

The diffuse palmoplantar keratodermas

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SUMMARY

Diffuse palmoplantar keratodermas belong to a diverse group of skin disorders affecting the palms and soles. These keratodermas manifest as a diffuse thickening of the palmoplantar skin, which can often be associated with other ectodermal disorders. Classification within this group has often been difficult due to the overlapping of phenotypes between disorders and the diversity within one particular disease. During the last few years advances in the molecular characterization of many of the keratodermas has helped both in distinguishing the different diseases and increasing our understanding of skin biology.

Introduction

KEY WORDS

palmoplantar, keratoderma, hereditary, diffuse, molecular biology

Hereditary palmoplantar keratodermas (PPKs) are a highly heterogeneous group of skin diseases, which primarily affect the palms, and soles or palmoplantar skin and involve thickening and hyperkeratosis. They can be inherited in both an autosomal dominant and recessive fashion. PPKs can be divided into three subgroups according to their phenotype. *Simple keratodermas* manifest as lesions only on the palmoplantar skin, whereas *complex keratodermas* are associated with lesions of non-volar skin, hair, teeth, nails or sweat glands. *Syndromic keratodermas* are associated with abnormalities of other organs such as deafness, cancer, cardiomyopathy, and adrenal insufficiency.

Simple keratodermas can be divided, by the clinical pattern of keratoderma, into three main groups, the diffuse, focal and punctate PPK. *Syndromic forms* of

keratoderma are normally associated with either a diffuse or focal pattern of keratoderma, with secondary disorders including deafness and cardiomyopathy. As the name suggests, in diffuse PPK the pattern of keratoderma is uniform across the palmoplantar skin. This compares with focal PPK, in which the keratoderma develops at pressure points or sites of trauma and punctate keratoderma, which results in numerous small hyperkeratotic nodules.

Classification of the diffuse PPKs when relying on clinical findings can be ambiguous, due to the overlap of certain clinical features between disorders and heterogeneity within the same disorder. The heterogeneity seen in phenotype throughout the diffuse PPKs is partly reflected in the diversity of genetic mutations discovered to date. However in many PPKs there can be considerable variation in phenotype between families and within families with the same genetic defect. Mutations

so far have been found in *structural, adhesion and gap junctions proteins* (Figure 1), though there are other loci associated with PPK for which the specific gene defects have yet to be identified. In this review, we discuss a classification and the current molecular understanding of the diffuse PPKs.

Simple diffuse PPK

Two different forms of the simple PPK showing a diffuse pattern of lesion have been described, diffuse epidermolytic PPK (EPPK) and diffuse non-epidermolytic PPK (NEPPK).

EPPK also known as Vörner's disease, first described in 1901 and diffuse NEPPK also called Unna-Thost type, after the clinicians who first reported it, are often phenotypically confused (1-3). Both are present from infancy and are characterized by hyperkeratosis covering the entire palms and soles. EPPK tends to have thick fissured pattern, which is bordered with erythematous margins; compared with NEPPK (Figure 2a) which usually has a more yellow waxy appearance though the phenotype in both diseases can vary greatly even within a family. The lesions on the skin in NEPPK are often susceptible to secondary dermatophyte infection and hyperhidrosis is common. Spreading onto the dorsal surfaces of the hands and wrists with a sharp cut off is a feature of NEPPK, though knuckles pads can be present in EPPK. Nail changes may be observed in both disorders. Both diseases are inherited in an autosomal dominant fashion and are highly penetrant.

Histologically the two diseases can be easier to distinguish, with EPPK showing keratin filament clumping in the suprabasal cells of the epidermis. Perinuclear vacuolization of keratinocytes and large irregularly shaped keratohyalin granules in the granular layer are also a feature of EPPK not seen in NEPPK. NEPPK can be identified by the presence of orthokeratotic hyperkeratosis and epidermal hyperplasia.

Both disorders are linked to regions of the genome containing a keratin gene cluster, with EPPK linked to 17q12-21 harboring the type I keratin gene cluster (4) and NEPPK to 12q13 where the type II keratin gene cluster maps (5, 6). Keratins are a large family of structural proteins and are the major components of the cytoskeleton of keratinocytes. These intermediate filament proteins fall into two groups, the type I and type II keratins which form specific heterodimers and are expressed in a tissue and differentiation specific pattern (7). Many different epidermal diseases have been attributed to keratin mutations, which are proposed to disrupt the cytoskeleton of the cell leading to collapse of the cell and loss of adhesion (8).

The most likely candidate for EPPK was the type I

keratin, keratin 9, as the expression of this protein is restricted to the suprabasal keratinocytes in palmoplantar epidermis (9). Subsequently mutations have been found in keratin 9 in patients with EPPK (10), and have so far been shown to be a homogeneous disease with keratin 9 mutations being found in the majority of patients investigated (11-16). Most lie in the mutation hotspot region situated in the helix initiation motif in the 1A domain. This is a highly conserved protein domain both in keratin genes and other intermediate filaments and is involved in the dimerisation of intermediate filaments. The most common mutations have been shown to change the same residue that is altered in keratin 14 in epidermolysis bullosa simplex and keratin 10 in epidermolytic hyperkeratosis respectively (17, 18).

Families with NEPPK from both the UK and Northern Sweden have both been linked to 12q13. Sequence analysis of the UK and Swedish families excluded the type II suprabasal keratin 1 and keratin 6 which are present in palmoplantar epidermis. Further mapping studies using more families has placed the disease locus proximal to the keratin cluster suggesting that a keratin is not responsible for the British and Northern Swedish form of NEPPK (19). Further studies to identify the gene is in progress, genes localized in this region include elastase 1 which has been excluded from this disease (20).

A keratin 1 mutation has been found in a family with NEPPK (21). This family however showed more epidermal involvement with hyperkeratosis of the navel and areolae not seen in other families with NEPPK. This phenotypic difference is probably a consequence of the generalized expression of keratin 1 throughout the epidermis of all body sites with affected sites being those which may be subject to greater physical stress.

Complex diffuse PPK

Erythrokeratoderma Variabilis

Erythrokeratoderma variabilis (EKV) is a phenotypically variable disease and was first described in 1925 (22). It is an autosomal dominant disease, which presents either at birth or within the first year as diffuse thickening of the palmoplantar epidermis with persistent generalized pigmented rough hyperkeratosis (fig. 2c). Patients also suffer from symmetrically distributed fixed hyperkeratotic plaques, which are sharply demarcated and can persist for months or years. Transient erythematous areas occur independently to the hyperkeratosis, lasting from minutes to days, and are usually preceded by a burning sensation (fig. 2d). Both the hyperkeratosis and erythematous patches can be triggered by trauma

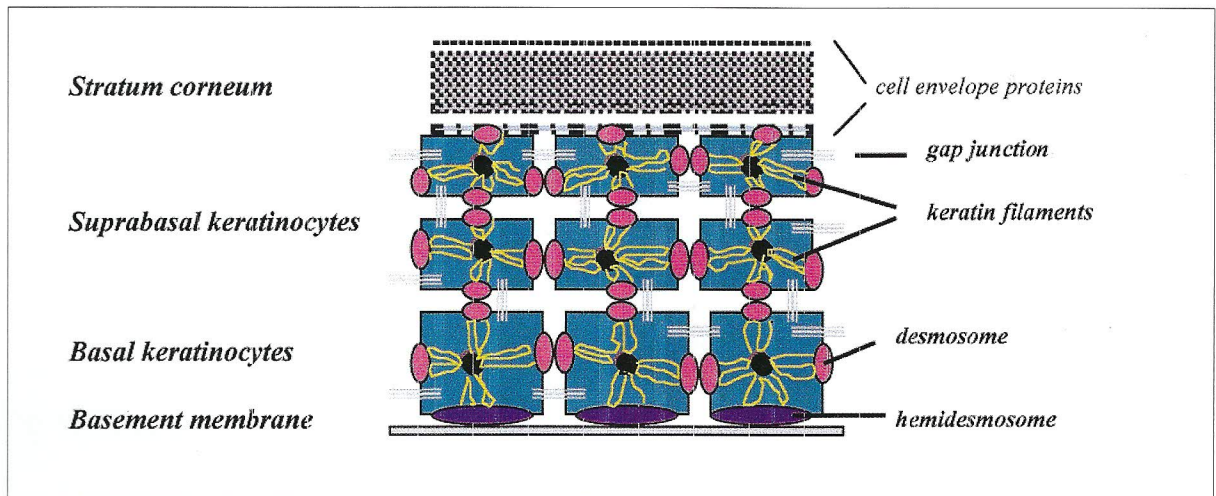


Figure 1. (a) Diagram showing the components of palmoplantar epidermis associated with diffuse palmoplantar keratodermas (PPK).

to the skin, temperature changes, UV exposure, and emotional stress. The lesions affect the whole body but are more often found on the face, buttocks and extensor surfaces of the limbs. Histologically EKV shows no specific features, but there is generalized hyperkeratosis, acanthosis, papillomatosis, dilated capillaries and perivascular infiltration. With increasing age the areas of the body affected by EKV become more restricted to the palmoplantar epidermis.

In a number of families with EKV, the disease has been linked to 1p34-p36 (23) and subsequently mutations have been found in the gap junction β -3 gene (GJB3) which encodes connexin 31 (24, 25). Four mutations causing EKV have been identified so far in the intercellular, extracellular and transmembrane domains of connexin 31. Gap junctions are composed of co-

nnexin proteins, a diverse group of proteins expressed in a tissue and differentiation specific manner of which 13 human forms have been described so far. These connexins oligomerise to form connexons which are situated in the plasma membrane and colocalise homotypically or heterotypically with connexons on adjacent cells to form a direct inter-cytoplasmic channels (fig. 1b). These channels play an important role in cell-cell communication by regulation of the transport of small molecules, such as signaling molecules and metabolites between cells. This communication is likely to control a wide range of cellular activities such as growth and differentiation.

A disease phenotypically similar to EKV, progressive symmetric erythrokeratoderma (PSEK), has been described in a Japanese family. Overlapping phenotypic

Figure 1. (b) Electron microscopy showing structure of desmosomes and gap junctions.

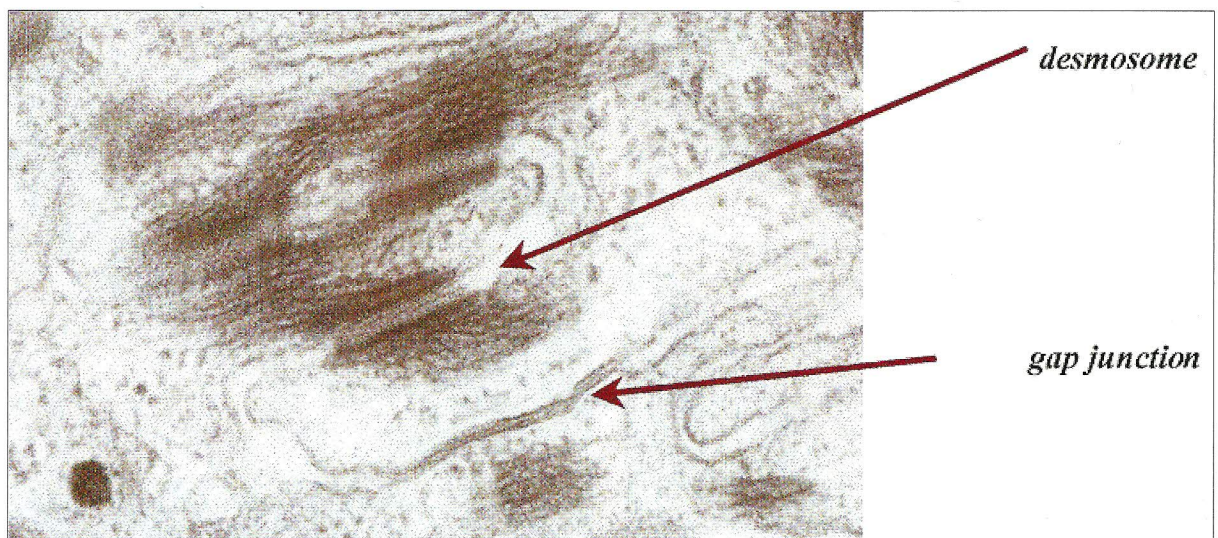




Figure 2. Photographs showing the different phenotypes of diffuse palmoplantar keratodermas (PPKs): (a) hyperkeratosis of the sole in non-epidermolytic palmoplantar keratoderma (NEPPK); (b) Pseudo-ainhum on the fingers in Vohwinkel's syndrome; (c) and (d) erythrodermia variabilis (EKV) with palmoplantar hyperkeratosis and erythematous keratotic patches.



