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Invited Article

Epidermolysis bullosa House Austria as a role model for the care of a rare disease

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The evolution of the Epidermolysis bullosa (EB) House Austria in Salzburg has demonstrated from its beginning in 2005 in an exceptional way the establishment of an optimized health care for a hitherto neglected group of patients, suffering from a rare but devastating skin disease: Epidermolysis bullosa. Patients with this hereditary mechanobullous skin disease, characterized by a heterogenous clinical course, multisystemic manifestations and increased morbidity and mortality, find in the EB House Austria a multidisciplinary, medical and psychosocial, family-centered support, optimally customized to this condition and individualized to each patient. Its unique structure of four divisions (Outpatient Unit, Research Laboratory, Academy, Clinical Research and Study Center) has set the basis for the delivery of best medical practice and state-of-the-art care as well as the establishment/performance of high quality and patient centered research and translational medicine. Initially the (ongoing) close collaboration with the powerful patient group and medical research charity "DEBRA Austria" that is dedicated to a multidimensional support of EB patients and their relatives living in Austria and neighboring countries, has enabled the construction of the EB House Austria. The acknowledgement of this institution as a successful model has been officially obtained in 2017 by its designation as a national Center of Expertise for Genodermatoses with special focus on EB and its inclusion into the European Reference Network (ERN) for Rare Skin Disorders in September 2018. Therefore, the history of the EB house is worth reviewing since it can be regarded as a role model for the care of other rare and multisystemic diseases.

Key words: epidermolysis bullosa, rare disease, genodermatoses, DEBRA, multidisciplinary support

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Epidermolysis bullosa (EB) encompasses a group of rare hereditary mechanobullous diseases, characterized by increased skin (and mucous membrane) fragility, as well as prototypic, mechanically inducible blistering. Clinical and genetic features are broadly heterogeneous and include various extracutaneous manifestations, making EB a multi-system disease marked by significant morbidity and mortality [1].

As in (mono)genetic disorders, disease-causing mutations in 20 different genes, encoding for proteins maintaining intra-epidermal cohesion and dermo-epidermal adhesion of skin and mucous membranes, account for the genetic heterogeneity of EB. The main subtype is determined by the level of cleavage, which can occur intra-epidermally (EB simplex), junctionally in the lamina lucida (junctional EB), through dermolysis below the lamina densa (dystrophic EB) or be mixed (Kindler Syndrome). Those four major subtypes are further divided into a total number of 30 sub-entities by discriminating geno- and phenotypical features (Fig. 1) [2].

Symptoms and degrees of severity vary broadly. Some patients show following traumatic exposures mild, limited blistering beginning in adolescence on predilection sites, such as hands and feet. Others face extensive, generalized and even (early) fatal involvement with seemingly spontaneous blistering of

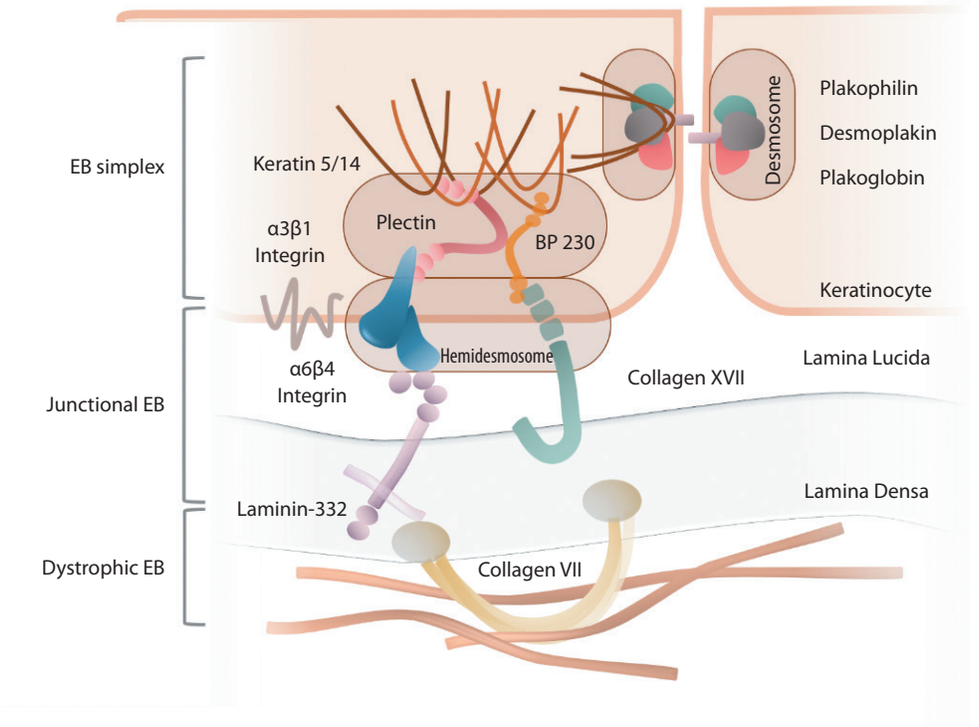

Fig. 1. Schematic representation of the dermo-epidermal junction zone. Mutations in structural components (selection shown) of hemidesmosomes, desmosomes, intermediate filaments, actin microfilaments, focal contacts and cell vesicle transport underlie epidermolysis bullosa (EB)

the skin and mucous membranes already at birth. Secondary sequelae like chronic ulcerations, inflammation, scarring and fibrosis are common, especially in dermolytic subtypes, where additional serious complications such as strictures, stenoses and pseudosyndactyly cause a tremendous reduction of quality of life. For severe forms (junctional EB generalized severe, recessive dystrophic EB), the risk of (early) death is strikingly increased, due to malnutrition, failure to thrive, infections, organ failure and later on an aggressive form of squamous cell carcinoma of the skin (Fig. 2) [3–5].

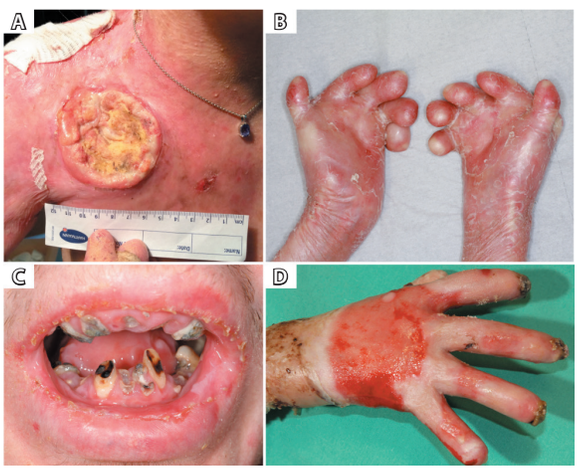

Fig. 2. Complications in patients with recessive dystrophic epidermolysis bullosa; **A** Aggressive squamous cell carcinoma of the skin on the thorax; **B** Pseudosyndactyly; **C** Rampant dental caries, oral erosions; **D** Chronic wounds and erosions, denuded skin

A characteristic finding in several EB patients (various types) are the so-called EB naevi, typically showing clinical (e.g. rapid growth, irregular borders, multiple colors) and dermatoscopical features of atypical or malignant melanocytic proliferations. They commonly arise in the areas of previous blistering. Although these exceptional melanocytic lesions are rarely associated with melanoma, a clinical follow up with histopathological evaluation of highly suspicious lesions is mandatory (Fig. 3) [2, 6, 7].

As no specific therapy for EB exists, current treatment is still largely supportive and mainly relies on symptomatic (wound) therapies, control of infection, nutritional supplementation and prevention, as well as management of complications [3, 8]. Therapeutic interventions and care for EB patients, but also patients with other rare diseases, have to be individualized, considering multiple factors like age, disease severity, complications and patient concerns.

Diagnosis

Cutaneous blistering in newborns and children is associated with a long list of differential diagnoses, including infectious, traumatic, autoimmune or hematologic causes [9]. After ruling them out, a clinical suspicion for EB in a newborn should lead to the determination of the level of split formation as the first diagnostic step. This is usually achieved by routine histopathology (intra-epidermal versus sub-epidermal cleavage), immunofluorescence antigen mapping and/or transmission electron microscopy (today largely obsolete) after performing a perilesional biopsy of a fresh blister (mostly induced by the trauma of the biopsy) [10]. Immunofluorescence mapping of antigenic determinants within the dermal-epidermal junction has been introduced in the 1980s at the Department of Dermatology in Innsbruck as a new methodology that paved the way for a rapid, simple to perform and accurate diagnosis of mechanobullous diseases (until then based on the time consuming electron microscopy). It allows for an accurate detection of the level of split formation, thus permitting to discern between the four major subtypes of EB [11, 12].

The relative protein content can then be visualized through immunofluorescence staining with a panel of specific (mostly monoclonal) antibodies directed against structural proteins of the epidermis or components of the dermo-epidermal junction. In addition, whenever possible, molecular analysis focusing on candidate genes, selected by immunofluorescence mapping, should be performed to identify the causative mutation. Finally, the patient's family history may suggest the mode of inheritance, which poses a precondition for subsequent prenatal and preimplantation diagnostics [5, 9, 13, 14].

DEBRA Austria

Packed with specific experiences in research of blistering skin diseases, as well as management of patients with autoimmune and hereditary bullous diseases, obtained in Innsbruck and abroad, Prof. Helmut Hintner has been recruited as the Chairman of the Department of Dermatology, General Hospital Salzburg in 1992. Together with the biologist Gabriele Pohla-Gubo, PhD, he established a research laboratory in Salzburg, with the focus on immunology and blistering skin diseases.

Thus, from the early 1990s on, more and more patients with EB have been seen/diagnosed in Salzburg, frequently after years of diagnostic uncertainty (a general feature of rare diseases). Regularly follow-up visits of a growing number of EB patients soon obviated the unmet need for an organized

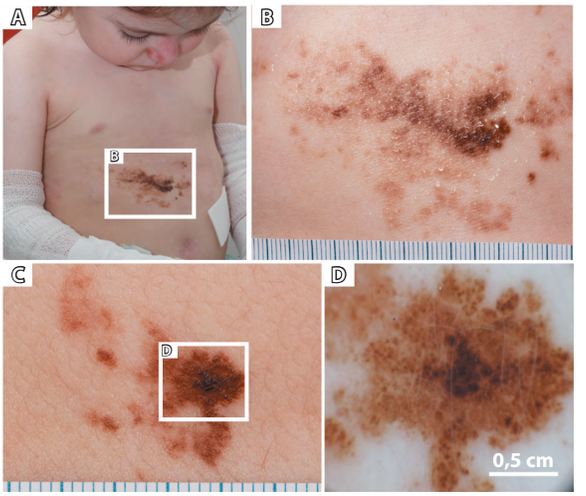

Fig. 3. Epidermolysis bullosa (EB) naevi. **A** An EB naevus in a 3-year-old child with recessive dystrophic EB. **B** Close up of naevus in (A). **C** EB naevus in a junctional EB patient. **D** Dermatoscopic image of (C).

management and adequate care of these patients. This was the time, when the idea to establish a patient group similar to the outstanding example of the "parent institution" DEBRA UK (since 1978), was born in Salzburg. In 1995, a group of patients and their families founded together with physicians and caregivers the patient group, as well as the medical research charity "DEBRA Austria". This institution is fully dedicated to a multidimensional support of patients and relatives living with EB in Austria and neighboring countries. To name a few services, it provides a platform for exchange of experiences, offers generous assistance that includes dealing with regulative affairs and financial support for dressings and it promotes an improved and more efficient healthcare by establishing a network of specialists and distributing knowledge.

DEBRA Austria started numerous initiatives, fund raising and publicity campaigns. Simultaneously experienced physicians, researchers and caregivers at the Department of Dermatology in Salzburg have formed a multidisciplinary team to centralize as well as individualize the demanding EB care. Together, as soon as enough money has been collected (with financial support from private donors and partly also from public sources), they built the world's first EB special clinic on the grounds of the General Hospital in Salzburg, opened in 2005 to the immense delight of patients, relatives and caregivers as an interdisciplinary clinical unit for diagnosis, medical care, academic affairs and research related to EB [15].

The non-profit organization DEBRA Austria has been supporting EB-related research activities in

Austria from the beginning, based on the funds derived solely from donations. In some areas of sponsored research, therapeutic strategies developed through basic research have now reached the clinical study phases, reflecting a huge success, since translation of research into treatments for patients is a long process and bottleneck. It requires profound knowledge (regulators, patents, orphan drug designation), intense collaboration (with researchers and industry), funding and preclinical as well as clinical studies (www.debra-austria.org).

Research focuses in the EB field are currently broadly scattered, due to rapid advances in scientific knowledge and developments in technology, and range from protein- and cell-based therapy via bone marrow transplantation to gene therapy. To deal with the massive amount of new data and the "velocity" of research progresses, it has become even more necessary to further coordinate and centralize research, on the national, as well as international, level. To achieve that, DEBRA UK / DEBRA International have installed a Medical and Scientific Advisory Panel (MSAP), whose members are experts in the field of EB and biological research. Through a centralized "peer review process", research grant applications are evaluated and, in case of a positive assessment, financially supported [16].

EB House Austria

The EB House Austria poses one outstanding example of a Center of Expertise (CE) in the European Union (EU), dedicated to the multidisciplinary support of patients with EB and their families and devoted to the principles of best medical practice and state-of-the-art care (www.eb-haus.eu) [16]. The evolution of this facility is worth reviewing since it can be regarded as a role model for the care of other (rare) multisystemic diseases.

In the last decade, EU has acknowledged the very high added value of cooperative actions at national and international levels in the management of rare diseases, generally characterized by great heterogeneity, limited number of patients, scarcity of relevant knowledge and expertise, as well as enormous costs. Although rare, the cumulative number of patients with a rare disease is high, evident by considering for instance the existence of more than 560 rare skin diseases [17]. Therefore, the EU Committee of Experts on Rare Disease (EUCERD) has introduced an overall community strategy to support member states to integrate national actions and initiatives into comprehensive intersectoral national action plans, e.g. by implementing reference centers (CE) or CE clusters at the national level as well as into transnational European reference networks (ERN) for rare diseases. Since CEs are thought to provide expert structures at highest standards, the access and equity to efficient prevention, diagnosis, treatment, care, and research for patients suffering from a rare disease throughout the EU should be facilitated [18–21].

The EB House Austria has been designated in 2017 as a CE for Genodermatoses with special focus on EB in the course of the Austrian National Action Plan for Rare Diseases (NAP.se) and has become a part of the ERN for Rare Skin Disorders since September 2018. Located in the center of Europe, it is committed to the principles of equality, solidarity, and universality, implying that patients from all EU member states (cross border health care directive [22]) and worldwide are invited to profit from its various services. Its basic principles are expert consultation according to international standards, adherence to clinical practice guidelines, implementation of outcome measures and independent quality validation as well as demonstration of a multidisciplinary approach of care. Especially the documentation of knowledge by means of guidelines, standard operating procedures, manuals a.s.o., and the establishment and continuous measurement of goals ensures a permanent control of performance, thereby implementing permanent improvements [23].

An essential component for the successful establishment of the EB House Austria is its unique structure, based on operations via three distinct, but closely interacting divisions. A fourth division, of clinical research and clinical study center, was added in 2017 (Fig. 4).

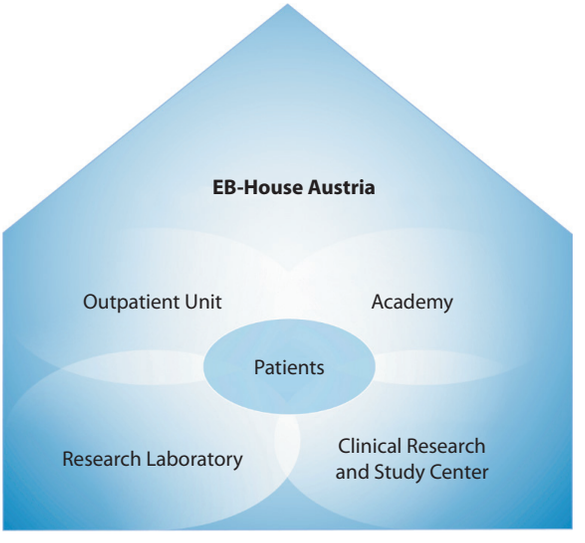

Fig. 4. Structure of the Epidermolysis Bullosa (EB) House Austria with its four closely collaborating divisions. The interaction with patients is central to all subunits

EB Outpatient Unit (head: Anja Diem, MD)

In the EB outpatient unit, the state of the art medical care is ensured by specially trained and experienced medical personnel including 2 EB physicians, 2 EB nurses and further 15 EB experts in nearly all disciplines of medicine, who are mainly consulted on demand. Routine visits, visits on request and grand rounds, as well as teledermatology, accessibility on call and emergency care day and night are all available to patients. A multidisciplinary management concentrated on a single location has the highest priority and is exerted through the implementation of recommendations and decisions made at expert round tables (rare diseases boards), as well as through performing individualized care in a convenient way for outpatients (all necessary investigations on one day in a week) and time-efficiently, if surgeries are necessary (all in one). Continuous internal quality assessment has been set up as a basic principle and allows the patients' access to the newest clinical studies, e.g. with orphan drugs. Expert experiences and knowledge are continuously being critically reviewed, updated, and libraried. For example, in 2009, Jo-David Fine and Helmut Hintner summarized for example their experiences and collected information and practical treatment guidelines on the disease in the book "Life with Epidermolysis Bullosa: Etiology, Diagnosis, Multidisciplinary Care, and Therapy", which is based on evidence-based data derived from large patient cohorts in Austria and from the American EB Registry [1]. Another comprehensive updated review on the local EB experience was recently published online in collaboration with international partners and is available in several languages (www.eb-handbuch.org).

EB Research Laboratory (head: Julia Reichelt, PhD)

The EB research laboratory has grown since it was founded in 2005 to around 30 scientists trained in molecular biology, immunology, and cancer biology. It is subdivided into closely collaborating research groups, currently focussing on (molecular) diagnostics, issues of basic research (e.g. carcinogenesis in EB) and establishment and advancement of therapeutic techniques, driven by the ultimate goal to develop a curative (molecular) therapy for EB. The scientific spirit is uniquely influenced by the closeness to the patients and the communication possibilities with caregivers due to the EB House structure. Collaborations with several international laboratories complement the fields of expertise, foster exchange of biotechnological know-how, realization and accessibility of infrastructural core units, as well as competitive consortial funding.

Currently, one of the most important collaboration is that with Prof. Michele De Luca, Modena, Italy. It has resulted in the development of a combined *ex vivo* gene/stem cell therapy for junctional EB [24]. This was recently successfully applied in two further patients, with the subtype LAMB3-deficient junctional EB, receiving transplants of epidermal sheets generated from genetically corrected (using a murine leukemia virus-based vector) autologous epidermal cultures with epidermal stem cells. Thereby the researchers succeeded in demonstrating that local transplantation of transgenic epidermal sheets can generate a fully differentiated and functional, long-term (follow up 9 years) mechanically stable and non-blistering epidermis in junctional EB patients [25, 26].

In 2015 the value of this method was again demonstrated by sequential transplantations of gene corrected epidermal sheets on a 7-year-old junctional EB patient at the burn unit in Bochum (Germany), regenerating 80% of his epidermis that he has lost due to a severe bacterial infection [27]. One month after the transplantation, a mechanically stable (even upon shear force by rubbing of skin) and micro-morphologically completely normal regenerated epidermis resulted. Subsequent *in vivo* analysis (proviral integration pattern, clonal tracing) confirmed that a limited number of long-lived holoclones (= epidermal stem cells) in the skin culture is sufficient to fully restore and sustain a structural and functional normal epidermis by producing terminally differentiated keratinocytes. So far, there are no signs of rejection, autoantibody formation nor tumorigenicity/clonogenicity.

Further collaborating projects, like gene therapy studies for recessive dystrophic EB (HOLOGENE7, 2017) and junctional EB (HOLOGENE17, 2018) are in progress.

Another fruitful collaboration has been established with the immunology group (leader: Iris Gratz, PhD) of the Faculty of Natural Sciences of the Paris-Lodron University of Salzburg. In the last years it has been discovered that many agonizing symptoms of EB are attributable to an over-reactive or deregulated immune system, probably resulting from the process of chronic blistering and status of permanent wound healing. The targeting and regulating dysregulated immune pathways leads to clinical improvement, as demonstrated by the application of the Diacerein cream. This small molecule therapy, developed at the EB House Austria, antagonizes the inflammatory molecule interleukin-1β that has been shown to be significantly upregulated in keratinocytes of patients with severe generalized EB simplex, an autosomal

dominant subtype caused by mutations in the keratin-coding genes KRT5 or KRT14 [28]. Diacerein is an example of a repurposed drug for orphan use, previously prescribed for arthritis patients due to its anti-inflammatory effect. In phase I/II studies Diacerein cream showed to improve wound healing for EB simplex through reduction of downstream cellular inflammation and is currently in a worldwide registration trial phase II/III (ClinicalTrials.gov Identifier: NCT03472287) [29, 30].

EB Academy (head: Gabriele Pohla-Gubo, PhD)

The EB Academy is primarily assigned to provide continuous multidisciplinary education and training for lay people, clinical professionals and scientists from Austria and worldwide. It strongly cooperates with national and international networks for rare diseases (e.g. EURODIS, ORPHANET, EB without Borders) to collect and distribute knowledge in this specific field. The Academy is further responsible for matters of public relations through printed and electronic media, organizes courses, congresses and in-coming/out-going expert visits, as well as coordination of the EB-CLINET project ("Clinical Network of EB Centres and Experts"). This network of more than 50 countries started in 2011 to overcome inequality of medical care by counterbalancing the discrepancy of markedly improved EB care in some countries and limited medical care access and facilities (e.g. due to financial obstacles, language barriers, need for exhausting travels) in many other countries. This is supposed to be achieved by sharing competence and knowledge supranationally, fostering clinical cooperation and facilitating access to clinical trials worldwide. Progress has been gained through data collection to initiate a global EB register by using a minimum data set (including patient consent, patient identification, treatment centre / physician in charge, diagnosis (according to the relevant classification system)) [31], publication of clinical practice guidelines for standardization of care, implementation and publication of directories for EB centres of expertise, biobanks and designing initiatives for professionals training and education, as well as through organization of regularly international meetings (the last one: 4th EB-CLINET conference 2017 in Salzburg) (www.eb-clinet.org).

A (global) EB registry constitutes a key instrument for future research and diagnostic, as well as therapeutic, developments, by pooling data to achieve a sufficient sample size for epidemiological and/or clinical research. It allows for deep insights into the natural history of EB, correlation of complex genotype/phenotype relationships and determination of prognostic markers, as well as identification and characterization of disease causing genes and molecular pathways. It is further the basis of prenatal and preimplantation diagnosis, carrier testing, classification as well as genetic counselling covering predictive diagnostics, prognostication and determination of recurrence risks.

Division of Clinical Research and Clinical Study Center (head: Martin Laimer, Assoc. Prof.)

In 2016, the division of Clinical Research and Clinical Study Center has been set-up as the fourth subunit committed to excellence in producing high quality data while meeting the highest ethical and professional standards, according to good clinical practice. The main objective is the implementation, coordination and regulation of clinical research activities at the EB House Austria, including the determination of safety and efficacy of investigational medicinal products for diagnostic or therapeutic purposes in patients with EB. Investigational medicinal products mainly represent either newly developed candidate substances emerging of (in-house) translational research initiatives or already commercially available medications or devices that are used off-label. The research portfolio comprises the conduction of academic and (industry-) sponsored studies, as well as participation in collaborative multicenter research programmes. Investigational medicinal products' assessment in clinical trials thereby follows a validated, pre-defined protocol according to good clinical and scientific practice guidelines.

The close collaboration of all four subunits of the EB House Austria is seen as the basis for its successful development in the past, its profound, stable position in the present and constitutes a solid scaffold for coping with future challenges. A key determinant is the tight relation of all subunits with the patients, who always are in the central position.

Genodermatoses

In addition to EB, the center of expertise in Salzburg serves as an important shelter for other rare skin diseases (genodermatoses), affecting less than 1 in 2 000 citizens, like neurofibromatosis, ichthyosis, tuberous sclerosis and hereditary angioedema, to name a few (Fig. 5). They are chronic, often progressive, degenerative, disabling and potentially life threatening; patients are confronted with delayed or inaccurate diagnosis, difficulty accessing care, knowledge and expertise, resulting in significant direct and indirect costs. The diagnosis and management of genodermatoses is challenging, since heterogeneous and overlapping phenotypes are typical and relevant knowledge

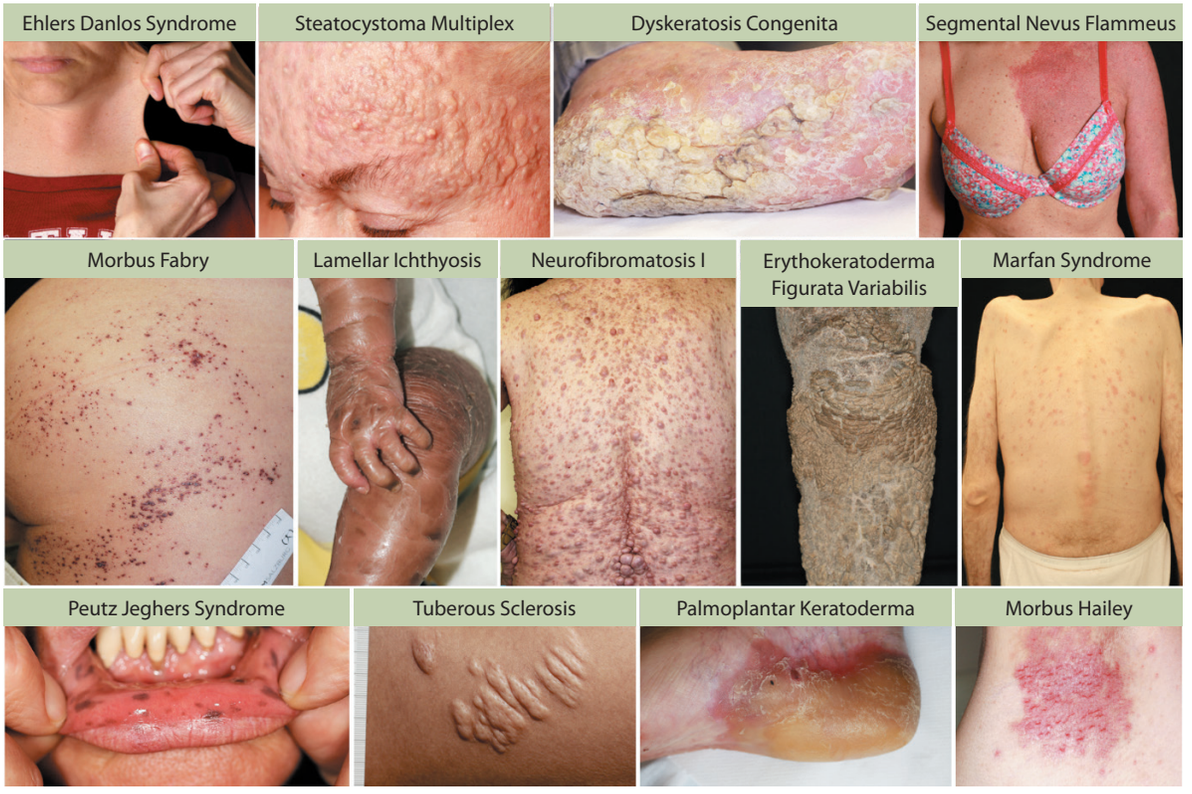

Fig. 5. Composite figure with selected genodermatoses out of the > 500 described rare skin diseases

and expertise is scarce. Therefore the centralization and coordination of multidisciplinary care, based on recommendations and decisions made at expert round tables (board of rare disease takes place every month) and as exemplified in the EB House Austria, efficiently improves the management and care of those patients, suffering from one of the > 500 rare skin diseases.

Outlook

The history of the EB House Austria is demonstrating in an exceptional way (pioneer) the establishment of an optimized health care for an in many ways (esp. socially, medically, economically) hitherto neglected group of patients and is primarily based on a powerful patient group, medical caregiver efforts and close interprofessional and disciplinary collaborations. The outstanding performance of the EB House Austria, evidenced not only but firmly by the contentment of patients and their social environment and by its scientific output with promising therapeutic modalities, confirms that patient centricity is mandatory. True patient engagement is critical to every step of improving care for rare diseases, from research and clinical trials in the context of development of new orphan drugs, to patient diagnosis and adherence.

Informed consent statement

All patients have given informed, written consent for publication of images.

Conflict of interests

The authors declare that they have no conflict of interest.

Author contributions

All authors have contributed equally to the paper. All authors have read and approved the final manuscript.

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