Summary
Palmoplantar keratodermas comprise a diverse group of acquired and hereditary disorders marked by excessive thickening of the epidermis of palms and soles. Early onset and positive family history suggest a genetic cause. While hereditary forms of palmoplantar keratoderma (PPK) may represent the sole or dominant clinical feature, they may also be associated with other ectodermal defects or extracutaneous manifestations. In recent years, much progress has been made in deciphering the genetic basis of PPK, which has led to the emergence of new disorders and syndromes. The elucidation of disease mechanisms has opened new avenues for specific therapies, increasingly sparking interest in this field. Given the high heterogeneity with respect to clinical features, genetic defects, and disease mechanisms, the classification of PPK is based on various criteria. These include extent of disease manifestations, morphology of palmoplantar skin involvement, inheritance patterns, and molecular pathogenesis. Though not always feasible, the clinical distinction of various PPK entities is based on fine-tuned criteria or clues. Remarkably, apparently distinct disorders have been shown to be allelic, as they are caused by mutations in the same gene. By contrast, similar clinical pictures may result from mutations in different genes. Because of this complexity, mutation analysis is required to determine the precise type of PPK. The best-defined entities are described in this review.

Introduction
Palmoplantar keratodermas comprise a diverse group of acquired and hereditary disorders marked by excessive thickening of the epidermis of palms and soles. The present review focuses on hereditary palmoplantar keratodermas, which include a large number of distinct entities. While palmoplantar keratodermas may represent the sole or dominant clinical feature, they may also be associated with other ectodermal defects or extracutaneous manifestations. Early onset and positive family history suggest a genetic cause.

Precise figures on the incidence and prevalence of hereditary palmoplantar keratoderma (PPK) are not available. Although, when considered separately, most
types of hereditary PPK are rare, such patients are quite frequently seen in clinical practice. Given that individuals only mildly affected either do not seek specialized medical care or have possibly been diagnosed incorrectly, the actual number of affected individuals may be underestimated [1]. In our special genodermatosis clinic, we have cared for 36 PPK patients over the past five years. This figure does not include patients whose PPK occurred in association with ichthyoses, ectodermal dysplasias, or epidermolysis bullosa, neither those seen in our routine outpatient clinic. In recent years, much progress has been made in deciphering the genetic basis of PPK using next-generation sequencing methods, which has led to the emergence of new disorders and syndromes. The elucidation of disease mechanisms has opened new avenues for specific therapies, increasingly sparking interest in this field. In the past, eponyms have typically been used to designate many hereditary PPKs, and their classification has been based on clinical-morphological criteria [2]. However, in the present era of molecular medicine, eponyms have become rather obsolete and should be replaced by clinical-molecular designations. A revised clinical-molecular classification is expected. Due to space limitations, only the most recent references – from a very large number of papers available – are mentioned in this review article.

Classification of hereditary PPK

Given the high heterogeneity with respect to clinical features, genetic defects, and disease mechanisms, the classification of PPK is based on various criteria. These include extent of disease manifestations, morphology of palmoplantar skin involvement, inheritance patterns, and molecular pathogenesis.

Extent of involvement:

- Isolated PPKs in which thickening of the skin of palms and soles is the main disease manifestation.
- Syndromic PPKs include other ectodermal defects and/or extracutaneous manifestations besides palmoplantar involvement.

Clinical-morphological aspects of keratoderma:

- diffuse – affecting the entire surface of palms and soles,
- transgredient – lesions extend beyond palmoplantar skin,
- cicatrizing or mutilating – with constricting bands around digits,
- focal or striate – the areas of palmoplantar skin most exposed to pressure are disproportionately thickened,
- punctate – with multiple scattered discrete round lesions.

Possible inheritance patterns of PPK:

- autosomal dominant,
- autosomal recessive,
- X-chromosomal,
- mitochondrial.

The molecular pathogenesis of PPK may include various dysfunctions that – among others – affect

- keratin intermediate filaments,
- desmosomes,
- gap junctions,
- water channels,
- EGFR signaling.
Clinical manifestations

Although clinical manifestations of hereditary PPK usually begin at birth or soon thereafter, some forms first present in childhood or adulthood. The disease course is marked by either life-long persistence or clinical exacerbation. In syndromic forms, involvement of other organs may occur later in life, and is crucial with respect to prognosis.

The exact morphological evaluation of keratoderma – diffuse, focal, striate, punctate, transgressant, or cicatrizizing/mutilating – is diagnostically helpful. The degree of severity may vary in the same family or among individuals bearing similar mutations. Fissures and focal keratoderma may be particularly painful. Hyperhidrosis is common, especially on the feet, and frequently gives rise to bacterial and fungal infections. Although the functionality of hands and feet is largely maintained in almost all forms of hereditary PPK, affected individuals may be hampered in everyday life, with regard to their ability to walk, or in the context of occupational activities. Cicatrizizing/mutilating forms of PPK are disabling, and result in the amputation of fingers and toes.

Patients should be carefully questioned and examined to identify other manifestations involving the integument (e.g. scaling, skin fragility), nails (e.g. thickening, absence), hair (e.g. hypotrichosis, woolly hair), or extracutaneous organs (e.g. teeth, ears, heart, eyes). Such findings should potentially be regarded as part of the same syndrome, unless an unequivocally independent etiology has been confirmed. Finally, a positive family history suggests the inherited nature of PPK.

Though not always feasible, the clinical distinction of various PPK entities is based on fine-tuned criteria or clues. Remarkably, apparently distinct disorders have been shown to be allelic, as they are caused by mutations in the same gene. Therefore, from a clinical-molecular perspective, they might be defined as a spectrum of phenotypes associated with the same genetic defect. By contrast, similar clinical pictures may result from mutations in different genes. Because of this complexity, mutation analysis is required to determine the precise type of PPK. The best-defined entities will be outlined in the following paragraphs.

Isolated palmoplantar keratodermas

The most frequently seen variants in clinical practice, isolated PPKs are extremely heterogeneous from a clinical and molecular point of view.

Diffuse epidermolytic PPK, autosomal dominant with keratin 9 or 1 gene mutations (syn. type Vörner or Thost-Unna [3, 4])

Usually caused by mutations in the gene encoding keratin 9 (KRT9), this is the most common form of autosomal dominant PPK. Mutations in the gene coding for keratin 1 (KRT1) may, however, also result in epidermolytic PPK. The onset is at birth or in early childhood. Hyperkeratoses are yellowish, compact, surrounded by erythematous margins, and cover the entire surface of the palms and soles (Figure 1a). Painful fissures and hyperhidrosis are frequent, whereas blistering is rare. In some families, knuckle pads have been described. Histopathology shows epidermolytic hyperkeratosis. Acting in a dominant-negative manner, missense or frameshift KRT9 mutations have been reported in the majority of patients. Keratin 9 is a type I intermediate filament protein whose expression is confined to the suprabasal layers of the palmoplantar epidermis [5].
Diffuse nonepidermolytic PPK, autosomal dominant with keratin 1 gene mutations

Diffuse nonepidermolytic PPK may be caused by mutations in the keratin 1 gene. Rarely occurring in adulthood, the condition may present in the first few months of life and is characterized by very thick, yellow hyperkeratoses on the entire surface of the soles, subsequently also on the palms (Figure 1b). Lesions are sharply demarcated and have erythematous-violaceous borders. Hyperhidrosis is common; dermatophyte infections and pitted keratolysis are a frequent finding. It is conceivable that epidermolytic and nonepidermolytic forms of PPK show clinical overlap, and cannot be distinguished in routine everyday practice, as lesions are usually not biopsied for histopathological evaluation. Depending on the type and location, KRT1 mutations may cause either PPK or epidermolytic ichthyosis. Keratin 1 is a constituent of keratin intermediate filaments in the suprabasal epidermal layers, building heterodimers with keratin 9 or 10 [6].
Diffuse nonepidermolytic PPK, autosomal dominant with aquaporin 5 gene mutations (syn. Bothnian type)

First described in 1994 as a clinically distinct form of diffuse PPK, this disorder has a prevalence of 0.3–0.55 % in Northern Sweden (around the Gulf of Bothnia). A diagnostic clue is the white, spongy appearance of affected areas upon exposure to water [7]. There is a frequent association with dermatophyte infections. Histopathological findings are noncharacteristic. The condition is caused by monoallelic missense mutations in the gene coding for aquaporin 5 (AQP5) [7]. Aquaporins are channel proteins primarily responsible for rapid osmotic water movement across the plasma membrane in many cell types. Expressed in eccrine sweat glands, aquaporin 5 is believed to be important for secretion. However, the precise disease mechanism remains to be elucidated [8].

Diffuse transgredient nonepidermolytic PPK, autosomal recessive with SERPINB7 mutations (syn. Nagashima type)

Diffuse transgredient nonepidermolytic PPK with autosomal recessive inheritance was first described in 1977. So far, more than 30 cases have been reported, all of them in Asia (China and Japan). The onset is during childhood. Clinical features include erythema, mild to moderate keratoderma of palms and soles, involvement of the extensor aspects of hands and feet, wrists, Achilles tendons, elbows, and knees, as well as hyperhidrosis and fungal infections. The disease course seems to be stable, showing no exacerbation with age. Histopathological findings are nonspecific. In 2013, whole-exome sequencing allowed for the identification of the genetic defect in the SERPINB7 gene. SERPINB7 belongs to the serpin superfamily, a group of structurally conserved, but functionally diverse proteins involved in inflammation, immunological processes, and metastasis [9].

Diffuse transgredient nonepidermolytic PPK, autosomal recessive with SLURP1 mutations (syn. Mal de Meleda)

Mal de Meleda was initially described in patients native to the Croatian island of Meleda (Mljet). The onset is in early childhood. The development of hyperkeratosis is preceded by erythema, which is prominent and persistent. Waxy hyperkeratotic patches cover the entire palms and soles, and also extend to the dorsal aspects of hands and feet, as well as knees and elbows (Figure 1c). Additional features are: knuckle pads, hyperhidrotic maceration, malodor, fungal superinfections, sclerodactyly, digital constrictions, and nail changes [2]. Histopathology reveals a thickened corneal layer, a more pronounced stratum lucidum, marked acanthosis, pseudospongiosis, and a prominent perivascular lymphohistiocytic infiltrate [2]. Electron microscopy shows a less-abrupt-than-normal transition between stratum granulosum and stratum corneum [2]. Mal de Meleda is caused by biallelic mutations in the SLURP1 gene, encoding SLURP-1 (secreted Ly-6/uPAR-related protein 1), a member of a superfamily of secreted as well as receptor proteins that play a role in transmembrane signal transduction, cell activation, and cell adhesion. A secreted epidermal neuromodulator, SLURP-1 is likely to be essential for both epidermal homeostasis and inhibition of TNF alpha release by macrophages during wound healing [10]. Palmoplantar keratoderma type Gamborg-Nielsen, described in Northern Sweden, has recently been shown to be an allelic variant also caused by mutations in SLURP1 [11].
Diffuse mutilating PPK with ichthyosis, autosomal dominant with loricrin gene mutations (syn. loricrin keratoderma, Vohwinkel syndrome, Camisa syndrome)

Mutilating keratoderma with ichthyosis – also known as loricrin keratoderma, Vohwinkel or Camisa syndrome – is caused by heterozygous mutations in the gene encoding loricrin (LOR), a component of the epidermal differentiation complex. Nevertheless, classic Vohwinkel syndrome is caused by mutations in the gene for connexin 26 and also associated with deafness [2]. This example perfectly illustrates the confusion brought about by the mere clinical-morphological classification of PPK and the use of eponyms. The phenotype of loricrin keratoderma is heterogeneous and ill-defined, primarily because fewer than 20 pedigrees have so far been reported in the literature. In fact, this entity delineates a severity spectrum. Common clinical features include palmoplantar keratoderma – usually with a honeycomb pattern – and generalized ichthyosis. Other features, such as knuckle pads, pseudoainhum/hyperconstricting bands with autoamputation of digits, and collodion babies, have been reported to varying degrees [12]. Histopathology sometimes shows pathognomonic findings such as hyperkeratosis with round retained nuclei and hypergranulosis. Monoallelic frameshift insertion or deletion LOR mutations have so far been described.

Loricrin, along with involucrin, constitutes a major component of the crosslinked cornified cell envelope.

Mutilating PPK and periorificial keratotic plaques (syn. Olmsted syndrome)

With an onset at birth or in the first year of life, this rare and severe PPK presents with symmetric, sharply demarcated palmar and plantar keratoderma surrounded by erythema, as well as flexion deformities and constrictions [2]. Other anomalies involve hair and nails; pain and pruritus are frequently severe [13]. Deformities and autoamputation of digits may impair walking [13]. Mutations in the TRPV3 (transient receptor potential vanilloid-3) gene have recently been identified in autosomal dominant (gain-of-function mutations) and recessive forms, whereas mutations in the MBTPS2 (membrane-bound transcription factor protease, site 2) gene have been observed in patients with recessive X-linked inheritance [13].

PPK with scleroatrophy, autosomal dominant (syn. Huriez syndrome)

First reported in 1968, this rare autosomal dominant transgredient keratoderma is characterized by scleroatrophy of the fingers and a high frequency of squamous cell carcinomas in affected skin [2]. Palms are more often involved than soles; dermatoglyphics are frequently absent. The causative gene maps to chromosome 4q23, but has not yet been identified [14].

Focal PPK, autosomal dominant with KRT6C or KRT16 mutations

Painful focal keratoderma associated with occasional blistering – with or without minor nail changes – has been linked to monoallelic in-frame deletions in the gene for keratin 6c (KRT6C) (Figure 1d). This keratin is expressed in plantar epidermis, which is thus predominantly affected. Interestingly, one of the mutations,
p.Asn172del, was found in a heterozygous state in three out of 335 population controls. The authors speculated that this keratin 6c mutation might exist at a low level within the general population, but that the relatively mild plantar callus formation associated with the mutation was not always diagnosed as PPK [15].

In a family with autosomal dominant mild focal nonepidermolytic PPK, a 23 bp deletion and a separate 1 bp deletion downstream were found in the gene for keratin 16 (KRT16). These deletions affect the helix termination motif (HTM), which is conserved across intermediate filaments and has a dominant-negative effect [5].

**Striate/focal PPK, autosomal dominant**

Striate PPK is characterized by longitudinal hyperkeratotic lesions extending along all fingers onto the palm and by focal plantar lesions at the sites of maximum mechanical pressure. Three forms can be distinguished according to their molecular defects. In this type of PPK, it is essential to carefully distinguish between isolated palmoplantar and syndromic disorders.

**Striate PPK I**

Striate PPK I is caused by monoallelic mutations in the desmoglein 1 gene (DSG1). It is noteworthy that diffuse forms, too, may be caused by similar mutation constellations. Marked intrafamilial variation has been reported. The lesions are more pronounced in areas frequently exposed to mechanical stress. Histologically, there is orthohyperkeratosis in the epidermis with widening of intercellular spaces and disadhesion of keratinocytes in the upper spinous and granular cell layers [16]. The transmembrane protein of the cadherin family, desmoglein 1 is expressed in the suprabasal epidermal layers where it contributes to the formation of desmosomes.

**Striate PPK II**

Striate PPK II is caused by monoallelic mutations in the desmoplakin gene (DSP). Palmoplantar keratoderma develops in the first or second decade of life. Palmar lesions are linear, whereas plantar lesions are focally distributed; there is a tendency for the development of fissures. Histopathology of affected skin reveals hyperkeratosis, acanthosis, and loosening of intercellular connections [17]. This phenotype is caused by haploinsufficiency of desmoplakin, a plakin protein involved in the formation of the inner desmosomal plaque and in the anchorage of keratin intermediate filaments.

**Striate PPK III**

Striate PPK III results from a frameshift mutation in the V2 domain of keratin 1 (KRT1). During early childhood, affected individuals develop striate keratoderma on the palms and more diffuse changes on the soles. Transmission electron microscopy reveals fine intermediate filaments of suprabasal keratinocytes; the inner plaques and midline structures of the hemidesmosomes are attenuated [18].

**Punctate PPK, autosomal dominant**

Three types of punctate PPK can be clinically and genetically distinguished.
Punctate PPK I

Punctate PPK I (syn. Buschke-Fischer-Brauer type, PPKP1) is an autosomal dominant disease characterized by hyperkeratotic papules that develop on the palms and soles in early adolescence or later (Figure 1e). There are broad interfamilial and intrafamilial variations in severity. Monoallelic mutations have been identified in the AAGAB gene coding for the alpha- and gamma-adaptin-binding protein or p34. This cytosolic protein with a Rab-like GTPase domain may be involved in membrane trafficking and interact with proteins of the adaptor complexes of clathrin-coated vesicles, having a role in protein sorting [19, 20].

Punctate PPK II

Punctate PPK II (PPKP2) presents with spiny lesions at or around puberty. Male members of the family also exhibit facial sebaceous hypoplasia. The molecular defect is unknown.

Punctate PPK III

Punctate PPK III (PPKP3), also known as acrokeratoelastoidosis, primarily involves the palms and soles. In severe cases, however, lesions (yellow nodules with a hyperkeratotic surface) may also affect the dorsal aspects of hands and feet. The molecular defect has not yet been identified.

Syndromic palmoplantar keratodermas

The correct diagnosis of syndromic PPK is crucial with respect to prognosis and patient management. These disorders will be described in the following paragraphs according to their major extracutaneous manifestations. Without being the dominant feature, PPK may also occur in other genodermatoses. These disorders, their main clinical characteristics, and the affected genes are summarized in Table 1.

PPK with deafness

The association between PPK and deafness with autosomal dominant inheritance is mainly caused by mutations in the gene for connexin 26 (GJB2). The phenotypic spectrum is broad, ranging from diffuse to mutilating PPK with or without keratitis:

- PPK with deafness (Figure 2a),
- knuckle pads, leukonychia and deafness (syn. Bart-Pumphrey syndrome),
- mutilating PPK with deafness (syn. Vohwinkel syndrome),
- keratitis-ichthyosis-deafness syndrome (syn. KID syndrome) (Figure 2a).

Connexin 26 is a gap junction subunit expressed in the developing cortex, cochlear cells and epidermis. Gap junctions are composed of two hemichannels, each made up of six connexin subunits, that form a porus between the cytoplasm of two adjacent cells [21].

Moreover, maternally inherited PPK with deafness may also be caused by a point mutation in the mitochondrial MTTS1 gene. The resultant deafness is progressive, postlingual, and involves high frequencies. Penetrance and expressivity of this phenotype are variable, suggesting that further modifying environmental and/or genetic factors are involved [22, 23].
Pliko with cardiac involvement and woolly hair 
(syn. Carvajal and Naxos syndromes)

Two disorders, known as Carvajal syndrome and Naxos syndrome, are characterized by PPK, cardiomyopathy, and woolly hair. They are caused by mutations in the genes for desmoplakin (autosomal dominant or recessive) or plakoglobin (autosomal recessive), respectively. While the clinical distinction was initially based on which ventricle was affected, extensive molecular studies have shown that there is an overlap of clinical features. Beginning in childhood, PPK may present striate, focal, or merely minimal lesions. Hair involvement may range from woolly hair to hypotrichosis. Sudden death due to arrhythmia may occur in adolescence or early adulthood. Early diagnosis and cardiologic management are crucial. A recent review of the literature suggests that the association between PPK and hair shaft anomalies is a strong indicator of severe arrhythmogenic cardiomyopathy [24].
PPK with erythroderma and hyper-IgE, autosomal recessive (SAM syndrome)

Only few families with biallelic loss-of-function mutations in the gene for desmoglein 1 have so far been reported. The patients described in the initial report had severe metabolic wasting, erythroderma, multiple allergies, high IgE levels, PPK, and hypotrichosis and died at a young age [25]. Other cases were less markedly affected, exhibiting severe PPK with striate hand as well as focal foot lesions as the most prominent feature (Figure 2b), food allergies, and dermatitis [25–27]. A similar phenotype has been reported to be caused by a novel heterozygous DSG1 mutation [28].
Tylosis with esophageal cancer, autosomal dominant

Tylosis with esophageal cancer is an autosomal dominant syndrome characterized by nonepidermolytic PPK, oral precursor lesions, and a high lifetime risk of esophageal cancer (up to 95 % by age 65). Monoallelic missense mutations in \( RHBDF2 \) have recently been detected. \( RHBDF2 \) (also known as RHBDL6 or iRhom2) belongs to the rhomboid family of transmembrane proteins, which are serine intramembrane proteases linked to epidermal growth factor receptor (EGFR) signaling [29].

PPK with periodontitis, autosomal recessive (Papillon-Lefèvre syndrome and Haim-Munk syndrome)

Mutations in the gene encoding cathepsin C (\( CTSC \)) are responsible for a phenotypic spectrum including Papillon-Lefèvre syndrome, Haim-Munk syndrome, and juvenile periodontitis. Also known as Papillon-Lefèvre syndrome, PPK with periodontitis is an autosomal recessive disorder characterized by PPK, periodontitis, and premature loss of dentition. Although apparently clinically distinct, Papillion-Lefèvre and Haim-Munk syndromes represent varying degrees of severity of the same disorder, and may both result from the same \( CTSC \) mutation [30]. Cathepsin C, or dipeptidyl aminopeptidase, is a lysosomal protease that removes dipeptides from the amino terminus of protein substrates, thus processing a variety of serine proteases considered essential for antimicrobial defense.

Tyrosinemia type II, with punctate PPK, keratitis, and mental retardation, autosomal recessive (syn. tyrosine aminotransferase deficiency, Richner-Hanhart syndrome)

Tyrosinemia type II includes keratitis, painful punctate PPK, mental retardation, and elevated serum tyrosine levels. The mutations lead to deficiency of tyrosine aminotransferase, a liver-specific enzyme, that converts tyrosine to p-hydroxyphenylpyruvate in a pyridoxal phosphate-dependent transamination reaction [2].

Punctate PPK with calcinosis cutis, autosomal dominant (syn. Cole disease)

A rare autosomal dominant disorder first described in 1976, it is characterized by congenital or early-onset punctate keratoderma associated with irregular hypopigmented macules on arms and legs as well as calcinosis cutis or early-onset calcific tendinitis. In 2013, Eytan et al. performed whole-exome capture and next-generation sequencing identifying three different heterozygous missense mutations in the \( ENPP1 \) gene that segregated with disease. \( ENPP1 \) encodes ectonucleotide pyrophosphatase/phosphodiesterase 1, which controls the generation of inorganic pyrophosphate, a natural inhibitor of mineralization. Importantly, biallelic mutations in \( ENPP1 \) cause ectopic calcification [31].

Striate PPK with woolly hair, autosomal recessive

The combination of palmoplantar keratoderma and woolly hair is uncommon and has been reported as part of the Naxos and the Carvajal syndrome, both caused
by mutations in desmosomal proteins and associated with cardiomyopathy. In two large consanguineous families with autosomal recessive striate PPK and woolly hair, yet without cardiomyopathy, a homozygous missense mutation in KANK2 was identified using whole-exome sequencing. KANK2 encodes the steroid receptor coactivator-interacting protein, an ankyrin repeat-containing protein, which regulates the formation of actin stress fibers and sequesters SRCs in the cytoplasm. It also controls transcription activation of steroid receptors, including the vitamin D receptor [32].

**Pigment anomalies, PPK, and cutaneous carcinoma, autosomal recessive**

In two siblings from a consanguineous family, the association of hypo- and hyperpigmented macules on the trunk and face as well as reticular hypo- and hyperpigmentation of the extremities, alopecia, PPK, nail dystrophy, and recurrent squamous cell carcinoma was caused by a homozygous variant in SASH1[33]. SASH1 codes for the sterile alpha motifs- and sh3 domain-containing protein 1, a tumor suppressor gene that plays a role in the tumorigenesis of a number of solid malignant tumors. Heterozygous SASH1 variants have been shown to cause dyschromatosis.

**Molecular pathogenesis of PPK**

The molecular defects underlying PPK are numerous and very diverse. A single unifying pathogenetic model is therefore not conceivable. Excessive proliferation of the epidermis and hyperproduction of the stratum corneum may be induced in various ways. They may either represent a response to an inherent fragility of the epidermis (e.g. defects of keratins or desmosomal proteins) or a direct dysregulation of proliferation (e.g. alterations of signaling, transport, receptors). On the other hand, the stratum corneum serves as a biosensor, transmitting signals to the underlying epidermal keratinocytes to initiate homeostatic responses. While the hyperplastic response is aimed at repairing the barrier, the same signals may also induce inflammation. Proteins affected in hereditary PPK fulfill various functions, including mechanical stabilization, interconnection, signaling, and communication among keratinocytes. The precise function of several newly identified proteins is still unclear. In hereditary PPK, some of the affected proteins are only expressed in the epidermis of palms and soles (e.g. keratin 9 or keratin 6c), thus explaining the limited disease manifestations. In other cases, hyperproliferation of palms and soles occurs in response to the excessive mechanical stress to which these regions are exposed. Expression of the affected proteins in myocardium, eyes, or other organs is responsible for syndromic manifestations.

It is noteworthy that mutations in the same gene (see above desmoplakin, cathepsin C, or connexin 26) may give rise to different phenotypes, while similar clinical pictures may have different causes (see above keratin 9 and 1). The nature and location of the mutation correlates with the phenotype. However, the precise molecular and cellular abnormalities underlying various disorders have only been elucidated for few mutations, for example, with respect to the desmosomal protein desmoplakin. Monoallelic mutations cause a dominant striate PPK phenotype, while biallelic loss-of-function mutations give rise to PPK with heart disease and hair anomalies or severe skin fragility. In case of connexin 26, a gap junction protein, the consequences of the mutations primarily depend on the location within the protein. The modifying factors that determine the phenotypic variability among individuals carrying the same mutations or among affected members of the same family are currently unknown. They may represent a combination of genetic and environmental influences.
Clinical findings including the distribution of keratoderma on palms and soles, involvement of the integument, nails, hair, and teeth, as well as manifestations affecting other organs and systems are highly relevant with respect to the diagnosis.

**Diagnostic algorithm**

The diagnostic algorithm proposed for hereditary PPK is shown in Figure 4. Clinical findings including the distribution of keratoderma on palms and soles, involvement of the integument, nails, hair, and teeth, as well as manifestations affecting other organs and systems are highly relevant with respect to the diagnosis. The family history may be helpful in establishing the inheritance pattern. Histopathology of a biopsy from affected skin should be part of the diagnostic workup. Besides nonspecific findings, such as hyperkeratosis, hypergranulosis, and acanthosis, it may reveal more characteristic features such as epidermolytic hyperkeratosis, disadhesion of keratinocytes (clue for desmosomal defects), or retention of nuclei in the stratum corneum (clue for loricrin keratoderma) [34]. The distinction between epidermolytic and nonepidermolytic forms of PPK is therapeutically relevant, given that epidermolytic forms tend to worsen on systemic retinoids. Immunostaining may point to the reduction or absence of affected proteins (e.g. desmoglein 1 deficiency). In addition, histopathology is crucial in ruling out differential diagnoses. Electron microscopy is rarely used for diagnostic purposes. Microbiology smears are indicated in the diagnosis of bacterial and fungal infections, which frequently
Disease-causing molecular defects may be identified using either sequencing of candidate gene or more comprehensive next-generation sequencing-based approaches.

Keratoderma of hands and feet may represent a feature in a multitude of conditions, both genetic and acquired (Table 2, Figure 5) [1]. Inflammatory disorders such as chronic dermatitis, lichen planus, psoriasis, or Reiter’s syndrome can be distinguished based on clinical (more prominent erythema and scaling than hereditary PPK) and pathological findings. Paraneoplastic keratoderma or cutaneous lymphoma should in particular be considered in the context of late-onset PPK and lack of a positive family history. Infectious causes including common warts, tinea, scabies, or syphilis can be recognized on the basis of clinical and laboratory criteria.

Genetic disorders associated with PPK are summarized in Table 1. Moreover, Darier’s disease and acrokeratosis verruciformis also present with punctate keratotic lesions. Whether hereditary painful callosities represent a distinct entity or a minor form of focal PPK remains to be established. Once these differential diagnoses have been ruled out, the various types of hereditary PPK can be differentiated based on the algorithm provided in Figure 5.

Management of hereditary PPK

In the majority of patients with hereditary PPK, life expectancy is not impaired. Nevertheless, severely affected individuals may be faced with a lifelong burden,

Table 2 Differential diagnoses of hereditary PPK.

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<th>Acquired disorders with palmoplantar features that may resemble PPK</th>
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<td>‣ Chronic hand-/foot dermatitis</td>
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<td>‣ Palmoplantar psoriasis</td>
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<td>‣ Reiter’s syndrome</td>
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<td>‣ Lichen planus</td>
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<td>‣ Paraneoplastic keratoderma</td>
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<td>‣ Cutaneous lymphoma</td>
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<td>‣ PPK induced by exposure to chemicals (e.g. arsenic, chlorinated hydrocarbon fluids)</td>
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<td>‣ Drug-induced PPK (e.g. lithium, chemotherapeutic agents)</td>
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<td>‣ Metabolic disorders (e.g. hypothyroidism)</td>
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<td>‣ Keratoderma climactericum</td>
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<td>‣ Verruca vulgaris/plantaralis</td>
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<th>Genetic disorders with palmoplantar manifestations that may resemble PPK</th>
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<tr>
<td>‣ Darier’s disease</td>
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<td>‣ Acroderkeratosis verruciformis</td>
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<td>‣ Epidermodysplasia verruciformis</td>
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<td>‣ Cowden syndrome</td>
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both physically and psychologically. Not only may the functionality of hands and feet be impaired, but visible hand involvement may also impact socialization. The correct diagnosis is extremely important in syndromic PPKs in which patients may experience sudden cardiac death or esophageal carcinoma at a young age; thorough multidisciplinary management is required (Figure 4). In case of early diagnosis of deafness, periodontitis, or tooth anomalies, patients will benefit from appropriate treatment.

Topical treatment of palmoplantar lesions using keratolytics and emollients must be performed on a regular basis, as it only reduces disease manifestations without providing a cure. Painful fissures can usually be avoided with rigorous care. However, patients are frequently disappointed by the minor therapeutic results obtained despite such cumbersome topical measures. In some PPK types, local baths and professional foot and hand care provide symptom relief. Oral retinoids (acitretin, alitretinoin) are usually effective; in their long-term use, side effects should be

In the majority of patients with hereditary PPK, life expectancy is not impaired. Nevertheless, severely affected individuals may be faced with a lifelong burden, both physically and psychologically. Not only may the functionality of hands and feet be impaired, but visible hand involvement may also impact socialization. The correct diagnosis is extremely important in syndromic PPKs in which patients may experience sudden cardiac death or esophageal carcinoma at a young age; thorough multidisciplinary management is required (Figure 4). In case of early diagnosis of deafness, periodontitis, or tooth anomalies, patients will benefit from appropriate treatment.

Topical treatment of palmoplantar lesions using keratolytics and emollients must be performed on a regular basis, as it only reduces disease manifestations without providing a cure. Painful fissures can usually be avoided with rigorous care. However, patients are frequently disappointed by the minor therapeutic results obtained despite such cumbersome topical measures. In some PPK types, local baths and professional foot and hand care provide symptom relief. Oral retinoids (acitretin, alitretinoin) are usually effective; in their long-term use, side effects should be

Figure 5  Acquired PPK in dyshidrotic eczema (a); chronic dermatitis (b); psoriasis (c); mycosis fungoides (d); syphilis (Courtesy of Dr. C Huhn, Dept. Dermatology, Freiburg) (e).
weighed against benefits. In some cases, in particular in epidermolytic PPK, oral retinoids may even lead to disease exacerbation and thus cause pain when walking. Even in nonepidermolytic types, such as Mal de Meleda, it is advisable to start with a rather low acitretin dose, for example, 0.2–0.3 mg/kg. Dermatophyte or bacterial infections are common and should be diagnosed and treated with antifungal and antibacterial agents. Hyperhidrosis should be equally treated in order to avoid infections and malodor. Customized footwear to reduce mechanical pressure is often helpful in overcoming pain in everyday activities. If PPK is diagnosed early, we also inform patients on the chronic nature of the disease, and explain to them that occupational activities associated with increased mechanical stress on the hands as well as orthostatic activities may contribute to disease exacerbation. Palmoplantar keratoderma associated with mutilations is disabling, and may require surgical treatment.

Although the majority of PPK are not life-threatening, genetic counseling regarding the mode of inheritance is recommended once a hereditary condition has been diagnosed in a family. For syndromic disorders, prenatal diagnosis may be an option. Experimental therapies using siRNA technology have been attempted for painful keratoderma lesions in patients with pachyonychia congenita. Moreover, there is ongoing research and clinical trials aimed at repurposing drugs that might be able to interfere with dysregulated molecular pathways.

References

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Fragen zur Zertifizierung durch die DDA

1. Which genetic disorders include PPK as an associated feature?
   a) Neurofibromatosis type I
   b) Tuberous sclerosis
   c) Epidermodysplasia verruciformis
   d) EEC syndrome
   e) Epidermolysis bullosa

2. PPK and keratitis are features of:
   a) Mal de Meleda
   b) Tyrosinemia type II
   c) PPK with calcinosis cutis
   d) Diffuse types of PPK
   e) None of the above

3. The association between PPK and woolly hair may represent an indicator for:
   a) Keratitis
   b) Cardiac involvement
   c) Renal disease
   d) Periodontitis
   e) Nail dystrophy

4. Mutations in the connexin 26 gene are associated with:
   a) PPK with mild ichthyosis
   b) PPK with deafness
   c) PPK with severe periodontitis
   d) Isolated PPK
   e) None of the above

5. The molecular basis of PPK does not include anomalies of:
   a) Keratin intermediate filaments
   b) Gap junctions
   c) Desmosomes
   d) EGFR signaling
   e) DNA repair

6. The following statement does not apply to the management of PPK:
   a) Treatment of PPK should always include topical keratolytics and emollients.
   b) Systemic retinoids are often helpful in reducing keratoderma and associated symptoms.
   c) Management of syndromic PPK is multidisciplinary.
   d) There is no treatment for patients with PPK.
   e) Genetic counseling and prenatal diagnosis are possible.

7. Which statement regarding inheritance of PPK is wrong?
   a) May be inherited in an autosomal dominant manner.
   b) May be inherited in an autosomal recessive manner.
   c) May be inherited in a X-linked manner.
   d) There are rare forms with mitochondrial inheritance.
   e) PPK are always inherited in an autosomal dominant manner.

8. Which statement regarding punctate PPK is wrong?
   a) It is always an isolated clinical feature.
   b) It is always associated with extracutaneous involvement.
   c) It is clinically and genetically heterogeneous.
   d) It may remain under diagnosed.
   e) The genetic background is not fully elucidated.

9. Mutations in the gene encoding desmoplakin may cause:
   a) Isolated punctate PPK
   b) SAM syndrome
   c) PPK with pili annulati
   d) PPK with periodontitis
   e) None of the above

10. Mutations in which of the genes below are not associated with PPK?
    a) KRT10
    b) KRT1
    c) KRT14
    d) KRT6
    e) KRT6C

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