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REVIEW

# Genetic disorders of palm skin and nail

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## Abstract

The outer part of the skin, the epidermis, is specialized to protect the human body from its environment. Because of the high levels of physical stress experienced by the human hand in everyday use, the epidermis of the hand is especially toughened. In particular, the epidermis of the palm is highly specialized to resist mechanical trauma. Like the epidermis, the nails are composed of specialized epithelial cells and are especially strong. In recent years it has become apparent that the physical strength of epithelial cells comes from the keratin cytoskeleton – a dense meshwork of filaments extending throughout the cytoplasm. Keratins are a large family of intermediate filament proteins encoded by more than 50 distinct genes in humans. These different keratin genes are expressed in well-defined combinations in specific epithelial tissues. Several keratin genes are expressed in palmoplantar epidermis and in the stratified epithelia of the nail bed. Genetic mutations in these genes lead to fragility of these tissues and result in a range of genetic disorders characterized by blistering and thickening of palm and sole skin and/or nails. Study of these diseases has shed new light on the vital structural role of keratins in maintaining the integrity of epithelial cells.

**Key words** epidermolysis bullosa simplex; genodermatoses; hyperkeratosis; intermediate filaments; keratin; keratoderma; pachyonychia congenita.

## Keratins protect epithelial cells from physical damage

The exterior of a fully developed human hand possesses a number of complex epithelial structures (Swensson et al. 1998). The epidermis of the back of the hand is very similar to that found elsewhere on the body and is covered in hair. The epidermis of the palm is known variously as ridged skin, thick skin, glabrous skin or palmoplantar epidermis and it completely lacks hair. Furthermore, palm skin has deep ridges (fingerprint lines or dermatoglyphs); is much thicker; has regular arrays of eccrine sweat glands; and is highly specialized to resist the high levels of mechanical trauma encountered in everyday life. Nails are also a complex epithelial mini-organ system of the hand (De Berker et al. 2000). Again, nails encounter high levels of physical trauma and have evolved mechanisms to resist damage.

Mammalian cells lack any type of exterior cell wall and their strength to resist damage comes from a molecular scaffold, or cytoskeleton, within the cytoplasm (see Fuchs & Cleveland, 1998). Epithelial cells possess three cytoskeletal systems: actin microfilaments, microtubules and keratin intermediate filaments. The actin cytoskeleton is involved in cell attachment and cell migration and the microtubule system is involved in the movement of organelles within the cell. The main role of the keratin intermediate filament cytoskeleton is to protect the cell from traumatic damage (see McLean & Lane, 1995; Irvine & McLean, 1999). The dense meshwork of keratin filaments within an epithelial cell is shown in Fig. 1. The protective structural role of keratins was clearly revealed in the early 1990s, when mutations in human keratin genes were discovered in a variety of human genetic diseases characterized by fragility and/or overgrowth (hyperkeratosis) of specific epithelial tissues (reviewed in Irvine & McLean,

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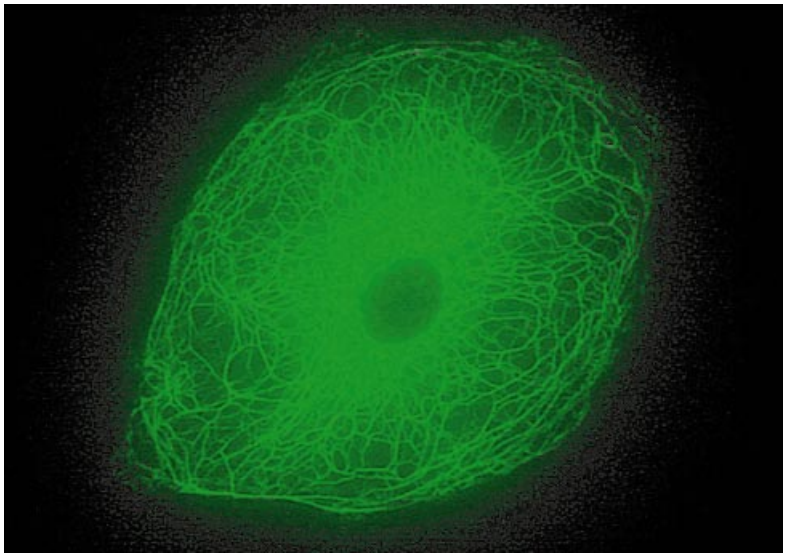

**Fig. 1** PtK2 (potoroo kidney) epithelial cell in tissue culture stained with a monoclonal antibody against keratin K8.

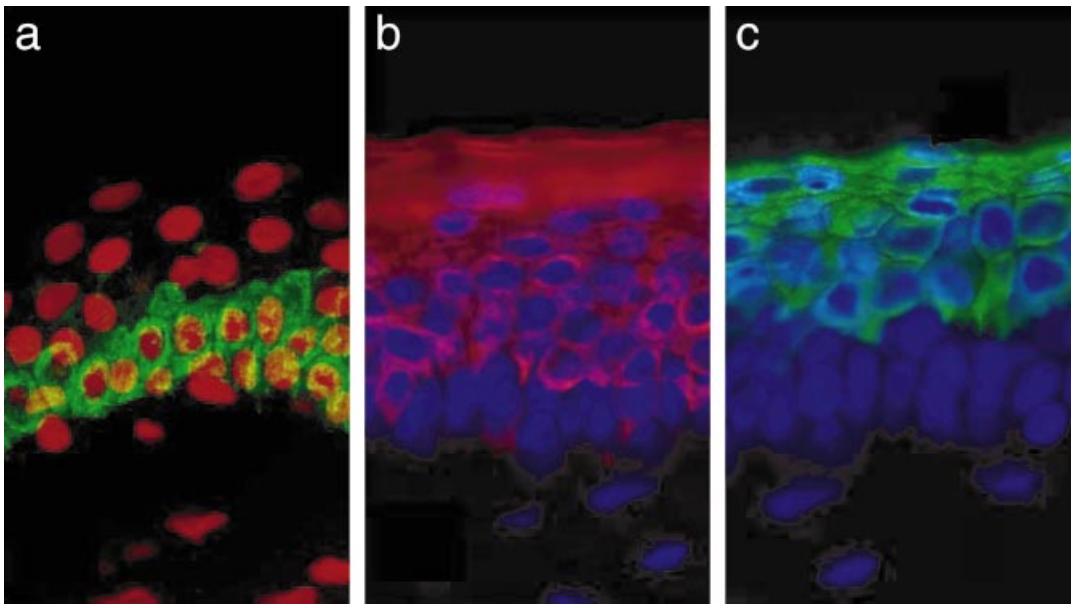


**Fig. 2** The expression patterns of three epithelial keratins in human epidermis revealed by indirect immunofluorescence staining with monoclonal antibodies. (a) K5 (green) is restricted to the basal cell compartment. Nuclei counterstained with ethidium bromide (red). (b) K1 (red) is absent from the basal cells but is found in all suprabasal layers. Nuclei counterstained with DAPI stain (blue). (c) K2e (green) is absent from the basal and epibasal layers but expressed in the uppermost suprabasal cells. Nuclei counterstained with DAPI stain (blue).

1999). Since many keratin genes are expressed in the palmoplantar epidermis (Moll et al. 1982; Swensson et al. 1998), fragility and hyperkeratosis of this tissue is a common feature of many human keratin diseases. Similarly, the keratinocytes of the nail bed, layers of cells lying below the nail itself, express a number of differentiation-specific keratins (De Berker et al. 2000). Mutations in these keratin genes have been shown to result in fragility of the nail bed keratinocytes and hyperkeratosis of the nails (reviewed by Irvine & McLean, 1999).

## Keratins are intermediate filament proteins

Keratins are a large family of intermediate filament proteins encoded by more than 50 distinct genes in humans (Hesse et al. 2001). About half of these are the epithelial keratins that are found in soft epithelial

**Table 1** Cytokeratin disease associations and expression patterns

| Keratin (pair) | Main expression pattern(s) |
|---|---|
| K5*, K14* | Basal keratinocytes of epidermis and other stratified epithelia; basal cells in ectodermal appendages |
| K15 | Basal keratinocytes |
| K1*, K10* | Suprabasal cells of stratified, cornified epithelia |
| K2e* | Late suprabasal cells of stratified, cornified epithelia |
| K2p | Keratin specific for the hard palate |
| K6a*, K16* | Palmoplantar epidermis, mucosa, wound healing, epidermal appendages |
| K9* | Palmoplantar epidermis |
| K17*, K6b | Epidermal appendages |
| K7 | Mesothelial cells, ductal epithelia, some simple epithelial cells |
| K4*, K13* | Mucosa, stratified noncornified epithelia |
| K3*, K12* | Cornea specific keratins |
| K8*, K18* | Simple epithelia |
| K19 | Simple epithelia, epidermal appendages |
| K20 | Gastrointestinal tract epithelia, neuroendocrine cells |

*Mutations in this keratin have been found to cause human disease.

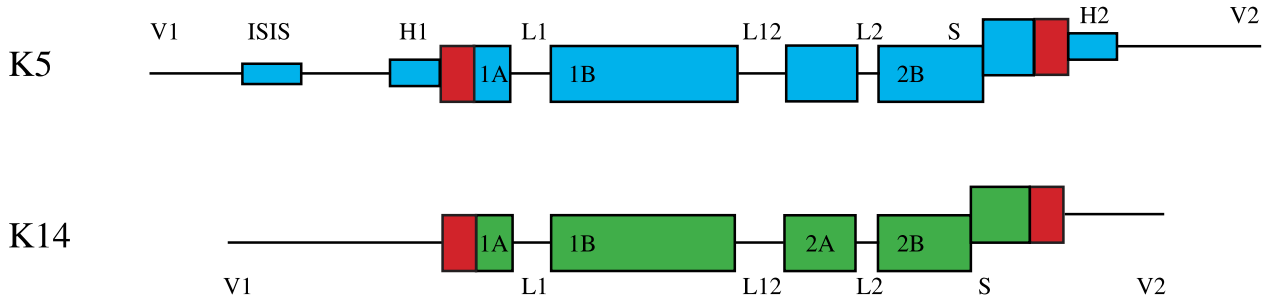


**Fig. 3** Schematic diagram showing the protein domain organization of keratins 5 and 14 (K5 & K14). These proteins polymerize to form the stress-bearing keratin cytoskeleton within basal keratinocytes of the epidermis. Both types of keratin have a similar protein structure consisting of a central helical rod domain which is responsible for polymerization of these proteins to form keratin tonofilaments. This rod domain is subdivided into 1A, 1B, 2A and 2B segments by flexible linkers L1, L12 and L2. The rod domain is flanked by variable domains V1 and V2 in both proteins; however, these domains are longer in type II keratins such as K5. In addition, type II keratins have conserved homology domains H1 and H2, and certain type II proteins such as K5 have an 'ISIS motif' within V1, which has been implicated in mediating attachment of keratins to desmosomes.

tissues of the human body. The rest are the trichocyte or high-sulphur, hard keratins of which hair and nail is composed. Both epithelial keratins and hard keratins can be further subdivided into type I and type II proteins, on the basis of their size, charge and amino acid sequence characteristics (Smith et al. 2002). They form obligate heteropolymers consisting of a specific pair of type I and type II keratins (Lane, 1993). To this end, keratins are normally expressed in specific type I/type II pairs according to well-defined tissue-specific and differentiation-specific patterns, although in some tissues, there is expression of additional accessory keratins that are not part of an obvious expression pair. For example, the basal keratinocytes (lowest layer) of stratified epithelia such as the epidermis predominantly express the keratin pair K5 (type II) and K14 (type I). The suprabasal cells of the epidermis (upper layers) express K1 (type II) and K10 (type I) and the uppermost layers also express a third type II accessory keratin K2e. The compartmentalized expression of three keratins in the human epidermis is shown in Fig. 2. The keratins that have so far been linked to human diseases and their main expression patterns are listed in Table 1.

Keratins share a common domain structure with other intermediate filament proteins (Quinlan et al. 1994; Coulombe et al. 2001), as shown in Fig. 3. This consists of a central alpha-helical rod domain which is important for polymerization. The rod domain is subdivided into four helical segments, 1A, 1B, 2A and 2B, by three flexible non-helical linker domains, L1, L12 and L2. The rod domain is flanked by globular variable domains V1 and V2, which vary widely in size and

amino acid sequence between the individual members of this protein family. Type II keratins have additional regions of sequence conservation within the variable domains, the homology subdomains H1 and H2. Like the rod domain, these subdomains are also thought to be important for polymerization. Of particular importance in filament assembly are two short regions at the start and the end of the rod domain, termed the helix initiation motif and helix termination motif, respectively (or collectively, the helix boundary motifs). These sequences of about 20 amino acids show remarkable evolutionary sequence conservation and are thought to mediate end-to-end interactions in keratin assembly.

Keratins assemble firstly by forming parallel, in-register heterodimers consisting of a type I and a type II protein through coiled–coil interaction of the two rod domains. Dimers undergo further assembly into tetramers which have been shown by chemical cross-linking experiments to exist in a variety of configurations (Steinert et al. 1993a). The tetramers undergo further stages of assembly to produce 10-nm keratin filaments. The precise details of higher order assembly are currently unclear because intermediate filament proteins are highly insoluble *in vitro* and it has therefore proven difficult to obtain X-ray crystallography data for these proteins However, atomic structure data have recently become available for small regions of the homopolymeric type III intermediate filament protein vimentin (Herrmann et al. 2000; Strelkov et al. 2001). Further crystallographic data are expected to follow which, by analogy, should shed light on the assembly of keratins.

## Human keratin diseases

The first human inherited disorder to be linked to keratin mutations was the hereditary skin blistering disorder, epidermolysis bullosa simplex (see Irvine & McLean, 1999, for review). Ultrastructural observations of the skin of epidermolysis bullosa simplex patients revealed electron-dense cytoplasmic aggregates, which, by immunolabelling, were shown to be composed of keratin K5 and K14 (Ishida-Yamamoto et al. 1991).

Similarly, transgenic mice expressing a dominant-negative mutant K14 in the epidermis developed intraepidermal blisters histologically similar to those seen in epidermolysis bullosa simplex patients (Vassar et al. 1991). Genetic linkage analysis showed that epidermolysis bullosa simplex was likely to involve keratin genes (Bonifas et al. 1991a) and, also, K14 and K5 mutations were found in patients with various subtypes of epidermolysis bullosa simplex (Bonifas et al. 1991b; Coulombe et al. 1991; Lane et al. 1992). Skin blistering in a typical epidermolysis bullosa simplex patient is shown in Fig. 4.

Early in the study of epidermolysis bullosa simplex, it emerged that mutations located in the helix boundary motifs cause more severe phenotypes than those located outside these highly conserved areas. This was consistent with the proposed function of these motifs in mediating end-to-end interactions, in that mutations in these regions prevent filament elongation and therefore have a more devastating effect on keratin assembly (Steinert et al. 1993b). Over the last decade, mutations have been found in a total of 18 keratins in association with a range of epithelial fragility disorders

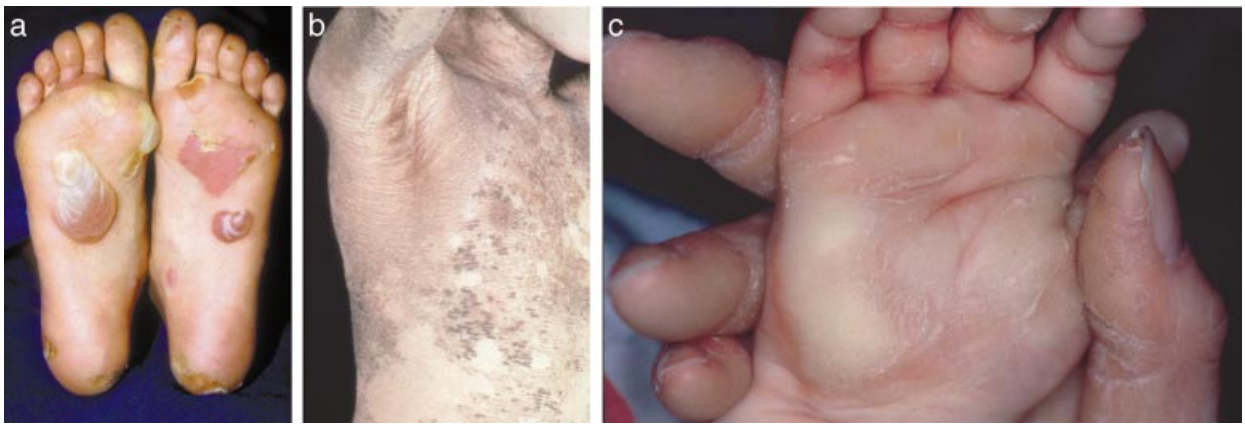


**Fig. 4** Clinical features of three keratin diseases. (a) Blisters on the soles of a patient with the milder Weber–Cockayne form of epidermolysis bullosa simplex. (b) Widespread epidermolytic hyperkeratosis in a bullous congenital ichthyosiform erythroderma patient. (c) Site-restricted epidermolytic hyperkeratosis of the palms in a mother and child with epidermolytic palmoplantar keratoderma.

(see Ku et al. 1997, 2001; Irvine & McLean, 1999). Of these, 16 are epithelial keratins and two are high-sulphur hair keratins. The vast majority of reported keratin mutations are missense mutations (exchange of one amino acid for another) or small in-frame insertion/deletion mutations and result in expression of a defective protein in addition to wild-type protein produced by the normal allele. Since keratins are polymeric proteins, these mutations tend to act in a dominant-negative fashion and so most keratin diseases are inherited as autosomal dominant traits.

A small number of mutations have been reported that introduce a premature termination codon into the K14 mRNA (Chan et al. 1994; Rugg et al. 1994). These loss-or-function mutations produce epidermolysis bullosa simplex that is inherited as an autosomal recessive trait. Details of all the reported mutations in human keratins and other intermediate filaments can be found in the Intermediate Filament Mutation Database (http://www.interfil.org).

Keratins K5 and K14 are expressed in basal keratinocytes in all regions of the skin and other stratified epithelia, including the palmoplantar epidermis and so epidermolysis bullosa simplex patients suffer blisters of the hands and feet as well as other sites, in response to mild mechanical trauma. Patients with mutations outside the helix boundary motifs, such as the Weber–Cockayne variant of epidermolysis bullosa simplex (Chan et al. 1993; Rugg et al. 1993), have a milder phenotype and predominantly get blisters on hands and feet, where trauma is highest.

Mutations in K1 and K10, which are expressed in the suprabasal cells of the epidermis, lead to the skin thickening disorder bullous congenital ichthyosiform erythroderma (Cheng et al. 1992; Chipev et al. 1992; McLean et al. 1994). In this disorder, loss of the structural integrity of the suprabasal keratinocytes leads of breakdown of these cells under trauma. In stratified epithelia, proliferating cells are found only in the basal cell compartment. In epidermolysis bullosa simplex, these dividing cells are destroyed by blister formation and the wound re-epithelializes through the division of undamaged basal cells at the margins of the blister. In bullous congenital ichthyosiform erythroderma and other disorders of suprabasal keratins, the fragile cells in the layers above leak out inflammatory cytokines which act on the basal cells below, leading to uncontrolled proliferation of the affected epithelium (Stoof et al. 1994). This process is known as hyperkeratosis and presents phenotypically as gross thickening of epithelial structures. Since K1 and K10 are found in all regions of the epidermis, including palm and sole skin, affected individuals suffer from widespread hyperkeratosis (Fig. 4), particularly of the palmoplantar skin where physical trauma is highest (known as palmoplantar keratoderma). Patients with mutations in K1 tend to have more severe palmoplantar keratoderma because the palm and sole epidermis express an additional type I keratin, K9, in addition to K10 (Langbein et al. 1993). The presence of this accessory keratin is thought to 'dilute' the effect of K10 mutations.

## Keratin diseases of the palm and sole: palmoplantar keratoderma (PPK)

Mutations in the palmoplantar-specific keratin K9 (Reis et al. 1992; Reis et al. 1994) produce hyperkeratosis which is strictly limited to ridged skin in the autosomal dominant condition epidermolytic palmoplantar keratoderma (Fig. 4). The suprabasal cells of palmoplantar skin in epidermolytic palmoplantar keratoderma undergo cytolysis owing to the defective keratin cytoskeleton within these cells, which is histologically very similar to bullous congenital ichthyosiform erythroderma. Epidermolytic palmoplantar keratoderma tends to affect both palm and sole and the keratoderma is diffuse and covers the entire surface of the ridged skin.

A large number of other keratins, including K6a, K6b, K16, K17, are expressed in the palmoplantar skin (Swensson et al. 1998), presumably as an adaptation to the enormous stresses experienced by this area of the skin. Of these, K9 is only one which is entirely specific to the palm and sole and therefore epidermolytic palmoplantar keratoderma affects only this tissue. Mutations in the additional keratins of palm and sole produce palmoplantar keratoderma but this keratoderma tends predominantly to affect the pressure points of the sole (focal palmoplantar keratoderma) and usually the hands are spared. Also, since these keratins are also expressed in other sites, the phenotypes of their associated genetic conditions are more complex and, in particular, tend to affect another structure of the hand: the nails.

## Thick nails: pachyonychia congenita

Pachyonychia congenita is a group of autosomal dominant ectodermal dysplasias whose most obvious phenotype

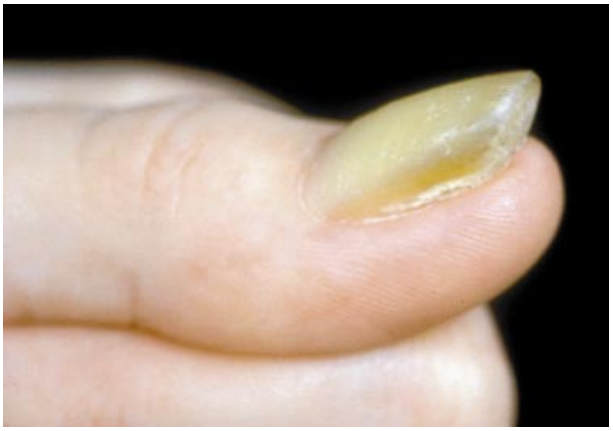

**Fig. 5** Clinical features of pachyonychia congenita. Hypertrophic nail dystrophy seen here in a pachyonychia congenita type 1 patient carrying a K6a mutation. Identical nail changes are seen in pachyonychia congenita type 2.

is hypertrophic nail dystrophy leading to a phenotype of grossly thickened nails (Fig. 5). There are two main types of pachyonychia congenita: the Jadassohn–Lewandowsky form (type 1) and the Jackson–Lawler form (type 2). In pachyonychia congenita type 1, the nail dystrophy is accompanied by focal palmoplantar keratoderma and, often, hyperkeratosis of the lingual and/or buccal mucosae. The epithelia affected in pachyonychia congenita type 1 express the keratin pair K6a and K16, and the condition is caused by dominant-negative mutations in these genes (Bowden et al. 1995; McLean et al. 1995).

The pachyonychia congenita type 2 variant is caused by mutations in keratins K6b and K17 (McLean et al. 1995; Smith et al. 1998). In this disorder, nail dystrophy is accompanied by mild palmoplantar keratoderma and multiple pilosebaceous cysts. The latter are caused by hyperkeratosis of the hair follicle opening (infundibulum) and the accompanying sebaceous gland. Some patients also have natal teeth (abnormal deciduous teeth present at birth), twisted hair (pili torti), hoarseness and other minor ectodermal features. All the tissues affected in pachyonychia congenita type 2 express K6b and K17. It is not precisely known how mutations in these keratins lead to hyperkeratosis of the nail, but fragility of the underlying nail bed keratinocytes presumably leads to release of cytokines and other inflammatory factors which act upon the proliferative cells of the nail matrix and produce overgrowth of the nail (Stoof et al. 1994; De Berker et al. 2000).

## Other molecules involved in genetic hand disorders

Genetic mutations affecting molecules that interact with the keratin cytoskeleton have also been shown to cause skin disorders where palmoplantar keratoderma is a major feature. These include such protein components of the desmosome, such as desmoplakin (Armstrong et al. 1999) and desmoglein-1 (Rickman et al. 1999), where mutations cause a striated form of keratoderma. Desmosomes are molecular complexes that interconnect the keratin cytoskeleton of neighbouring epithelial cells. Similarly, mutations in loricrin (Maestrini et al. 1996) and connexin 26 (Maestrini et al. 1999) cause mutilating forms of keratoderma, in which the concentric bands of keratoderma can restrict blood flow to the fingers so severely that autoamputation of digits can occur. Loricrin is a keratin-binding protein involved in production of the cornified cell envelope, the tough outermost layer of the epidermis. Connexins are the proteins that form gap junctions – communication channels allowing the exchange of small molecules between cells. A number of connexin proteins have now been linked to diseases of the skin, many of which affect the palm and nail (Richard, 2001).

There are still many disorders affecting the palm and sole epidermis for which the underlying genetic defect remains to be elucidated. The ectodermal dysplasias are a very large and highly heterogeneous group of genetic disorders that affect the structure and function of a range of epithelial structures. Many of these disorders affect the palmoplantar epidermis and/or nails, as reviewed recently (Stevens et al. 1996; Kimyai-Asadi et al. 2002). Undoubtedly, many of these disorders will involve structural molecules; however, others may involve signalling molecules that are involved in the control of hand, skin and nail development. For example, mutations in the transcription factor p63 have been shown to be the molecular basis of Hay–Wells syndrome (McGrath et al. 2001), whose symptoms can include dystrophic or absent nails, cleft palate, syndactyly (fusion of digits) and a range of other developmental defects.

The gene causing Naegeli–Franceschetti–Jadassohn syndrome has recently been mapped (Whittock et al. 2000), although the gene itself has not yet been identified. This syndrome is an ectodermal dysplasia in which, interestingly, the fingerprint ridges (dermatoglyphs) are absent. This gene is predicted to be an

important factor in dermatoglyph formation, as well as exerting effects on other epithelial structures.

Anonychia congenita is a rare recessive disorder in which there is congenital absence of all nails (Hopsu-Havu & Jansen, 1973). Here, the causative gene is likely to be a key developmental switch without which there is complete failure of nail development. In some forms of brachydactyly (congenital shortened fingers), reviewed elsewhere in this issue by Andrew Wylie, there is also congenital absence of nails due to developmental failure of the distal phalanx and associated epidermal structures. Currently, my laboratory is studying a large family with a rare form of brachydactyly in which just the terminal phalanx of the fourth finger is absent, including its nail (see cover illustration of an X-ray of an affected hand). Using genetic linkage analysis in which highly variable segments of DNA are used to track the inheritance of a disease gene through the generations of large families, we should be able to identify a small region of whatever chromosome harbours the defective gene and, we hope, the gene itself. Identification of this gene may increase our understanding of how the development of the distal digit is controlled and perhaps shed light on other disorders of nail development such as anonychia congenita.

## Concluding remarks

Of all the epithelial tissues in the human body, the epidermis covering the palm and sole and the nails are subjected to some of highest levels of mechanical trauma during everyday life. Through the study of genetic diseases that cause fragility of these tissues, we have learned over the last decade the vital role that keratins play in maintaining the structural integrity of a wide range of epithelial tissues by forming a tough meshwork of intermediate filaments from within the cell. There are a number of questions that still remain unanswered in keratin biology. For example, why are there so many differentially expressed keratin genes and what are their tissue-specific functions? Keratins differ from one another in the size and composition of their variable domains and it is therefore likely that protein–protein interactions mediated by these domains are somehow responsible for a number of as yet undefined tissue-specific functions. A number of laboratories are now involved in identifying these protein interactions and some of these interactions, such as binding to desmosome components, have already been linked to genetic skin disease, as discussed above.

A major task in the years ahead is to develop treatment for these diseases. Gene replacement therapy may not be appropriate for keratin disorders due to the dominant-negative action of keratin mutations. However, data derived from recent inducible mouse models of epidermolysis bullosa simplex (Cao et al. 2001) and bullous congenital ichthyosiform erythroderma (Arin et al. 2001) have shown that reducing the expression of the mutated keratin genes by as little as 50% may be sufficient to restore normal skin function. These animal models are now being used to test a variety of gene therapy strategies and we hope novel and efficacious therapies for these incurable diseases will soon be available.

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