Plantar involvement correlates with obesity, pain and impaired mobility in epidermolysis bullosa simplex: a retrospective cohort study

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Abstract
Background  Epidermolysis bullosa simplex (EBS) is the most common type of EB, a group of rare genodermatoses. Affected individuals suffer from skin blistering and report a high disease burden. In some EBS subtypes, plantar keratoderma (PK) has been described.

Objectives  This study investigated the presence and correlation of PK with body mass index, pain and mobility in EBS.

Methods  Individuals (n = 157) with genetically characterized EBS were included in this retrospective cohort study, and clinical data were collected over 16 years (referral patients to the largest German EB centre). Descriptive statistics and mixed linear models were used to assess correlations.

Results  PK was found in 75.8% of patients beginning at a mean age of 4.3 years. Both focal and diffuse PK were observed, and 60% of adults with localized and severe EBS were preobese or obese, with ~30% of patients reporting severely reduced mobility. The presence of PK, especially diffuse PK, correlated significantly with local infections, obesity, pain and requirement of a wheelchair.

Conclusion  Along with treating skin fragility and blistering, PK should be considered a potential marker of increased morbidity and may represent a target of EBS therapy development.

Received: 8 January 2021; Accepted: 7 April 2021

Conflicts of interest
None.

Funding source
The project was funded by a promotional award issued by the German Foundation for Pediatric Dermatology (Deutsche Stiftung Kinderdermatologie e.V.) to ART and by a grant provided by DEBRA international to ART and CH. ART was supported by the Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg. Open access funding provided by the DEAL project.

Introduction
Epidermolysis bullosa simplex (EBS) is considered the mildest type of EB;1 however, the disease burden is high, even in localized forms.2 EBS is most commonly caused by mutations in keratin (KRT) 5 and KRT14, with rare subtypes arising from mutations in plectin (PLEC), kelch-like protein 24 (KLHL24), exophilin 5 (EXPH5) or bullous pemphigoid antigen 1 (BPAG1).3 While the exact number of people affected by EBS is unclear, figures from Scotland suggested a point prevalence of 28.6 per million.3 Given that people with EBS have trouble coping with everyday activities3,4 and can potentially be unable to work,2 EBS has considerable socioeconomic impact.

Blistering, inflammation and pain contribute to EBS disease burden. Pain is caused mainly by acute blisters, although neuropathic pain has also been described in localized EBS2 and in pachyonychia congenita (PC), another keratinopathy.5,6 Plantar keratoderma (PK) has been described in severe and intermediate EBS subtypes,7,8 but its prevalence, characteristics, and impact on pain and EBS natural history are unknown. Another distinct feature of EBS is obesity10; however, neither
the prevalence, onset, nor consequences of obesity in EBS have been characterized.

We hypothesized that PK represents a determining factor in EBS, contributing to significant local and systemic complications, such as pain and obesity. If true, targeting PK could be a therapeutic strategy for this yet incurable disease, thereby minimalizing the need for wheelchair use and job-related constraints. We tested this hypothesis by characterizing PK in different EBS subtypes and correlating PK with obesity, pain and underlying molecular defects in linear models in a well-characterized cohort from the main German EB centre.

Methods

Study population
This retrospective cohort study was performed in a referred sample of individuals with genetically confirmed EBS and presenting to the Epidermolysis bullosa Center Freiburg (Freiburg, Germany) over a period of 16 years (February 2003 to July 2019). EB subtypes were classified according to the latest EB consensus reclassification.1 Ethics approval was obtained (EK-Freiburg: #78/17).

Data collection
Data were collected during patient visits and retrieved from patient records. Information on palmoplantar hyperhidrosis (PH), skin care, use of analgesics, wheelchair use, education, profession, social participation and disability were obtained in semi-structured interviews. Pain was recorded on numeric rating scales (NRS; 0–10) and categorized as follows: ‘None’ (0), ‘Mild’ (1–3), ‘Moderate’ (4–7), ‘Severe’ (>8)11,12 and ‘Present, not quantified’ (pain was reported, but no NRS value was given). Pain in children, localization and quality of pain, and quality of life were not systematically assessed. No records of individual nutritional habits or parental BMI were available. Classification of PK types was performed from clinical photographs and descriptions.

Laboratory analyses
Mutation analysis was performed using Sanger sequencing before 2016 and for targeted testing for known familial mutations.13 As of 2016, next-generation sequencing panel diagnostics were applied.14 When skin biopsies of feet had been obtained for diagnostic purposes, haematoxylin-eosin stained sections were assessed for the presence of blisters, hyperkeratosis and inflammation.

Statistical analysis
The data set included continuous (e.g. age and BMI) and categorical variables (e.g. PK, pain and job status). Descriptive statistics were computed in R15 using the tableone package.16 For patients presenting repeatedly, measurements were aggregated at patient level. For continuous variables, average and maximum values are reported, whereas for categorical variables, either lifetime occurrence (binary categorical variables, such as presence of PK) or the most frequently observed answer (variables with more than two categories, such as level of pain) was considered.

Correlations between continuous and categorical variables were analysed with mixed linear models, and correlations between categorical variables with mixed log-linear models, using the lme4 package17 in R.15 A random intercept for the individual patient was employed to account for repeated measurements per patient. Fixed-effects models were employed for variables without repeated measurements. Z-tests were employed to assess the significance of a variable, with significance established at P = 0.05. All analyses were performed by a statistician (MH).

Results

Characteristics of the patient cohort
The study included 157 patients, of which 147 had autosomal dominant EBS subtypes: 75 localized, 39 severe (previously called generalized severe), and 11 intermediate (previously called generalized intermediate), eight with mottled pigmentation, seven intermediate with cardiomyopathy, six intermediate due to abnormal plectin (previously called EBS Ogna), and one with circinate erythema. Seven patients had nonsyndromic forms of autosomal recessive EBS and three EBS with muscular dystrophy (Table 1). The mean age at presentation was 19.0 ± 18.0 years, and 77 patients were adults (>16 years). Patients with severe EBS presented earlier (age: 11.5 ± 14.8 years) than those with localized EBS (average age: 25.1 ± 18.5 years; Table 1). Eighty-one were single and 76 were familial cases.

Genetic findings
Mutations in KRT14 (43.9%) and KRT5 (43.9%) were the most common causes of EBS, followed by PLEC (6.4%), KLHL24 (4.5%), EXPH5 (0.6%) and DST (0.6%) (Table 1 and Table S1). To the best of our knowledge, 16 variants have not been reported previously; all were predicted as disease-causing (Mutation Taster scores > 0.9) and have not been reported in the Genome Aggregation Database.

PK and genotype correlations
Across all EBS subtypes, 75.8% (n = 119) of patients suffered from PK. Infants mainly showed plantar blisters and no PK, with the mean age of PK onset at 4.3 years (range: 0.8–12.0 years). Biopsies of hands and feet were available for 31 patients and obtained at a mean age of 18.7 years (range: 0–55 years). In children <2 years of age, blisters accompanied by inflammatory infiltrates were the dominant histopathologic finding (63.6%). Hyperkeratosis was observed in 36.4% of patients, although these children did not clinically show PK. After the age of 6 years,
### Table 1 Molecular and clinical characteristics of the EBS patient cohort

| Variable                          | EBS total | EBS localized | EBS severe | EBS intermediate | EBS circinate erythema | EBS mottled pigmentation | EBS muscular dystrophy | EBS intermediate with cardiomyopathy | EBS intermediate autosomal recessive |
|-----------------------------------|-----------|---------------|------------|------------------|------------------------|--------------------------|-------------------------|-------------------------------------|-------------------------------------|
| N(%) of cohort                    | 157       | 75 (47.8)     | 39 (24.8)  | 11 (7.0)         | 1 (0.6)                | 8 (5.1)                  | 3 (1.9)                 | 6 (3.8)                            | 7 (4.5)                             |
| Female sex (%)                    | 82 (52.2) | 35 (46.7)     | 27 (69.2)  | 6 (54.5)         | 1 (100.0)              | 3 (37.5)                 | 1 (33.3)                | 2 (33.3)                           | 5 (71.4)                            |
| Mean age (SD)                     | 19.0 (18.0)| 25.1 (18.5)   | 11.5 (14.8)| 14.9 (21.8)      | 4.3 (NA)               | 6.14 (10.6)              | 17.9 (13.2)             | 30.9 (15.0)                       | 14.5 (16.3)                         |
| Nof adults (<16 years)            | 77        | 46             | 12         | 3                | 0                      | 1                        | 2                       | 6                                   | 3                                   |
| Gene (%)                          |           |               |            |                  |                        |                          |                         |                                     |                                     |
| DST                               | 1 (0.6)   |               |            |                  |                        |                          |                         |                                     | 1 (14.3)                           |
| EXPH5                             | 1 (0.6)   |               |            |                  |                        |                          |                         |                                     | 1 (14.3)                           |
| KLHL24                            | 7 (4.5)   |               |            |                  |                        |                          |                         | 7 (100.0)                          |                                     |
| KRT14                             | 69 (43.9)| 36 (48.0)     | 23 (59.0)  | 6 (54.5)         |                        |                          |                         |                                     | 4 (57.1)                           |
| KRT5                              | 69 (43.9)| 39 (52.0)     | 16 (41.0)  | 5 (45.8)         | 1 (100.0)              | 8 (100.0)                |                         |                                     |                                     |
| PLEC                              | 10 (6.4)  |               |            |                  |                        | 3 (100.0)                | 6 (100.0)               |                                     | 1 (14.3)                           |

**PK-associated local complications**

| Occurrence of PK during lifetime (%) | 119 (75.8)| 52 (69.3) | 33 (84.6) | 9 (81.8) | 1 (100.0) | 5 (62.5) | 2 (66.7) | 6 (100.0) | 4 (57.1) | 7 (100.0) |
|-------------------------------------|-----------|-----------|-----------|----------|-----------|----------|----------|-----------|----------|-----------|

| PK pattern                        | Absent    | Focal     | Diffuse   | Bacterial plantar infections in lifetime (%) | 22 (14.0) | 3 (4.0) | 9 (23.1) | 4 (36.4) | 1 (100.0) | 2 (66.7) | 1 (16.7) | 2 (28.6) |
|------------------------------------|-----------|-----------|-----------|---------------------------------------------|-----------|---------|---------|---------|-----------|----------|---------|----------|

| Palmoplantar hyperhidrosis in lifetime (%) | 65 (41.4)| 37 (49.3) | 14 (35.9) | 4 (36.4) | 1 (100.0) | 3 (37.5) | 1 (33.3) | 3 (50.0) | 2 (28.6) |

**Weight**

| Underweight (BMI <18.5 kg/m², %) | 67 (42.7)| 22 (29.3) | 21 (53.8) | 7 (36.3) | 1 (100.0) | 5 (62.5) | 2 (66.7) | 1 (16.7) | 4 (57.1) | 4 (57.1) |
|---------------------------------|-----------|-----------|-----------|----------|-----------|----------|----------|----------|----------|----------|

| Normal weight (BMI 18.5-24.9 kg/m², %) | 40 (25.5)| 22 (29.3) | 8 (20.5) | 3 (27.3) | 1 (12.5) | 1 (33.3) | 1 (16.7) | 3 (42.9) | 1 (14.3) |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

| Preobesity (25.0-29.9 kg/m², %)       | 21 (13.4)| 15 (20.0) | 3 (7.7)  | 1 (9.1)  | 1 (12.5) | 1 (16.7) | 1 (25.0) |           |           |           |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

| Obesity (BMI >30 kg/m², %)            | 19 (18.5)| 13 (17.3) | 4 (10.3) |            |            |          |          |          |          | 2 (28.6) |
|---------------------------------------|-----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|

**Pain**

| Mild (NRS <4, %†)                     | 5 (3.2)  | 2 (4.3)  | 1 (2.9)  |           | 1 (100.0) | 1 (20.0) |          |          |          |          |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

| Moderate (NRS 4-8, %†)                | 18 (11.5)| 9 (19.6) | 5 (14.7) | 2 (20.0) |           | 1 (20.0) |          |          |          | 1 (50.0) |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

| Severe (NRS 8-10, %)                  | 20 (12.7)| 14 (30.4) | 2 (5.9)  | 1 (10.0) |            |          |          |          |          | 3 (75.0) |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

| Present, not quantified (%†)         | 36 (22.9)| 8 (17.4) | 17 (48.6) | 6 (60.0) | 1 (20.0)  |          |          |          |          | 1 (25.0) |
|---------------------------------------|-----------|-----------|----------|----------|-----------|----------|----------|----------|----------|----------|

**Impact on mobility and working capability**

| Requirement of a wheelchair (%)      | 13 (8.3) | 3 (4.0)  | 7 (17.9) | 1 (9.1)  |          |          | 2 (66.7) |          |          |          |
|--------------------------------------|-----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|

| Occupational disability (%)          | 14 (18.1)| 6 (13.0) | 5 (41.6) |          | 2 (100.0) |          |          |          | 1 (25.0) |
|--------------------------------------|-----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|

Abbreviations: BMI: body mass index, EBS: Epidermolysis bullosa simplex, PK: plantar keratoderma, NRS: numeric rating scale.

The following previously unreported mutations were found in KRT14: c.380C>A; p.A127D; c.980T>C; p.M327T; c.413_415delAGG; p.E138del; c.1232A>G, p.E411G; c.1113_1114del, p.Q327Dfs*110; c.1256T>C, p.L419R; c.1153_1116del, p.A385Rfs*93, in KRT5: c.523C>G; p.L175V; c.927+2T>C, c.1219-1G>C; c.1402G>C, p.A468P; c.997C>A; p.L333M; c.1396G>C, p.E466Q; c.1409dup, p.Y470* and in PLEC: c.8570A>G, p.Y2857C; c.11794G>A, p.E3932K.

†Percentages refer to the subset of patients for whom pain data was available.

‡Percentage of individuals in occupational disability refer to adults (<16 years) within the cohort.
90.0% of patient samples showed moderate-to-pronounced hyperkeratosis, with 65.0% of these accompanied by mild inflammatory infiltrate and 55.0% by acanthosis.

Although the majority of patients with EBS caused by KRT5 and KRT14 mutations presented PK, it was more common in patients carrying KRT5 (78.3%) rather than KRT14 (63.8%) mutations ($P = 0.063$). Phenotype analysis of PK distinguished five patterns: focal, focal at sites of mechanical pressure, progressive from focal to diffuse, diffuse, and diffuse with striate aspect and scleroderma-like fingers (Fig. 1, Table 1). Focal PK unassociated with mechanical pressure sites was predominantly observed in patients with PLEC mutations (Fig. 1). Focal PK located at areas of mechanical pressure was the most common type among all EBS subtypes. In a subgroup of seven patients (10.6%) with localized EBS, this PK subtype progressed over the soles into a diffuse pattern. Diffuse PK was mainly a feature of severe and intermediate EBS. We observed a particular genotype-phenotype correlation in a subset of six patients with severe EBS who showed diffuse PK with striate aspect and scleroderma-like fingers. Patients with this phenotype carried mutations in either helix-initiation or -termination peptides in KRT5 [amino acid positions 176–181 ($n = 2$), 477 ($n = 2$), and 468 ($n = 1$)] or in a helix-initiation peptide in KRT14 [amino acid position 123 ($n = 1$)], respectively. All these patients showed palmar keratoderma, whereas in other EBS subtypes, this was seen only in relation to recurrent mechanical stress.

For further statistical analyses, PK subtypes were grouped into focal (including ‘focal’ and ‘focal at sites of mechanical pressure’) and diffuse (including ‘progressive from focal to diffuse’, ‘diffuse’, and ‘diffuse with striate aspect and scleroderma-like fingers’).

**Local PK-related complications**

PH was present in 41.4% ($n = 65$) of patients and especially common in the localized subtype ($n = 37; 49.3%$; Table 1). PH correlated strongly and significantly with the presence of PK.

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**Figure 1** Different types of plantar keratoderma (PK) observed in epidermolysis bullosa simplex (EBS) in infants, children and adults. Left: Focal PK; Middle-left: focal PK at distinct sites of mechanical pressure, predominantly over metatarsal and heels; Middle: PK progressing from focal-mechanical type to diffuse; and Middle-right: Diffuse PK. In all these types, the palms were only affected in cases of regular mechanical stress and, if so, showed calluses on pressure sites. Right: Diffuse PK showing striate features on both palms and soles. The fingers of those patients were pointed and scleroderma-like (arrows). This phenotype was unique to patients with severe EBS. Abbreviations: m: male; f: female; int: EBS intermediate; loc: EBS localized; sev: EBS severe; mus. dystr.: EBS with muscular dystrophy.
but was never reported by patients carrying KLHL24 mutations.

Infections of the feet were a common complication, with bacterial foot infections arising in 22 patients (14.0%), more commonly in severe and intermediate EBS (26.0%) than localized EBS (4.0%; \( P < 0.005 \)), and mostly caused by *Staphylococcus aureus*. Twelve patients had mycotic infections which more often accompanied severe (\( n = 7; 17.9\% \)) rather than localized EBS (\( n = 4, 5.3\%; P = 0.336 \)). Mycotic infections significantly correlated with the presence of diffuse PK (\( P = 0.014 \)) and were mainly caused by *Trichophyton rubrum*. One patient developed squamous cell carcinoma of the foot.\(^{18} \)

**Natural history of weight associated with EBS**

Irrespective of EBS subtype, 86.5% of children <10 years of age were underweight (BMI \(< 18.5 \text{ kg/m}^2\)). By contrast, 32% of adults (>16 years) with localized EBS were preobese (BMI: 25–30 kg/m²), and 30% were obese (BMI >30 kg/m²), and 22% of those with severe EBS were preobese and 44% obese (Fig. 2, based on data available for 52/58 adults). These percentages were higher than the rates of obesity and preobesity within the German population in 2017 (16.3% and 36.4%; Federal Statistical Office, www.destatis.de). The shift from underweight or normal weight to preobese and obesity occurred earlier in severe EBS (age: 10–16 years) as compared with localized EBS (age: >16 years) (Fig. 2). In adults of all EBS subtypes, the presence of PK was associated with higher BMI [significant for diffuse PK (\( P = 0.017 \)) but not for focal PK (\( P = 0.303 \))] (Fig. 2).

**Pain associated with EBS**

Pain occurred in all EBS subtypes but was most common and severe in localized and severe EBS (Table 1). Seventy-five percent of patients with PK reported pain (significant correlations for both diffuse and focal PK: \( P < 0.001 \) and \( P < 0.005 \), respectively), with blisters occurring underneath PK reported as the most painful, and of those without PK, only 13.3% reported pain. Analgesics were used by 24 patients (23 taking nonsteroidal anti-inflammatory drugs and 1 opioids), and one used promethazine as a pain modulator. Although analgesics were mostly taken by those experiencing moderate or severe pain, only 35.0% of patients with severe pain and 33.3% with moderate pain used analgesics.

**Impact of EBS on mobility and working life**

Walking capability was severely reduced in 33.1% of patients, with blister-free walking distances of <600 m (<0.4 miles) or even fewer during the summer months. Wheelchairs were occasionally or permanently required by 8.3% of patients (mean age: 24.5 years, range: 1.8–57.5 years; Table 1), with the need for a wheelchair significantly more common when PK was present (\( P = 0.036 \)), especially diffuse PK (\( P = 0.001 \); for focal PK \( P = 0.285 \)). Patients with PK that used a wheelchair had higher BMI than those with PK and not using a wheelchair (mean values: 25.9 vs. 21.1 kg/m²; \( P = 0.165 \)). Additionally, parents frequently reported that their EBS-affected children walked later and required strollers longer than did healthy siblings.
Fourteen of 38 patients for whom information was available were incapable of working (18.1% of adults in the cohort, Table 1). Moreover, six patients (7.8% of adults) reported a need to undergo occupational retraining, with five changing from occupations causing mechanical stress (e.g. carpenter, toolmaker, cook and nurse) to those requiring physically less strenuous work.

Discussion
The soles of the feet account for only 2% of our body surface but carry all the body weight and are thus essential for everyday activities. In EBS, feet are predominantly affected by blistering, and PK afflicted 75.8% of patients within our cohort. Although PK was previously reported primarily in severe EBS,\textsuperscript{7-9} we showed that it occurs in all subtypes and has tremendous impact, especially in localized EBS, a presumably ‘mild’ EB subtype. Due to significant correlations between the presence of PK and foot infections, PH, obesity and wheelchair requirement, we hypothesize that PK plays a key role in EBS natural history and disease burden and visualize this as a vicious cycle of pain, physical inactivity and excessive weight gain (Fig. 3).

In our cohort, PK arose at a mean age of 4.3 years, comparable with PC.\textsuperscript{19,20} We found clear genotype–phenotype correlations between EBS caused by \textit{PLEC} mutations and focal PK and between certain \textit{KRT5/14} mutations and diffuse PK with striate aspects and scleroderma-like fingers. Overall, diffuse PK was most frequently associated with complications, such as infections, obesity, and pain and occurred either primarily or evolved from focal PK on pressure points, suggesting that foot shape, physical exercise and body weight also influence PK patterns. Treating PK should be a focus in EBS care and should include regular check-ups by podiatrists.\textsuperscript{21}

Because PK is a common finding in obesity\textsuperscript{22,23}, caused by higher plantar pressures,\textsuperscript{24-26} obesity will likely aggravate PK in

\textbf{Figure 3} The cycle of epidermolysis bullosa simplex (EBS) natural history. Blisters and keratoderma develop on mechanically stressed areas (mainly the soles of feet). These lesions are painful and require the patient to rest and avoid physical activity. As a consequence, body weight and body mass index (BMI) increase. Higher body weight leads to increased pressure on the feet, which subsequently increases the formation of blisters and plantar keratoderma. This results in increased pain, inactivity, and BMI, often in combination with palmpiantar hyperhidrosis. A considerable number of patients (8.3% within our cohort) might require a wheelchair.

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We demonstrated a high prevalence of obesity in EBS and its onset in early adolescence. Moreover, weight gain might further be influenced by psychological aspects, such as social isolation and depression, possibly leading to overeating as a response mechanism. Due to its retrospective character, this study has limitations with regard to dietary habits, screening of insulin resistance, family history of obesity and psychological assessment; therefore, future studies should consider these aspects. Furthermore, infants with severe EBS are lighter and struggle to gain weight, likely because of higher nutritional demands due to generalized blistering. In adulthood, no additional nutrients are required as blistering concentrates on the feet and mobility is reduced. This shift in energetic balance requires careful management and timely intervention, ideally by involving a nutritionist in the medical team on a regular basis.

Pain is frequent in EBS and was observed in both our and other cohorts; however, selection bias is likely (i.e. patients experiencing more pain more frequently ask for medical care). Pain experienced in EBS is supposedly primarily nociceptive, caused by a combination of blisters, inflammation, oedema and mechanical stress. Although the pain assessment in our cohort was limited with regard to precise localization of pain and its character, neuropathic pain has previously been described in both localized EBS and PC. The low rates of EBS patients using analgesics in both our and previous studies could be explained by insufficient effects of conventional analgesics on neuropathic pain. Restricted blood circulation in hyperkeratotic areas might further reduce the efficacy of analgesics. Furthermore, patients may have found strategies other than drug intake to reduce pain, for example by releasing pressure through soft shoe inserts or special dressings, by reducing PK through podologic treatment, or, less desirable, by avoiding to walk.

The mobility of the patients in our cohort was strongly impaired. Future studies should quantify walking distances using objective measures, such as those from pedometers. The 8.3% wheelchair requirement in our cohort was much higher than that reported previously (0.3% of all EBS and 2.1–2.7% of severe EBS patients according to the American National EB Registry), highlighting the extent of disability potentially caused by EBS. The higher rate of wheelchair use could partly relate to the German healthcare system, which is comparably generous with regard to coverage of medical aids. Additionally, working life was severely impaired, as we noted permanent occupational disability in 18.1% of adults, which is in line with previous studies reporting occasional sick leave and unemployment in 35% and 10% of cohorts, respectively. Moreover, for PC, >70% patients report considerable effects on everyday life. Although a selection bias is possible, these findings emphasize the socioeconomic impact of EBS and other keratinopathies. The working history of the patients in our cohort that underwent occupational retraining prompted us to provide early counselling on occupational choice for people with skin fragility.

In conclusion, we showed that plantar involvement and PK are serious complications of all EBS subtypes that correlated with obesity, pain, and impaired mobility, as well as adversely affected working life. We suggest that these aspects influence each other in a vicious cycle that requires timely interruption. By treating PK, reducing pain, and avoiding overweight through regular and interdisciplinary consultations, the quality of life of people with EBS can potentially be increased. Although early targeting of plantar blistering and PK might represent a potential therapeutic strategy, effective therapy options remain to be elucidated. Furthermore, despite likely underdiagnosis of patients affected by EBS, the challenges faced in everyday life should not remain underestimated.

Acknowledgments

We acknowledge the work of our fellow physicians involved in patient care in the Epidermolysis bullosa Center Freiburg. Additionally, we thank the laboratory staff of our department for their excellent work in diagnostics. From 2003–2016, analyses were performed by CH in cooperation with Jürgen Kohlhase, Synlab Freiburg, Julia Kopp at the Institute of Human Genetics, University of Freiburg, was involved in genetic sequencing and analysis from 2016 onwards. The patients in this manuscript have given written informed consent to publication of their case details.

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Supporting information
Additional Supporting Information may be found in the online version of this article:
Table S1. Novel and recurrent mutations associated with EBS in this study.