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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation

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Summary

Keratins are obligate heterodimer proteins that form the intermediate filament cytoskeleton of all epithelial cells. Keratins are tissue and differentiation specific and are expressed in pairs of types I and II proteins. The spectrum of inherited human keratin diseases has steadily increased since the causative role of mutations in the basal keratinocyte keratins 5 and 14 in epidermolysis bullosa simplex (EBS) was first reported in 1991. At the time of writing, mutations in 15 epithelial keratins and two trichocyte keratins have been associated with human diseases which include EBS, bullous congenital ichthyosiform erythroderma, epidermolysis palmoplantar keratoderma, ichthyosis bullosa of Siemens, diffuse and local non-epidermolysis palmoplantar keratoderma, pachyonychia congenita and monilethrix. Mutations in extracutaneous keratins have been reported in oral white sponge naevus and Meesmann’s corneal dystrophy. New subtleties of phenotype–genotype correlation are emerging within the keratin diseases with widely varying clinical presentations attributable to similar mutations within the same keratin. Mutations in keratin-associated proteins have recently been reported for the first time. This article reviews clinical, ultrastructural and molecular aspects of all the keratin diseases described to date and delineates potential future areas of research in this field.

Key words: genetics, genodermatosis, intermediate filaments, keratin, mutation

Distribution and function of human keratins

The cytoplasm of animal cells is structured by scaffolding composed of actin microfilaments, microtubules and intermediate filaments. The intermediate filaments are so named because their 7–10 nm diameter is intermediate between that of microfilaments such as actin (6 nm) and microtubules such as tubulin (23 nm). The intermediate filaments have long been presumed to have a predominantly structural function, a role that was clarified when human epithelial fragility syndromes became attributed to mutations within epidermal keratin genes. More than 50 intermediate filaments are expressed in human tissues and are classified into six subgroups based on sequence homologies. The largest group within this protein family consists of the keratins (types I and II intermediate filament proteins), which are expressed specifically in the cytoplasm of epithelial cells where they form a dense meshwork of 10 nm filaments. More than 30 cyto-keratins and trichocyte keratins ('hard' or hair/nail keratins) have been identified to date and it is thought that several more remain to be discovered. In 1977, work on sheep wool keratins had suggested a classification of keratins into two subtypes. This classification has been strengthened by sequence analysis and keratins are now classified as type I or acidic keratins (cytokeratins K9–K20; Ha trichocyte keratins) and type II or basic keratins (cytokeratins K1–K8; Hb trichocyte keratins). Keratins are expressed as obligate heterodimers of type I/type II pairs in a tissue- and differentiation-specific fashion.

Intermediate filaments share a common structural theme

Keratins have a basic molecular structure common to all intermediate filaments (Fig. 1). A central α-helical rod domain of about 310 amino acids is responsible for dimerization and higher order polymerization. This domain exists in four segments interrupted by three non-helical linkers (L1, L12 and L2), and an apparent...
Keratins exhibit a high degree of tissue specificity

Keratins were initially characterized by immunohistochemical techniques that allowed their subclassification into some 30 different types. It was soon recognized that the keratins were coexpressed in pairs, which showed great tissue specificity (Table 1). Variations in the head and tail domains largely account for differences between the individual keratin proteins within each type and may account for functional fine tuning between the different keratin pairs. K8 (type II) and K18 (type I), thought to be the oldest keratin pair in evolutionary terms, are the first embryonic keratins expressed in the oocyte and preimplantation blastocyst. The genes for K8 and K18 are, uniquely for keratin pairs, located on the same chromosome, chromosome 12. The genes encoding other human keratin pairs are spatially separated in two compact, gene-dense clusters on chromosomes 12q (type II keratins) and 17q (type I keratins). The tissue-specific distribution of keratins can be exemplified by the keratin expression profile of the interfollicular epidermis (Fig. 2). K5 (type II) and K14 (type I) are the primary keratins of basal cells in the many types of stratifying squamous epithelia. Throughout the suprabasal keratinocytes of the epidermis expression is downregulated and replaced by K10 and K1 expression. From the upper spinous layer outwards, an additional type II keratin, K2e, is also expressed (Fig. 2). The reason why there are so many tissue-specific keratins is unknown but it is probable that there are particular qualitative requirements for cytoskeleton in different epithelia and in addition, as yet unknown tissue-specific functions may reside in the head and tail domains. Type II keratins are almost always expressed ahead of their type I partner in differentiating epithelia, possibly reflecting a differential stringency in the gene regulation of types I and II keratins.

Keratin pseudogenes cause major problems in molecular analysis

Keratins are a good example of a multigene family, with two chromosomal clusters as described above. As is the case with other multigene families, several pseudogenes exist, which probably developed as a result of tandem gene duplication. Some of the keratin pseudogenes are transcriptionally silent; however, others are expressed to various degrees. An example of this is K6 whose gene exists as six highly homologous copies of the gene.
Table 1. Expression patterns of keratins

<table>
<thead>
<tr>
<th>Keratin</th>
<th>Main expression pattern(s)</th>
<th>Disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1, K10</td>
<td>Suprabasal cells of stratified, corneal epithelia</td>
<td>BCIE/EH, DNEPPK</td>
</tr>
<tr>
<td>K2a</td>
<td>Late suprabasal cells of stratified, corneal epithelia</td>
<td>BIS</td>
</tr>
<tr>
<td>K2p</td>
<td>Hard palate-specific keratin</td>
<td>None known</td>
</tr>
<tr>
<td>K3, K12</td>
<td>Cornea-specific keratin</td>
<td>MCD</td>
</tr>
<tr>
<td>K4, K13</td>
<td>Muscosa, stratified non-cornified epithelia</td>
<td>WSN</td>
</tr>
<tr>
<td>K5, K14</td>
<td>Basal keratinocytes of epidermis and stratified epithelia</td>
<td>EBS</td>
</tr>
<tr>
<td>K6a, K6c-f, K16</td>
<td>Palmoplantar, muscosa, wound healing, epidermal appendages</td>
<td>PC-1, FNEPPK</td>
</tr>
<tr>
<td>K7</td>
<td>Myoepithelial cells, simple epithelia</td>
<td>None known</td>
</tr>
<tr>
<td>K8, K18</td>
<td>Palmo-plantar epithelium</td>
<td>Cryptogenic cirrhosis</td>
</tr>
<tr>
<td>K9</td>
<td>Simple epithelium</td>
<td>EPPK</td>
</tr>
<tr>
<td>K15</td>
<td>Basal keratinocytes</td>
<td>None known</td>
</tr>
<tr>
<td>K17, K6b</td>
<td>Epidermal appendages</td>
<td>PC-2</td>
</tr>
<tr>
<td>K19</td>
<td>Simple epithelium, epidermal appendages</td>
<td>None known</td>
</tr>
<tr>
<td>K20</td>
<td>Gastrointestinal tract epithelia</td>
<td>None known</td>
</tr>
<tr>
<td>hHb6*, hHb1*</td>
<td>Cortical trichocytes</td>
<td>Monilethrix</td>
</tr>
</tbody>
</table>

*Indicates that mutations have been found to cause human disease.

BCIE: Bullous congenital ichthyosiform erythroderma
EH: Epidermolytic hyperkeratosis
DNEPPK: Diffuse non-epidermolytic palmoplantar keratoderma
MCD: Meesmann’s corneal dystrophy
BIS: Ichthyosis bullosa of Siemens
WSN: White sponge naevus
EBS: Epidermolysis bullosa simplex
PC: Pachyonychia congenita
EPPK: Epidermolytic palmoplantar keratoderma
FNEPPK: Focal non-epidermolytic palmoplantar keratoderma

(K6a–f), four of which are expressed, encoding mRNAs which differ by only a few base pairs. We have also observed low-level expression of the reported K14 pseudogene in cDNA derived from epidermolysis bullosa simplex (EBS) patients lacking K14, although this is not translated due to frameshift mutations in the pseudogene (McLean, Corden, and Jonkman, unpublished data).

Keratin mutations cause epithelial fragility syndromes

Since 1991, mutations in several keratin genes have been found to cause a variety of human diseases affecting the epidermis and other epithelial structures (Table 1). EBS was the first keratin disease to be identified, with mutations in both the K5 and K14 genes rendering basal epidermal keratinocytes less resilient to trauma and resulting in skin fragility. The site and type of amino acid substitution within the keratin protein correlates to a degree with phenotypic severity in this disorder. Since these first mutations were identified in basal cell keratins, the number of keratin genes associated with diseases has risen to 17.

Epidermolysis bullosa simplex

Epidermolysis bullosa (EB) describes a heterogeneous group of heritable skin-bluistering disorders categorized into three main subtypes, depending upon the level of the skin in which blistering occurs. About one in 20,000 people suffer from some form of EB. EBS involves blistering due to fragility of the basal layer of epidermal keratinocytes and was first reported as distinct from other subtypes of inherited EB in 1898. Autosomal dominant transmission of EBS was first reported in 1908. On ultrastructural examination, the level of split in the epidermis in EBS is within the basal keratinocyte itself, generally within the subnuclear cytoplasm. EBS was the first human inherited blistering disorder to be characterized at a molecular level and was also the first identified human keratin disease. There are three main subtypes of EBS.

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trauma. As with EBS–WC, there is a marked seasonal variation in severity.

_Epidermolysis bullosa simplex—Dowling–Meara_

The Dowling–Meara type of EBS (EBS–Dowling–Meara; EBS–DM; MIM 131760), originally reported in 1954, is the most severe EBS subtype. The autosomal dominant inheritance of this condition has been confirmed in several large pedigrees. Blisters are found in clusters at any body site (Fig. 3b), usually beginning within the first 5 days of life. The hands and feet are most severely affected. Patients with EBS–DM often also have palmoplantar keratoderma, nail dystrophy and oral ulceration. Extensive involvement occasionally occurs and can be fatal in neonates. As with other forms of EBS, the blistering tends to improve in adolescence and adulthood. In contrast to blistering, the palmoplantar keratoderma tends to become more marked with age. Unlike EBS–K and EBS–WC, patients do not usually display significant seasonal variation. The diagnosis of EBS–DM is confirmed by the typical appearance on electron microscopy of an intraepidermal cleavage plane and electron-dense aggregates (formed by keratin filament collapse) within the cytoplasm of basal cells.

A convergence of different approaches led to the discovery of keratin mutations in EBS. Expression of mutant keratins in cultured cells was shown to produce dense keratin aggregates. Subsequently, similar aggregates were seen in cells from patients with EBS–DM and were shown to label with K5 and K14 specific antibodies, using immunoelectron microscopy. When mutant K5/K14 genes were expressed in the skin of transgenic mice they developed a condition strikingly similar to EBS–DM. These mice had both the characteristic keratin aggregates within basal cells and intraepidermal blistering. Shortly after these key observations, mutations in K5 and K14 were reported in EBS patients.

In 1991–92, three independent groups almost simultaneously reported causative mutations in EBS. Genetic linkage between EBS–K and the type I keratin gene cluster on chromosome 17q was demonstrated and the causative mutation (L384P) discovered in the 2B segment of the K14 rod domain. The first EBS–DM mutation (R125H) was discovered in the highly conserved helix initiation motif at the beginning of helix 1A of K14. This tenth arginine codon of the 1A domain contains a CpG sequence conserved in most type I keratins and represents a mutation hotspot in these keratin genes.
proteins. A reciprocal mutation in the conserved helix termination motif of K5 was reported in a large EBS-DM family.20 Reports of K5/14 mutations in EBS-WC followed.46-48 In the milder forms of EBS, the mutations occur outside the highly conserved helix boundary motifs, and filaments appear to be essentially normal on electron microscopy.51 Following these initial findings, there have been many further reports of linkage and/or mutations in dominant EBS families.

Recessive epidermolysis bullosa simplex subtypes

EBS is most often expressed as an autosomal dominant trait but there have been a few reports of recessive EBS subtypes (MIM 6010001). The first of these was a point mutation in the 1A domain of K14 (A144E), outside the helix initiation motif. This mutation produced a very mild WC-like phenotype in homozygotes, whereas the parents who were heterozygous carriers of the mutation were clinically unaffected.49 This type of mutation has not been reported since, probably because of the rarity of recessive phenotypes and the very mild nature of this phenotype.

Following the above report, two further cases of recessive EBS where affected individuals of consanguineous parentage had severe generalized blistering due to complete ablation of K14 expression were reported.50,51 Both of these cases demonstrated severe and generalized blistering, and tonofilaments were absent on electron microscopy. K5 was detectable using immunohistochemistry, immunoelectron microscopy and immunoblotting, but K14 expression was undetectable. In one case, a homozygous two nucleotide deletion (313del2) led to a premature stop codon and truncation of K14 in the V1 domain.50 K14 mRNA was undetectable in the patient's skin due to nonsense mediated decay of the message. In a simultaneous publication, a homozygous nonsense mutation was described in K14 (Y200X), leading to a premature termination codon in the 1B domain and complete loss of K14 expression and identical clinical findings.51 These cases represented the first 'knockouts' of an epidermal keratin. Interestingly, the subsequent ablation of K14 in mice by gene targeting was found to be fatal by the age of 3 months not because of skin blistering, which recovers in mice following hair growth, but rather due to oesophageal damage.52 The data from these knockout mice led the authors to predict a poor prognosis for K14-deficient EBS patients.52 However, a third severe recessive EBS family was subsequently reported where the causative mutation was also loss of K14 expression, in this case due to a homozygous splice site mutation.53 There were several affected members in this family, including individuals in the seventh decade of life, so the phenotype would appear to be less severe in humans. The authors postulated that increased expression of K15 had a compensatory effect in humans,25 whereas expression of this keratin appears to decrease with age in mice, possibly explaining the mortality of K14-deficient mice.52 A fourth kindred has now been reported with a homozygous nonsense mutation in the helix 2 domain of K14, leading to K14 ablation and severe recessive EBS53 (Fig. 3c).
Figure 4. Clinical photographs of bullous congenital ichthyosiform erythroderma (BCIE) (a) and ichthyosis bullosa of Siemens (IBS) (b). The clinical appearances of IBS and BCIE may be similar and can lead to clinical confusion. In general, children with BCIE present with erythroderma as 'red scaly babies' whereas IBS patients do not. IBS typically manifests as keratotic lichenification over the extensor aspects of the knees and elbows (b). The presence of 'Mauering' or moulting is a clinical factor more in keeping with IBS, while palmoplantar keratoderma is more indicative of BCIE. Epidermolytic palmoplantar keratoderma has a characteristic clinical appearance with waxy hyperkeratosis surrounded by an erythematous border (c). The onset of keratoderma is usually within the first months of life as evidenced by this affected child and mother.

Figure 5. Histopathology demonstrates that the level of epidermolytic is helpful in distinguishing bullous congenital ichthyosiform erythroderma (BCIE) from ichthyosis bullosa of Siemens (IBS). In BCIE there is a normal basal layer with epidermolytic change in the lower spinous layers (a). The cytolysis occurs lower in the epidermis when compared with typical IBS histology (b). The degree of hyperkeratosis (seen histologically) is not of value in distinguishing these conditions.

Epidermolysis bullosa simplex with mottled pigmentation

EBS with mottled pigmentation (EBS-MP; MIM 131960) is a subtype of EBS, which is characterized by skin blistering, mottled pigmentation of the trunk and limbs (Fig. 3d), punctate hyperkeratoses of the palms and soles and dystrophic nails. Histologically and ultrastructurally the blistering in EBS-MP closely resembles that found in EBS-WC. EBS-K and EBS-DM in that there is a subnuclear split through the basal keratinocytes, which have few intact organelles. The genetic basis of EBS-MP is now known to be due to a heterozygous point mutation, P24L, in the non-helical V1 domain of K5. In vitro filament assembly studies using the mutant K5 reveal only slight deleterious effects, and expression of the mutant K5 produced keratin filament networks indistinguishable from wild type. It remains unclear how this mutation acts to disrupt keratin filaments, although it points to a subtle and hitherto undetected role for the V1 domain in filament dynamics. How these particular mutations produce pigmen tary changes is equally unclear but these findings do indicate a range of functions that might reside in the head and tail domains of intermediate filaments.

Bullous congenital ichthyosiform erythroderma

Bullous congenital ichthyosiform erythroderma (BCIE; MIM 113800; also known as epidermolytic hyperkeratosis/
bullous erythroderma ichthyosiformis congenita of Brocq) is an autosomal dominant disorder, the cardinal features of which are redness, blistering and scaling hypertrophy of the skin (Fig. 4a). In infancy, blistering and erythroderma are the dominant features, while in adulthood, severe hyperkeratosis with epidermolytic histology is predominant (Fig. 5a). The discovery of keratin gene mutations in EBs led workers to target BCIE as another potential keratin disease. Clues to potential underlying keratin mutations came from ultrastructural studies showing specific K10 and K1 tonofilament clumping in suprabasal cells of BCIE patients reminiscent of the K5 and K14 clumps seen in EBs–DM. An independent line of investigation using a transgenic mouse expressing mutant K10 demonstrated a phenotype remarkably similar to BCIE. Later in the same year linkage data implicated keratin genes, followed shortly by the first reports of mutations in K10 and K1. Since these initial reports, several more mutations have been described in BCIE, all clustering at the ends of the central helical rod domains in a manner analogous to EBs–DM. It has been suggested that the underlying keratin mutations may predict phenotype in BCIE, with K1 mutations giving rise to a phenotype with severe palmpoplantar hyperkeratosis while K10 mutations cause a phenotype lacking palmpoplantar involvement. These potential correlations await confirmation with further mutation studies.

A naevoid variant of BCIE has long been recognized where typical BCIE lesions occur in the distribution of Blaschko’s lines. This variant has been variously labelled as ichthyosis hystrix and linear epidermolytic hyperkeratosis. Women with this disorder were noted occasionally to give birth to children affected with generalized BCIE. A further subtlety of the BCIE story was the discovery of a heterozygous point mutation of K10 similar to those found in BCIE in this naevoid form. This mutation was not detected in normal skin, suggesting that the condition is due to a postzygotic mutation in early development. The patients with the naevoid variant who have affected children presumably have underlying gonadal as well as cutaneous mosaicism. To date BCIE is the only human keratin disease known to exhibit mosaicism.

**Diffuse non-epidermolytic palmpoplantar keratoderma**

In addition to the BCIE phenotypes described above, a K1 mutation has been reported in a single pedigree as causing diffuse non-epidermolytic palmpoplantar keratoderma. This mutation lies outside the central rod domain and lies within a 22 amino acid motif (labelled the ISIS box after part of the sequence), which is conserved in many type II keratins. The residue involved, K73I, is the residue most frequently found to be involved in cross-linking of the cornified cell envelope by transglutaminases. This ISIS box sequence has also been postulated to play a pivotal part in desmoplakin binding, so the K73I substitution may act by disrupting K1 interaction with other molecules.

**Ichthyosis bullosa of Siemens**

In 1937, Siemens described a type of epidermolytic hyperkeratosis which was milder in phenotype than that earlier described by Brocq and was predominantly localized to the flexures (Fig. 4b). Ichthyosis bullosa of Siemens (IBS; MIM 146800) can be distinguished from BCIE by the absence of erythroderma and the characteristic 'Mauserung' moulting of the outer layers of the epidermis. This said, mild BCIE and severe IBS can be very difficult to distinguish clinically and some authors disputed the existence of IBS as a discrete entity until it was characterized at a molecular level. The pattern of tonofilament aggregation and cytology in IBS showed limitation to the upper spinous and granular cell layers of the epidermis (Fig. 5b), a pattern of involvement which was consistent with the known tissue expression pattern of K2e. The first report of linkage to the keratin cluster on chromosome 12 was followed by three simultaneous reports of mutations in K2e. Rothnagel et al. found mutations in four families with IBS and in two that were initially misdiagnosed as BCIE. One mutation, a potential methyl-CpG deamination (E493K), appears to represent a disproportionate number of cases reported and probably represents a mutational hotspot in IBS.

**Epidermolytic palmpoplantar keratoderma**

Epidermolytic palmpoplantar keratoderma (EPPK; MIM 144200) is an autosomal dominant genodermatosis first described by Vörner in 1901 and is characterized by epidermolytic hyperkeratosis confined to the palm and plantar epidermis. The clinical appearance of waxy hyperkeratosis limited to the palms and soles surrounded by an erythematous border is strongly suggestive of EPPK (Fig. 4c). K9 is expressed in a very specific manner limited to palms and soles, making this a prime candidate for EPPK. Genetic linkage of
EPPK to the type I keratin cluster was demonstrated, and with the cloning of the K9 cDNA and corresponding gene, KRT9, missense mutations have been identified in a number of EPPK families. The expression partner of K9 has not been characterized but is thought to be K1 isoform; there are no reports in the literature of EPPK linked to the type II keratin locus but the pattern of mutations in other keratin diseases would predict that some families will be found. EPPK is possibly one of the commoner keratin diseases with an incidence of at least 4-4 per 100,000 in Northern Ireland (Irvine and McKenna, unpublished observation). To date, all reported mutations in K9 have been located in the IA domain.

Pachyonychia congenita, focal non-epidermolytic palmoplantar keratoderma and steatocystoma multiplex (MIM 167200, 167210, 184500 and 600962)

Pachyonychia congenita (PC) describes a group of inherited ectodermal dysplasias whose most prominent clinical feature is hypertrophic nail dystrophy (Fig. 6a). Two main clinical variants of PC are generally recognized, PC-1 and PC-2. In the PC-1 form, pachyonychia is accompanied by severe focal keratoderma (Fig. 6b). Features such as angular cheilosis, follicular keratosis, hoarseness and oral leukokeratosis (Fig. 6c) are not fully penetrant and occur in both types. The PC-2 form is most readily distinguished by the presence of multiple steatocysts, which appear at puberty (Fig. 6d). Mild focal keratoderma and pili torti are also found in PC-2. Natal teeth appear to be associated with PC-2 alone, but again this phenotype is not fully penetrant. Mutations have been identified in differentiation-specific keratins, which are expressed in the particular epithelia affected in each type of PC. Genetic linkage analysis in a large Glaswegian PC-2 family indicated a type I keratin defect. The mutation in this family was later found to be a point mutation in the IA domain of K17. It was also shown that PC-1 could result from similar mutations in K16. Another group of workers identified the first mutation in K6a, the expression partner of K16, also giving rise to PC-1. K17 mutations have since been shown to be consistently associated with the PC-2 phenotype, although K6b has recently been shown to be the expression partner of K17 and a mutation in this gene has been reported in a PC-2 family.

Intra-and interfamilial phenotypic variation has been observed in families carrying the K16 or K17 genes. K16 mutations can present as focal keratoderma without nail changes or other features of PC-1. Similarly, K17 mutations have been found in families presenting with steatocystoma multiplex, without abnormalities of nails or other ectodermal structures. The reason for these phenotypic differences is not clear but appears to be unrelated to the specific genetic mutation and is therefore thought to be due to the action of additional unknown modifying genes.

Monilethrix

Monilethrix (MIM 158000) is an autosomal dominant disorder characterized by varying degrees of alopecia.

Figure 6. Pachyonychia congenita (PC) is a group of ectodermal dysplasias, which have wedge-like subungual hyperkeratosis of all 20 nails (a) as a characteristic feature in both subtypes. Focal non-epidermolytic palmoplantar keratoderma (b) is predominantly a feature of PC-1; oral leukokeratosis (c) is a feature of both PC-1 and PC-2, while multiple steatocystomas are characteristic of PC-2 (d).
(Fig. 7a) and beaded hairs with an alternating structure of elliptical nodes and constrictions (known as internodes) (Fig. 7b). The affected hairs show an increased susceptibility to fracturing and weathering. The most common clinical presentation is alopecia that shows marked interindividual variation, even between members of the same family. Perifollicular hyperkeratosis is a consistent feature and keratosis pilaris is a common clinical accompaniment, as are nail abnormalities such as koilonychia, lamellar splitting and brittleness. Ultrastructural analysis of affected hair shafts showed defects in the microfibrillar structure of the hair shaft, making trichocyte keratins, the structural proteins of the hair, prime candidates for this disorder. The trichocyte keratins were known to map either to the type I keratin cluster on 17q12.21 or to the type II keratin cluster on 12q13.\footnote{24} and subsequently genetic linkage was established in two families to chromosome 12q13.\footnote{25} The first mutations in a human hair keratin (trichocyte keratin hIhB6) were reported in two families in 1997.\footnote{95} The same group has recently reported a mutation in another type II hair keratin, hFib1, which is also expressed in cortical trichocytes of the hair shaft.\footnote{96}

As with many of the keratin disorders, monilethrix exhibits a wide degree of clinical variation within families, suggesting a role for environmental factors or disease modifying genes.

**Extracutaneous keratin diseases**

Given the tissue-specific expression pattern of human keratins it is unsurprising that diseases have been identified in epithelial tissues outside the epidermis and its appendages. As with cutaneous keratin disorders, extracutaneous keratin diseases are inherited in an autosomal dominant fashion, in keeping with the destructive effect to the cytoskeleton of a single mutant keratin. The tissue-specific keratins of the oral mucosa are K4 and K13, with K3 and K12 specifically expressed in the corneal epithelium.\footnote{15,17}
White sponge naevus of Cannon

White sponge naevus of Cannon (MIM 193900) is a benign, autosomal dominant disorder which affects non-corneifying stratified squamous epithelia. It presents as white 'spongy' plaques in the mouth (Fig. 8a) and occasionally the oesophagus and anogenital mucosa.97 The oral lesions resemble the leukokeratosis seen in K16 PC patients.86 The first mutations in K498 and K1399 were reported simultaneously in 1995.

Juvenile epithelial corneal dystrophy of Meesmann

Juvenile epithelial corneal dystrophy of Meesmann, or Meesmann's corneal dystrophy (MCD; MIM 122100), is a bilaterally symmetrical, autosomal dominant disorder of the corneal epithelium, has a characteristic slit-lamp appearance of a myriad of fine round epithelial cysts (Fig. 8b) which become visible by 12 months of age and increase in number throughout life.100,101 Patients are usually asymptomatic until adulthood when rupture of the corneal microcysts may cause erosions, producing clinical symptoms such as photophobia, contact lens intolerance and intermittent diminution of visual acuity. Histological examination shows a disorganized and thickened epithelium with widespread cytoplasmic vacuolation and numerous small, round, debris-laden intraepithelial cysts; ultrastructural studies in MCD show cytoplasmic inclusions within the corneal keratinocytes, presumably keratin aggregates.102 The clinical and ultrastructural features make keratin proteins good candidate genes for this disorder and in 1997 the first mutations of the corneal keratins K3 and K12 were reported.103 Another group recently confirmed these findings with mutations in K12 in four families with MCD.104 All K3 and K12 mutations reported to date have been within the helix boundary peptides.

Cryptogenic cirrhosis

Transgenic mice with K18 mutations develop chronic hepatitis; this finding led researchers to consider K18 as a candidate gene in patients with cryptogenic cirrhosis. A K18 mutation (H127L) was found to associate with this disease105 in a single patient. This mutation was located in the L1 domain of K18, a site where there have been no analogous mutations described in any other keratin. This initial report has not been subsequently followed up by further K18 mutations and at present the exact role of K18 in this disease must be considered an unresolved issue.

The K8 knockout mouse phenotype includes colorectal hyperplasia with sparing of the small intestine.106 As yet, no analogous human diseases have been identified.

Diseases of keratin-associated molecules

The intermediate filament cytoskeleton directly associates with a number of subcellular structures, including desmosomes, hemidesmosomes and proteins of the cornified cell envelope.107,108 In recent years, epidermal fragility diseases have begun to emerge which are due to mutations in molecules of these attachment complexes. Mutations which cause loss of plectin, a high molecular weight intermediate filament-binding protein, have been shown to cause EBS with muscular dystrophy, demonstrating the essential role of this protein in hemidesmosomes and in mediating cytoskeletal cross-linking in muscle.109–111 Similarly, loss of plakophilin has been shown to lead to a phenotype of skin fragility and ectodermal dysplasia, revealing that this molecule is an essential link in keratin–desmosome association.112 In both these cases, essential biological functions for widely expressed proteins have been elucidated from the study of rare genetic disorders.

Future directions

Only a few cytkeratins now remain which do not have a known disease association and the future will probably see the completion of this work. There is currently little knowledge of the role of disease-modifying genes in the keratin disorders and this is a potential growth area for research. With regard to diseases of trichocyte keratins, only monilethrix has been identified as a hair keratin disorder. There are thought to be as many hair keratins as cytkeratins and so many more hair keratin diseases await discovery. Another future direction of the epithelial genetics field is the study of further molecules that interact with keratins. Some of these may be purely structural, such as plectin.109 Others may have functions that are partly structural but which may also be involved in cell signalling, such as members of the plakophilin/armadillo family of proteins.112 Another area for study is that of molecules which are purely involved in the control of intermediate filament dynamics. For example, mutations affecting kinases and phosphatases that are involved in the remodelling of the cytoskeleton during cell division113 could possibly lead to diseases characterized by aberrant cytoskeletal regulation.

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Another obvious direction is that of gene therapy. For keratin diseases, gene therapy is made especially difficult because most keratin mutations act in a dominant fashion. New technologies will have to be developed whereby mutant genes are silenced in some way. In addition, there are difficulties involved in implanting genes into the skin and maintaining their long-term expression. In view of these obstacles, gene therapy for these disorders is not going to appear in the clinic in the short term. However, many groups world-wide are actively engaged in this research and so new therapeutic strategies will undoubtedly emerge for these debilitating diseases in the future.

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References


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