**	P01 (HHD): When my disease flares up, it's impossible even to walk.
	Problems with leisure activities, sports, physical exercise	**11**	**73**	P2 (HHD): I can't go swimming; I can't go to the baths.
	Dressing issues (due to pain)	**6**	**40**	P2 (DD): I had such pain or I had to ask for help just to be able to put on a pyjama at all
	Dressing issues (due to shame related to skin lesions)	5	33	P1 (HHD): I was constantly getting sores(…)I kept changing my clothes constantly because the sores touched every single piece of a clothing I put on.

				P02 (DD): There are limited types of clothes I can wear because, you know, they irritate my skin, so I have to look for cotton clothes and find something that covers all my lesions.
	Working issues	**10**	**67**	P01 (HHD): I worked as a nanny for eighteen years, but I can't do it anymore because of my skin condition.
	Changes in life due to the illness (e.g. slowing down and limited activities due to the symptoms)	8	53	P02 (HHD): It affects our sexual life, everyday activities, work, and sports.
	Assistance needed to perform daily tasks	**7**	**47**	P15 (DD): For example, when my skin feels really tight, I can't put my shoes on by myself.
	Need for special cosmetics	7	47	P01 (HHD): The shower cream that I can only use for washing is like a pharmacy product.
	Limitations in certain activities (e.g. going to the beach or vacation)	6	40	P02 (DD): For the past 20 years, I definitely haven't been to the beach.
	Sitting difficulties	6	40	P07 (HHD): I can't sit for long periods because the wound gets stuck to the clothes.
	Frequent need to change clothes and take a shower	5	33	P04 (DD): I usually take a shower 10 times a day.
	Frequent change of bedding	5	33	P10 (HHD): I continuously used up five to six sets of bed linens in one day.
	Washing or bathing problems	**5**	**33**	P13 (HHD): Water absolutely irritates my skin, even bathing is very painful for me.
	Being disabled	4	27	P07 (HHD): The disability assessment process is humiliating. You have to appear before a committee.
	Financial implications	3	20	P10 (HHD): The medications cost a lot of money.
	Sleeping problems	3	20	P10 (HHD): I cried in my sleep because every movement hurt.
	Required to take a special diet	3	20	P07 (HHD): I don't want to constantly take antibiotics, so I try to make dietary and lifestyle changes.
Health care related issues	Treatment difficulties	13	87	P05 (HHD): I was allergic to some ingredient of the cream and that contributed to the worsening of the symptoms.
	Loss of therapy effectiveness	11	73	P02 (DD): I have used a lot of different medications and creams.
	Late diagnosis or misdiagnosis	10	67	P13 (HHD): Yes, I didn't get the diagnosis right away when lesions first appeared (...) it took approximately three or four years.
	Hospitalization due to the skin condition	5	33	P2 (DD): But I know that when pain appears, there's an 80% chance that hospitalization follows, because by then it's [skin lesion] already become infected.
	Dissatisfaction with doctors	4	27	P05 (HHD): I visited the dermatologist multiple times because they didn't know what to do with me.
	Trust in the treatment, faith in doctors	3	20	P07 (HHD): You're there to help and you're trying to research this disease.

The bolded subcategories refer to HRQoL areas covered by the EQ-5D-5L and the two bolt-ons.

4.3.3. Relevance and comprehensibility of the EQ-5D-5L and bolt-ons

Most patients found the EQ-5D-5L easy to complete and comprehensible, moreover, all participants found the five dimensions relevant to their disease. Patients also appreciated the inclusion of skin irritation and self-confidence bolt-ons. Interestingly, some patients interpreted self-care as the choice of clothes or cosmetics, rather than the physical act of dressing or washing.

4.3.4. Ranking of dimensions of the EQ-5D-5L and bolt-ons

After completing the EQ-5D-5L, six patients (40%) ranked all dimensions as equally relevant to their disease. Four (27%) patients considered usual activities as the most important, followed by mobility, self-care and pain/discomfort dimensions, each mentioned by three patients (20%). However, when the EQ-5D-5L with the two bolt-on dimensions was completed, the most relevant dimension was self-confidence (n=5, 33%), followed by skin-irritation (n=3, 20%), Additionally, five participants (33%) considered all seven dimensions equally relevant to their disease. Notably, only one patient indicated a 'least relevant' dimension, which was self-care (Table 13).

Table 13. Ranking of dimensions in the EQ-5D-5L and EQ-5D-5L+ bolt-ons [146].

	EQ-5D-5L				EQ-5D-5L+ bolt-ons			
	Most relevant		Least relevant		Most relevant		Least relevant	
Dimension	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Mobility	3	20	0	0	2	13	0	0
Self-care	3	20	1	7	2	13	1	7
Usual activities	4	27	0	0	2	13	0	0
Pain/discomfort	3	20	0	0	2	13	0	0
Anxiety/depression	1	7	0	0	0	0	0	0
Skin irritation	n/a	n/a	n/a	n/a	3	20	0	0
Self-confidence	n/a	n/a	n/a	n/a	5	33	0	0
All equally relevant	6	40	0	0	5	33	0	0

Note that some patients ranked more than one dimension as the most relevant. N/a = not applicable.

4.3.5. Overlapping dimensions and comprehensiveness of the EQ-5D-5L and bolt-ons

Two patients mentioned a conceptual overlap between usual activities and self-care, while another patient recognized a conceptual overlap between pain/discomfort and skin irritation.

All patients found the EQ-5D-5L and the two additional bolt-ons comprehensive, though some missing concepts were noted (Table 14). Six missing concepts were identified by four patients (27%) after completing the EQ-5D-5L. With the addition of the two bolt-

ons, six patients (40%) noted a total of 12 missing concepts. The most frequently mentioned missing concept was the financial impact of the disease (n=4, 27%). Other concerns included intimacy issues, difficulties related to sex life, work challenges, and the importance of education for non-physical work. One patient also pointed out the need for employers' tolerance. Other missing aspects included social life and relationship difficulties, the importance of special care or diet, seasonal fluctuations, and disease-related factors not considered usual activities. Interestingly, before completing the EQ-5D-5L with the two bolt-ons, one patient noted the absence of a self-esteem dimension, which is strongly connected to self-confidence with having an impact on the other. All patients preferred the EQ-5D-5L with the two bolt-ons over the version without them. The addition of the bolt-ons did not alter any responses on the core five dimensions for any of the patients.

Table 14. Missing concepts in EQ-5D-5L and EQ-5D-5L+bolt-ons [146].

	Patients mentioning each concept			
	EQ-5D-5L		EQ-5D-5L+bolt-ons	
Concepts	**n**	**%**	**n**	**%**
Financial impact	2	13	4	27
Impacts of any medical procedures affecting the skin (e.g. the use of adhesive tapes for wounds)	0	0	1	7
Intimacy	0	0	1	7
Seasonal fluctuation	0	0	1	7
Self-esteem	1	7	0	0
Sexual life	1	7	2	13
Shame caused by the disease	1	7	1	7
Social life, relationships	1	7	1	7
Special care (clothing, food, cosmetics, detergents etc.)	0	0	1	7
Special diet	0	0	1	7
Work issues: employer's toleration	0	0	1	7
Work issues: physical work limitations	1	7	1	7

4.3.6. Suggested changes in descriptors of the EQ-5D-5L and bolt-ons

Five patients (33%) proposed changes to at least one of the seven dimensions (Table 15). Suggestions were made for all dimensions except skin irritation. Three patients (20%) recommended separating the anxiety/depression composite into two distinct dimensions. One suggestion was to divide the usual activities dimension based on whether they require physical activity. Wording changes were proposed in three cases, including one patient who noted a distinction between 'walking' and 'mobility' and suggested expanding the self-care dimension to include eating. Another participant raised concerns about the term 'dressing.'

Table 15. Suggested changes [146]**.**

Themes	n	%	Example quote
Mobility			
Use the same terminology in the dimension title and response levels (i.e. mobility or walking)	1	7	P14 (HHD): Mobility for me doesn't necessarily only refer to walking but fundamentally to movement itself. I don't have a problem with walking, but mobility, in general, is already problematic for me. By mobility, I mean physical mobility in a general sense. Either change the word 'mobility' or the word 'walking', depending on what you're interested in.
Self-care			
Rephrase the word 'dressing'	1	7	P12 (HHD): 'Dressing' (Hungarian: öltözködés) means how someone appears, how they dress, in my opinion... it's more like 'getting dressed' (Hungarian: felöltözni).
Expand it to include eating	1	7	P14 (HHD): For me, self-care includes eating as well.
Usual activities			
Split usual activities based on whether they include physical activity or not	1	7	P14 (HHD): Here, I might consider separating it. I think, for most people, usual activities are related to mobility, physical movement. I might somehow reorganize it, distinguishing between activities that require physical activity and those that do not or involve less physical activity for example when someone has a physical job versus works when you mostly sit in front of a computer, sleeping, social life like going out, meeting friends, waiting for guests, studying, hobbies… even cooking.
Pain/discomfort			
Split into 2 questions	1	7	P4 (DD): Pain is different from discomfort. These could be two separate questions.
Anxiety/depression			
Split into 2 questions	3	20	P14 (HHD): I think it might be worth separating them because, I believe, they have different symptoms. I had a period of depression, and for me, depression and anxiety have different symptoms.
Change the word 'anxiety' and 'depression' to shame	1	7	P04 (DD): For me, it's not so much anxiety. It's more like fear or a bad feeling... Instead of depression, it's more about mood... There's a sense of shame in me (…) but that doesn't necessarily mean I should feel anxious or be depressed.
Self-confidence			
Specify whether the lack of self-confidence is related to the disease	1	7	P14 (HHD): Here, I think it's important to indicate whether this is related to it. Because I can easily imagine that someone might generally lack it, but not because of this.
The whole questionnaire			
Specify if the questionnaire is meant to be generic	2	13	P14 (HHD): I might specify this a bit. For example, if I kicked the door frame or got my period yesterday, I might be in pain, but it doesn't mean I have any issues with Hailey-Hailey now.

4.3.7. Response levels of EQ-5D-5L and bolt-ons

Table 16 shows participants' observations on the response levels. Most respondents were satisfied with the five-level scale. However, two participants suggested reducing the response levels to four or three for certain dimensions, such as mobility, self-care, or the skin irritation bolt-on. Some participants felt that terms like 'no problem' and 'unable to' didn't accurately describe their conditions. One patient mentioned that the differences between levels were unclear. Another patient suggested clarifying what constitutes mild

or severe pain by providing examples. Additionally, it was suggested that the description of itching should address both its intensity and duration.

Table 16. Thoughts about the response levels [146].

Themes	n	%	Example quote
Mobility			
'Unable' is an inaccurate term	1	7	P10 (HHD): Well, saying '*I'm unable*' isn't entirely true in this disease... it's a fact that it came with brutal pain when the skin around my knee was inflamed, but if you are forced to, you have to move as best as you can.
Self-care			
'Unable' is an inaccurate term	2	13	P07 (HHD): I don't know how others feel about it, but in my opinion, *'I am unable'* isn't quite accurate (....) '*Severe*' is okay, that's fine, but the '*I am unable*' part, I think, is not the thing in our cases. '*I am unable*' is for someone who has no hands or feet...
No need for a 'no problem' level	1	7	P07 (HHD): I believe that every patient like this has a problem.
Pain/discomfort			
Illustrate the severity of the pain with examples	1	7	P14 (HHD): I think it would be useful to illustrate the severity of the pain with examples.
Skin irritation			
Four levels would be sufficient	1	7	P07 (HHD): I don't think the word '*extremely*' is necessary (…) '*Severe*' is good, but to make it '*extreme*', there's nothing like that in Hailey-Hailey... there's no such thing as wanting to scrape my skin down to the bone, for example, that would be extreme for me.
Consider the duration of itching	1	7	P14 (HHD): One aspect is the intensity of the itching, and another thing is the duration. For instance, sometimes it itches intensely for a short period, or it itches all day but with low intensity.
All			
Difficult to differentiate between levels 2 and 3	2	14	P05 (DD): I sometimes don't know what the difference is between mild and moderate

4.3.8. EQ VAS

Eight patients (53%) associated the top endpoint of the EQ VAS (100: the best health you can imagine) and nine (60%) linked the lowest endpoint (0: the worst health you can imagine) specifically to their skin condition. A smaller group of patients (n=5, 33%) interpreted the endpoints in general. Three patients shared that they had already experienced the zero endpoint in their lives, describing severe pain and other symptoms

related to their disease. One patient was unsure whether the term ’health status’ in the instruction line of EQ VAS referred to skin lesions as well, while another questioned whether achieving a health status of ‘100’ was plausible.

4.3.9. Recall period of the EQ-5D-5L and bolt-ons

Two patients used an incorrect recall period in both the EQ-5D-5L and EQ-5D-5L with bolt-ons. None of the patients initially reported issues with the ‘today’ recall period. However, when they were asked about the appropriateness of ‘today’, one patient considered it appropriate, while seven patients suggested a recall period of 1 week to 3 months would be more fitting. Additionally, seven patients felt that the questions should focus on disease flare ups or symptomatic periods.

5. Discussion

Genodermatoses are a diverse group of inherited skin disorders that pose diagnostic challenges due to their rarity and clinical and genetic variability. Various phenotypes exist ranging from limited cutaneous disease to severe cutaneous and extracutaneous involvement [2]. With the growing number of preclinical and clinical studies exploring targeted and symptom-relief therapies in various conditions, there is an increasing need for non-invasive tools to improve the diagnostic accuracy [25, 43, 55]. Dermoscopy is a non-invasive, easily accessible technique that allows rapid clinical assessment of skin lesions and may help to detect characteristic morphologic features. This is especially valuable in genodermatoses, as most patients are children, making skin biopsy procedures challenging in this age group [109, 193]. Dermoscopic recognition of characteristic skin manifestations can facilitate early diagnosis of certain cutaneous and multisystemic conditions, which is crucial for initiating timely treatment and preventing complications. Beyond the diagnostic process, dermoscopy can also be utilized to follow therapeutic response [46].

Both standardized descriptive and metaphoric terminologies are recommended for evaluating dermoscopic features [107]. While metaphoric terms can be memorable and illustrative, they may also ambiguous, whereas descriptive terminology is clearer but may not fully capture complex dermoscopic structures.

In our first study, we conducted a systematic review of dermoscopic features in various genodermatoses and expanded the literature on our own analysis. For the dermoscopic evaluation of lesions in Fabry disease, neurofibromatosis type 1, basal cell nevus syndrome, Noonan syndrome with multiple lentigines, and CLYD cutaneous syndrome, we employed the standardized dermoscopic terminology established by *Kittler et al*. Expanded terminology on general dermatology by *Errichetti et al*. was utilized to characterize features in DD, HHD, XX ichthyoses, palmoplantar keratodermas, erythrokeratodermia variabilis et progressiva, Dowling-Degos disease, pseudoxanthoma elasticum, and tuberous sclerosis complex. According to previous recommendations by *Kittler et al.*, no new metaphoric terms were used [107].

It is important to emphasize that to establish the diagnosis, in addition to dermoscopic assessment, the overall clinical context of the patient needs to be considered including the age of onset, localization of the skin lesions, family history and molecular testing.

Molecular genetic testing may involve targeted mutation analysis, such as Sanger sequencing technique. In the first part of our second study, we performed a genetic analysis in DD, a rare inherited dermatosis, and identified a novel *ATP2A2* variant in a DD patient. Since DD is considered a multisystemic disease, identifying the precise gene mutation and understanding its function across different organs may contribute to a better understanding of the disease's pathomechanism [39]. In keratinocytes, mutations in the *ATP2A2* gene disrupt calcium homeostasis and lead to epidermal barrier dysfunction [34]. This compromised barrier function predisposes patients to recurrent secondary infections, particularly caused by *S. aureus* [25, 58, 100]. Dysbiosis, referring to an imbalance in the skin microbiome, has been implicated in both the onset and exacerbation of several dermatologic conditions [117, 118, 122, 256]. In the last part of our second study, we investigated the skin bacterial composition in DD patients and in healthy individuals. Our findings indicate that individuals with DD exhibit an altered skin microbiome compared to healthy controls in two predilectional skin sites, such as the chest and the back, with more pronounced changes observed in lesional areas [116]. We detected a reduced microbial diversity in lesional skin sites of DD patients, with a significant difference in microbial alpha diversity between lesional and non-lesional skin. However, no significant difference was observed when compared to healthy controls. This lack of significance may be attributed to the high variability within the control group, which could mask potential differences between groups. Another possible explanation is the predominance of the Cutibacterium genus in healthy controls compared to DD patients. Greater bacterial diversity that was observed in non-lesional samples may not be beneficial if key *Cutibacterium* species are absent [256, 257]. Our observations in microbial alpha diversity correlated with significant alterations in microbial beta diversity between lesional, non-lesional, and healthy skin.

Notably, one of the most significant alterations was the inverse correlation between the genera *Cutibacterium* and *Staphylococcus*. The relative levels of *C. acnes* and *C. acnes subsp. def.* were significantly lower in lesional DD skin sites compared to non-lesional areas and controls. Furthermore, both bacterial levels were significantly decreased in non-lesional sites compared to healthy controls. However, it remains unclear whether the initial decline of *Cutibacterium* genus led to an overgrowth of distinct *Staphylococcus* species or if early Staphylococci colonization suppressed Cutibacteria.

It is important emphasize that *C. acnes* plays a crucial role in maintaining skin health by inhibiting the colonization by pathogenic bacteria (e.g., *S. aureus*) and modulating the immune system through propionic acid production, which lowers skin pH and activates antimicrobial proteins. In contrast, the levels of *S. aureus, S. epidermidis, S. hominis, S. equorum,* and *S. haemolyticus* were increased in lesional areas. Interestingly, the relative abundance of various *Staphylococcus* species in non-lesional DD skin was nearly identical to that in healthy individuals, except for *S. aureus* and *S. haemolyticus*, which were nearly absent in controls.

S. epidermidis is a commensal bacterium that promotes innate immune responses and inhibits the growth of *S. aureus* and *C. acnes*. While generally considered harmless, a compromised epidermal barrier may cause *S. epidermidis* to shift towards a pathogenic state [258]. Supporting this theory, another research in AD patients has shown that, in addition to *S. aureus*, massive colonization of *S. epidermidis* at lesional sites may also correlate with disease severity [259]. In AD patients, *Francuzik et al.* also identified a negative correlation between *C. acnes* and *S. aureus*, suggesting that these microbial shifts are not disease-specific but rather linked to an impaired epidermal function shared across different skin conditions [260, 261].

While *S. equorum* is generally regarded as benign and non-pathogenic, *S. hominis* and *S. haemolyticus* can act as opportunistic pathogens- particularly in immunocompromised individuals, neonates, and those with indwelling medical devices- due to their potential role in bacteraemia, septicaemia, endocarditis, and device-related infections [262-264].

To the best of our knowledge, only two previous studies have investigated the skin microbiome composition in patients with DD. *Reiter et al.* examined four skin sites- the scalp, chest, axilla, and palm- and, in line with our findings, identified the genus *Staphylococcus* as a key driver of microbiome shifts between lesional and non-lesional chest skin [265]. However, their study did not report species-level resolution. In the other study, *Amar et al.* similarly observed an overgrowth of *S. aureus* and a depletion of *C. acnes* in DD patients. Additional findings included a significant increase in *S. warneri* abundance in lesional skin and a loss of potentially beneficial commensals, such as *Micrococcus luteus, Moraxella osloensis,* and *Paracoccus yeei*. In contrast to our findings, they found a drop of *S. epidermidis* and *S. hominis* in lesional samples [58]. It is important to note that the study focused on moist areas, such as the axillary, inguinal,

and submammary regions, whereas we investigated sebaceous sites, namely the chest and back. This may be an important difference, as skin microbiome is generally considered region-specific. We first demonstrated a significant decrease in the relative abundance of *C. acnes subsp. def.* This finding may represent a promising topic for further investigation, as previous *in vitro* data suggest that the *C. acnes subsp. def.* strain XYCM42 and its fermentation filtrate may provide benefits to the skin through antioxidant, anti-inflammatory, and selective antimicrobial activities. Furthermore, clinical observations have shown that a regimen containing XYCM42 supports a healthy skin environment by increasing skin hydration, reducing erythema, soothing the skin, and regulating sebum production [266].

According to knowledge, our study is the first that aimed to assess the bacterial composition of deeper epidermal skin layers in DD patients. Data on the bacterial composition in the deeper epidermal layers is limited. We found that some *Staphylococcus* species (e.g., *S. aureus* and *S. epidermidis*) were more abundant in biopsy samples than in lesional swabs, indicating bacterial penetration into deeper epidermal layers [116]. Previous studies suggest that the penetration of *S. aureus* into the deeper epidermal and dermal layers provoke inflammation in AD patients [267, 268]. These facts may support our findings and its potential disease-modifying role in DD as well [116]. Moreover, another previous study demonstrated that intradermal injection (rather than topical application) of *S. epidermidis* triggered inflammatory responses, including the infiltration of monocytes and neutrophils and the production of IFNγ-secreting Effector T cells [269]. *Zeeuwen et al.* previously suggested that deeper skin layers may play an essential role in the recolonization of the superficial layers in a previously injured skin [121]. We hypothesize that while the stratum corneum remains intact- as in non-lesional areas- it may help prevent excessive colonization of *Staphylococcus* species in both the superficial and deeper layers. This balance, however, may be disrupted if the outer epidermal layers are compromised. Adding to this, our findings also indicate that deeper skin layers exhibit a significantly decreased amount of various *Cutibacterium* species in DD patients [116].

Overall, our study suggests that decreased bacterial diversity in lesional skin- potentially driven by the overgrowth of distinct *Staphylococcus* species (e.g., *S. aureus* and *S. epidermidis*) and reduced levels of *C. acnes* and *C. acnes subsp. def.* contribute to

persistent inflammation and exacerbate disease severity in DD [116]. Limitation of this study was the small sample size, and the absence of patients' classification based on disease severity due to the lack of avaible standardized scoring system for DD. Additionally, viral DNA was not analyzed, however, previous investigations suggest the potential role of viruses like HSV-1 and SARS-CoV-2 in the development of the disease through increased cytokine levels (TNF-α, IL-6, IL-1β) *in vitro* [270, 271]. A further limitation of our study was the lack of non-lesional skin biopsies from DD patients and healthy skin biopsies from controls.

In recent years, efforts to better understand the precise pathomechanisms of certain genodermatoses have enabled the application of novel therapeutic agents [24, 272]. An increasing number of case reports and case series have recently been published, demonstrating the potential benefit of new therapeutic options in various inherited diseases [71, 74, 273-275]. Novel therapies often require more health resources, therefore, measuring their cost-effectiveness is a key factor. EQ-5D is a widely used instrument in various conditions for measuring HRQoL and for estimating QALYs which is commonly used in economic evaluations. In our third study, we firstly investigated the content validity (relevance, comprehensiveness and comprehensibility) of the EQ-5D-5L and skin-irritation and self-confidence bolt-on dimensions in two rare acantholytic dermatoses, such as DD and in HHD.

To date, only a single study has utilized the three-level EQ-5D (EQ-5D-3L) in DD, demonstrating good known-group validity [53]. While a condition-specific HRQoL measure (Darier Disease Quality of Life, DD-QOL) was recently developed for DD, it has notable limitations: it does not capture broader HRQoL aspects such as comorbidities, lacks utility valuation necessary for economic analyses, is available in a limited number of languages, and has limited validation evidence [53, 99]. In contrast, the EQ-5D-5L with skin irritation and self-confidence extra bolt-ons, is available in approximately 50 languages, moreover, the core instrument is supported by extensive validation across over 100 studies [96, 100]. To our knowledge, no prior research has applied the EQ-5D in HHD.

Its worth noting, most patients regarded all five EQ-5D-5L dimensions as relevant to their skin conditions. The majority of the patients mentioned multiple HRQol areas related to the EQ-5D-5L and the two bolt-ons, such as pain, various forms of skin irritation (i.e.

itching, tightness and burning sensation), mobility, work-related problems or difficulties with self-confidence or self-esteem before completing both questionnaires. Although the EQ-5D-5L was generally viewed positively by patients, the addition of the two bolt-ons appeared to further enhance its content validity in this population, particularly as one-third of patients identified self-confidence as the most relevant aspect, followed by skin irritation mentioned by one-fifht of patients. Furthermore, only two missing aspects were noted by more than one patient, such as financial impact and sexual life after adding the two bolt-ons.

Comparing these findings with previous studies on psoriasis, AD, and chronic urticaria suggests that the EQ-5D-5L's comprehensiveness was suboptimal and it had limitations in those three conditions, however, it demonstrated acceptable content validity for DD and HHD, which was further enhanced by the addition of the bolt-ons [138, 139, 142]. Another important finding of our research is that self-confidence was even more relevant in our patient group, possibly due to the major mental burden caused by common symptoms like odor, oozing, which are less present in psoriasis, AD or chronic urticaria. All three earlier studies confirmed the relevance and comprehensibility of the two bolt-ons, however some conceptual overlap between the bolt-ons and the five core dimensions were noted, especially between skin irritation and pain/discomfort and between anxiety/depression and self-confidence. We found a similar overlap between skin irritation and pain/discomfort, but only in one case, compared to the multiple overlaps observed in psoriasis, AD and chronic urticaria bolt-ons [138, 139, 142]. Although this potential conceptual overlap may limit the application of these additional bolt-ons, as it could lead to double-reporting of certain problems, evidence indicates that this impacts only a minority of patients and varies across different skin conditions. To gain a deeper understanding of the extent and contributing factors of this overlap, as well as the variations among different skin conditions, further psychometric studies across various populations are needed. A small number of participants suggested refinements, such as modifying response levels or adjusting recall periods, but no strong patterns emerged. Implementing such changes could affect the comparability of the EQ-5D-5L across different conditions.

A limitation of this study was that all participants were recruited from a single center. Although DD and HHD usually affect both males and females equally, the sample was

dominated by female patients, reflecting the gender distribution at our clinic. At the start of each interview, patients were asked about HRQoL challenges related to their skin condition, which may have led to a stronger focus on skin symptoms when completing the EQ-5D-5L. We observed that some patients treated the instrument as more condition-specific, especially in EQ VAS. Additionally, during the interviews, many participants viewed self-confidence and self-esteem as synonyms. leading us to combine these concepts when presenting the impacts of DD and HHD on patients' lives. This issue may be specific to language or culture, requiring further attention in future qualitative research on the self-confidence bolt-on. In conclusion, our findings suggest that there is no actionable evidence indicating gaps in the content validity of the EQ-5D-5L with two bolt-ons in DD and HHD.

To conclude, our findings in study I may support the use of dermoscopy and standardized dermoscopic terminology in the management of various genodermatoses, while also underscoring the need to extend the current standardized dermoscopic terminology to encompass a broader range of rare inherited diseases. Study II may contribute to a better understanding of the skin microbiome and its potential role in the pathogenesis of DD. Targeting skin dysbiosis could represent a future therapeutic approach in the management of DD. Finally, results of study III may be promising for future quantitative testing, which aims to confirm the EQ-5D-5L's measurement performance, including its ability to differentiate across different disease severity groups and its responsiveness to changes in HRQoL. We believe these studies collectively contribute to a more holistic approach to genodermatoses, especially acantholytic skin fragility syndromes, such as DD and HHD, focusing facilitating the diagnostic process, potential treatment options and also on the patients' quality of life.

6. Conclusions

6.1. Study I.: To investigate the dermoscopic features in various genodermatoses by conducting a systematic review and comparing its results to our own findings.

- 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.
- 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 syndomre with multiple lentigines, monilethrix, palmoplantar keratodermas (punctate, diffuse epidermolytic), and tuberous sclerosis complex.
- 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.
- 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.
- 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.

6.2. Study II.: To investigate the clinical and genetical aspects of Darier disease patients, and to investigate the skin microbiome of two predilectional sebaceous sites in Darier disease patients and in healthy individuals.

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).

II/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.
- 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.
- Significant differences in alpha and beta diversity of DD patients' lesional and non-lesional skin were observed.
- 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.
- 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.
- Region specific alterations by the two examined predilectional regions could be observed in DD patients and in healthy individuals.
- A marked increase in *Staphylococcus* (e.g. *S. aureus, S. epidermidis*) abundance along with significant decrease in *Propionibacterium* and *Cutibacterium* abundance was detected in the inner epidermal layers of lesional skin compared to the superficial layers.

6.3. Study III.: To investigate the content validity (relevance, comprehensiveness and comprehensibility) of the EQ-5D-5L and skin irritation and self-confidence bolt-ons among patients with Darier disease and Hailey-Hailey disease.

- 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.
- Most patients considered both the EQ-5D-5L and the two bolt-ons comprehensible and relevant to their skin diseases.
- Some missing concepts were identified, but only two (financial impact and sex life) were identified by more than one patient.
- There is only very limited conceptual overlap between the skin irritation bolt-on and the pain/discomfort dimension.
- 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.

7. Summary

Despite significant advances in recent years in understanding the pathomechanism, diagnosis, and management of several genodermatoses, these conditions continue to pose considerable challenges for clinicians in many cases. In study I, we were the first to perform a systematic review and dermoscopic assessment of various genodermatoses using standardized dermoscopic terminologies. In accordance with previous recommendations, no new metaphoric terms were introduced. Our findings may support using dermoscopy and standardized terminology in managing genodermatoses, and highlight the need to expand this terminology to cover more rare inherited diseases. Study II investigates the skin microbiome in DD, a rare genodermatosis. Analysis of lesional, non-lesional skin samples from DD patients alongside samples from healthy controls revealed an altered microbial composition in DD, characterized by an overrepresentation of distinct *Staphylococcus* species and a reduction in the amount of *C. acnes* and *C. acnes subsp. def.* Notably, we observed an increase in the abundance of the *Staphylococcus* genus in deeper epidermal skin layers, suggesting that skin barrier disruption may facilitate bacterial penetration. These findings indicate that microbial dysbiosis may contribute to DD's pathogenesis and inflammation, underscoring the potential of microbiome-targeted therapeutic strategies. In study III, we evaluated the content validity of the EQ-5D-5L and skin irritation and self-confidence bolt-on dimensions in DD and HHD, two rare acantholytic genodermatoses. While all five core dimensions were considered relevant, the addition of the two bolt-ons appeared to further enhance its content validity. After adding the two bolt-ons, only two missing HRQoL areas were mentioned by more than one patient. A conceptual overlap between skin irritation and pain/discomfort core dimension was noted in only one instance. These findings suggest that there is no actionable evidence of gaps in the content validity of the EQ-5D-5L with skin irritation and self-confidence bolt-ons in DD and HHD. Future studies are encouraged to perform quantitative psychometric testing of these bolt-ons in this and other chronic dermatological patient populations

In conclusion, this study may promote a more integrated approach to the diagnosis, monitoring, and management of certain genodermatoses- particularly acantholytic skin fragility syndromes, such as DD and HHD-, by combining clinical, microbiological, and patient-reported outcome assessments.

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9. Bibliography of the candidate's publications

9.1. Publications directly related to this thesis

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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.

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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.

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9.3. Conference presentations and posters

D. Plázár, N. Kiss, S. Zakariás, P. Anker, K. Farkas, E. Kuroli, B. Mayer, M. Medvecz. Genotype-phenotype correlation study and analysis of dermoscopy features in Darier disease (poster) PhD Scientific Days, Budapest 2021

D. Plázár, N. Kiss, S. Zakariás, P. Anker, K. Farkas, Zs. Metyovinyi, E. Kuroli, B. Mayer, M. Medvecz. Multimodal aspects of two skin fragility syndromes – comparative study of Darier disease and Hailey-Hailey disease (poster) PhD Scientific Days, Budapest 2022

D. Plázár, Zs. Metyovinyi, F. Rencz, M. Medvecz. Az egészség és az életminőség fontos területei Darier és Hailey-Hailey betegségben [Important aspects of health and quality of life in Darier and Hailey-Hailey disease] (presentation) Hungarian Dermatological Society Annual Meeting, Siófok 2023

D. Plázár, A. Bánvölgyi, B. Mayer, M. Medvecz. Therapeutic dimensions of Hailey-Hailey disease (e-poster) EADV, Berlin 2023

D. Plázár, M. Medvecz, Új perspektívák az örökletes epidermolysis bullosa kezelésben [New perspectives in the treatment of hereditary epidermolysis bullosa]. (presentation) Hungarian Pediatric Dermatological Society Annual Meeting, Budapest 2023

D. Plázár, N. Kiss, B. Mayer, E. Ostorházi, M. Medvecz. Microbiome alterations in Darier disease (e-poster) 2th Word Congress on Rare Skin Diseases, Paris 2024

D. Plázár. Pszichiátriai zavarok előfordulása és életminőség örökletes bőrbetegségekben [The occurrence of psychiatric disorders and quality of life in hereditary skin diseases] (presentation) Pruritus and Psychodermatology Professional Day, Pécs 2024

D. Plázár, Zs. Metyovinyi, N. Kiss, A. Bánvölgyi, N. Makra, Zs. Dunai, B. Mayer, P. Holló, E. Ostorházi, M. Medvecz. Mikrobiom alteráció szerepe Darier betegségben [The role of microbiome alteration in Darier disease] (presentation) Hungarian Dermatological Society Annual Meeting, Budapest 2024

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