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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.
Intermediate filaments in disease

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Intermediate filaments are major structural proteins encoded by a large multigene family. Their tissue-specific expression makes them important in studies of development, differentiation and pathology. Most intermediate filaments are keratins; recent discoveries of keratin mutations in a range of genetic skin disorders have clarified their role as providing essential structural support for cells in different physical settings.

Current Opinion in Cell Biology 1995, 7:118–125

Introduction

Five classes of intermediate filaments are recognized to date on the basis of sequence similarities in the rod domain, and are referred to as types I–V (Table 1). Their expression is strikingly tissue-specific, suggesting that the intermediate filament type present in a cell is fundamentally related to its function. In humans, keratins account for three-quarters of all known intermediate filaments, and it is in keratins that pathogenic mutations have been found that cause human diseases, as reviewed in this article.

All 50 or so known intermediate filament proteins have a similar protein domain structure consisting of a central α-helical rod domain flanked by non-helical head and tail domains (see the examples of a type I and a type II keratin in Fig. 1). The rod domain is the structural subunit of polymerized filaments, and is conserved in size and overall protein structure, with a long ‘leucine zipper’ heptad repeat pattern. Although the overall pattern is similar, the details of the rod sequences differ between intermediate filament proteins. The most conserved stretches are two short sequences at the start and end of the rod domain, the helix initiation peptide or motif (HIP) and the helix termination peptide (HTP). The HTP sequence is conserved in all intermediate filaments, and anti sera against this peptide recognize most intermediate filament proteins. The HIP sequence is also conserved but is more type-specific. The conservation of these helix boundary peptides suggests that these are regions in which no (or very little) sequence variation will be tolerated, if the structures are to retain acceptable function. In contrast, the non-helical ends vary widely and probably modulate the quality of the filaments to give the required tissue-specific attributes.

Keratins form the intermediate filament cytoskeleton of epithelial cells. Most intermediate filament proteins form homopolymeric structures but keratins assemble as obligate heteropolymers from type I (acidic) and type II (neutral to basic) keratin subunit heterodimers, which are expressed in specific, predictable pairs. The range of specialized types of epithelial cells are echoed in the tissue-specificity of the keratins they express, according to the physical requirements of each cell type.

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Number of isoforms</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Keratins (acidic)</td>
<td>16</td>
<td>K9–K20; trichocyte keratins Ha1–Ha4, Hax</td>
</tr>
<tr>
<td>Type II</td>
<td>Keratins (neutral to basic)</td>
<td>13</td>
<td>K1–K8, Hb1–Hb4, Hbx</td>
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<tr>
<td>Type III</td>
<td>Vimentin-related</td>
<td>4</td>
<td>Vimentin, desmin, peripherin, glial fibrillary acidic protein</td>
</tr>
<tr>
<td>Type IV</td>
<td>Neurofilaments</td>
<td>5</td>
<td>NF-L, NF-M, NF-H, nestin, α-intermixin</td>
</tr>
<tr>
<td>Type V</td>
<td>Laminas</td>
<td>4</td>
<td>A-type laminas (laminas A, C); B-type laminas (laminas B1, B2)</td>
</tr>
</tbody>
</table>

Abbreviations

BCIE—bullous congenital ichthyosiform erythroderma; EBS—epidermolysis bullosa simplex; EBS-DM—Dowling-Meara EBS; EBS-WC—Weber-Cockayne EBS; EPPK—epidermolytic palmoplantar keratoderma; HIP—helix initiation peptide; HTP—helix termination peptide; IBS—ichthyosis bullosa of Siemens.

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in its specific location in the body. In epidermis, all undifferentiated keratinocytes in the basal layer express the primary keratins K5 and K14, whilst suprabasal differentiating cells express secondary (differentiation-specific) keratins K1 and K10, or, when stressed, K6 and K16/K17 (normally present in hair follicles). Additional suprabasal keratins K9 and K2e are found in some regions of epidermis, such as in the palmoplantar skin (see Fig. 2).

Mutations in basal keratins K5 and K14 cause congenital blistering

Epidermolysis bullosa refers to a heterogeneous group of hereditary skin-blistering disorders. These are rare diseases: one of the best estimates of population incidence comes from a recent survey carried out in Scotland by the Dystrophic Epidermolysis Bullosa Research Association, where it was estimated that around 1 person in 20,000 has some form of epidermolysis bullosa. Most cases are mild forms of the disease.

There are three types of epidermolysis bullosa, classified according to the level in the skin at which blistering occurs (Fig. 2), and their genetic causes have all been elucidated in the last 3–4 years. In dystrophic epidermolysis bullosa, the skin splits in the lamina lucida of the basement membrane: this crippling disease is caused by defects in collagen VII [1], a major component of the anchoring fibrils that hold the epidermis to the dermis. In junctional epidermolysis bullosa, the split level is within the basal lamina; recent reports have demonstrated causative mutations in laminin V (a component of the basal lamina, otherwise known as nicein, kalmin, or epiligrin) [2]. In epidermolysis bullosa simplex (EBS), blistering is caused by fragility of keratinocytes in the basal layer of the epidermis. The various forms of EBS were the first human hereditary blistering disorders in which the underlying molecular defect was uncovered: they are all caused by mutations in the basal cell keratins K5 and K14. The mutational changes are not evenly distributed but are clearly clustered at certain sites or regions along the protein (Fig. 1; Table 2).

Within EBS disorders there are three main clinical types and a few rarer forms [3]. The three major variants are usually dominantly inherited disorders and there are both dominant and recessive minor forms. The Dowling-Meara variant (EBS-DM), or EBS herpetiformis, is characterized by clusters of blisters which form at any site on mild physical trauma; in newborn infants this can be life-threatening because of the dangers of secondary infection. Electron-dense aggregates of unpolymerized keratins can be seen in the keratinocyte cytoplasm using electron microscopy. The Köbner form of EBS is rare and associated with widespread blistering; the Weber-Cockayne (EBS-WC) form is mild, and the blisters are usually confined to hands and feet.

Before the mutations were identified, reports had pointed to possible keratin defects in EBS and related diseases. Transfection of epithelial cells with truncated keratins produced keratin aggregates [4] resembling those seen in EBS-DM. Ishida-Yamamoto et al. [5] reported that the EBS-DM aggregates seen under the electron microscope could be labelled with antibodies to keratins, but only with those directed against K5 and K14. Fuchs’s group [6] produced transgenic mice expressing a truncated chimeric K14 gene: the mice exhibited basal cell keratin filament (tonofilament) abnormalities and skin loss which bore a resemblance to the human EBS-DM phenotype.

Three reports of identified human mutations then appeared within six months of each other. Epstein’s group in San Francisco [7] demonstrated genetic linkage to the keratin gene cluster at chromosome 17q12–q21 in a family with Köbner EBS, and proceeded to identify a mutation in the rod domain of K14. Fuchs and colleagues [8] reported mutations in the HIP of K14 causing EBS-DM. Lane et al. [9] reported a reciprocal mutation in the HTP of K5 in an EBS-DM kindred, using a combination of immunoblotting and sequencing cDNA regions corresponding to altered epitopes. Subsequent mutations identified in EBS-DM patients are all in the helix boundary peptides in K5 or K14, mostly in residue Arg125 of K14 (see a recent review in Current Opinion in Genetics & Development [10]).
Table 2. Mutations in keratins that cause epidermolysis bullosa simplex.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Keratin</th>
<th>Mutation</th>
<th>Number of cases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dowling-Meara</td>
<td>K14</td>
<td>R125C</td>
<td>3</td>
<td>[8,23,44]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R125H</td>
<td>5</td>
<td>[8,44]</td>
</tr>
<tr>
<td></td>
<td>K5</td>
<td>E475G</td>
<td>1</td>
<td>[9]</td>
</tr>
<tr>
<td>Weber-Cockayne (recessive)</td>
<td>K14</td>
<td>E144A</td>
<td>1</td>
<td>[17**]</td>
</tr>
<tr>
<td>Weber-Cockayne</td>
<td>K14</td>
<td>V270M</td>
<td>2</td>
<td>[14**,45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ΔE375</td>
<td>1</td>
<td>[16*]</td>
</tr>
<tr>
<td></td>
<td>K5</td>
<td>N192K</td>
<td>3</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I161S</td>
<td>6</td>
<td>a; [11*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R331C</td>
<td>1</td>
<td>[14**]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M327T</td>
<td>1</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N329K</td>
<td>1</td>
<td>[15]</td>
</tr>
<tr>
<td>Köbner</td>
<td>K14</td>
<td>L384P</td>
<td>1</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M272R</td>
<td>1</td>
<td>[13*]</td>
</tr>
<tr>
<td></td>
<td>K5</td>
<td>L462P</td>
<td>1</td>
<td>[46]</td>
</tr>
<tr>
<td>Köbner (recessive)</td>
<td>K14</td>
<td>G107X</td>
<td>1</td>
<td>[18**]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Διι313−314</td>
<td>1</td>
<td>[19**]</td>
</tr>
</tbody>
</table>

Mutations are defined using the single letter code for amino acids.

Thus, EBS is caused by mutations in basal keratins K5 and K14; these mutations weaken the keratin cytoskeleton, which can then no longer enable the keratinocyte to resist the physical stresses of normal wear and tear on the skin, and the cell becomes fragile. The keratin cytoskeleton plays an essential role in the reinforcement of cells in one of the harshest environments of the body.

Mutations outwith the helix boundary peptides are less severe
The molecular basis of the Weber-Cockayne type of EBS was next to be elucidated. EBS-WC is the mildest variant and shows no obvious disruption of basal filaments by EM. Mutations in EBS-WC mostly fall outside the helix boundary peptides, and the full spread of these mutations will be informative in ranking the molecular interactions in polymerization.

Mutations in the H1 domain
Our group (E Rugg et al., abstract in Br J Dermatol 1993, 120:486a) and others [11*] reported identical mutations (Ile161→Ser) in the H1 subdomain of K5 as causing EBS-WC. Although this mutation may have arisen independently on more than one occasion, it is also likely that some of the families involved are related and so a ‘founder effect’ has produced a false impression of this being a hotspot for EBS-WC mutation. There is a need for analyses of relatedness between families whenever the same mutation is discovered in multiple families.

The H1 subdomain is a short region between the V1 domain and the start of the rod domain in type II and type III intermediate filament proteins (see Fig. 1b), postulated to be composed partly of α-helix (near the rod domain) and partly of regions of turn, loop and β-sheet conformation [12]. Type I intermediate filaments (type I keratins) lack this subdomain. This region is known to be important in filament assembly and/or integrity, and contains consensus phosphorylation sites. The Ile161→Ser mutation creates a potential protein kinase C phosphorylation site, which could theoretically provide a means of destabilizing the filaments by hyperphosphorylation (as in mitotic destabilization of intermediate filaments). This hypothesis has not been tested experimentally and other mutations in H1 do not appear to affect kinase sites, so these mutations may simply affect protein conformation.

Mutations in the L12 linker domain
One of the more surprising mutation clusters found in EBS was the one in the L12 region, the non-helical central linker that bisects the rod domain [13*,14**,15]. The function of the linkers is not fully understood but they

Fig. 2. Diagram of epidermis to show differentiation compartments and the expression patterns of major keratins within them (left). Parentheses indicate those proteins that are expressed specifically in palmoplantar epidermis. Cell layers affected by characterized keratin disorders are shown (right).
are likely to be involved in flexibility of the dimers and higher order structures which make up intermediate filaments; the domain is not known to be directly involved in filament assembly. Computer structural predictions suggest that these mutations increase the tendency of the linker domain to form helical structures: this may lead to a more rigid molecule, with less resistance to torsional stress. Mutant filaments do not appear to be significantly abnormal in their assembly [15], but they must be compromised in some way.

A diffuse cluster of mutations is found in helix 2B, 5’ to the HTP. In one case, a three-nucleotide deletion in K14 removes a single amino acid from the rod domain [16*]. This could interfere with alignment of the leucine zipper in dimerization, leading to major disruption of filaments, but the phenotype associated with the mutation was reported to be mild. The deleted residue is close to the helix inversion feature or ‘stutter’ in helix 2B (Fig. 1). There must be flexibility here to allow the change in polarity of the α-helix; the flexibility may explain why the deletion is not grossly disruptive.

**Autosomal recessive forms of EBS: Nature’s ‘knockouts’**

There have been three reports of genetic lesions causing EBS inherited as a recessive trait [17**–19**]. The first of these [17**] reported a homozygous point mutation in the helix 1A domain causing a very mild disease similar to EBS-WC. This Glu→Ala transition in the less conserved downstream half of helix 1A in K14 gave no discernible phenotype in heterozygotes in a consanguineous French family. Homozygous individuals showed a very mild EBS phenotype with blistering confined to plantar skin. The authors hypothesised [17**] that this glutamic acid residue may be involved in ionic stabilization of the keratin dimer, and that loss of the charged group could weaken this interaction. So far there is no firm evidence to support this hypothesis.

Two accounts of recessive EBS with a severe, generalised blistering phenotype have described absence of tonofilaments in the basel cell cytoplasm [18**,19**]. In both cases the affected individuals were of consanguineous parentage. Although K5 was detectable by immunohistochemistry and immunoblotting, K14 expression was undetectable, and K14 mRNA was greatly reduced in both cases. In our patient [18**], a homozygous deletion of two nucleotides in the head domain (V1 region) led to a premature stop codon and loss of the entire K14 rod domain. The heterozygotic parents are asymptomatic, as the truncated K14 lacks interactive rod domain sequences and therefore is not predicted to be a dominant disruptor. In the other case [19**], a point mutation produced a premature stop codon within the K14 rod domain (helix 1B). One would predict that such heterozygotes would be affected by expression of this partial K14 protein, but they appear to be protected by destabilization of the mutant mRNA. These cases show that single copy expression of K14 is sufficient for normal skin function. This, together with the lack of dominant-negative translation products in both cases, means that these homozygous individuals would be prime candidates for gene therapy.

There appears to be a spectrum of overlapping phenotypes in the different forms of EBS, and the accumulating evidence suggests that they fall along a continuous range of phenotype severity, depending on the location of the mutation within the keratin concerned. As these diseases may become better classified according to specific genetic abnormalities, a clear distinction between them may prove to be unnecessary or misleading.

**Mutations in the major suprabasal keratins K1 and K10**

After EBS, the next group of skin diseases found to be linked to mutations in keratin was bullous congenital ichthyosiform erythroderma (BCIE; Table 3). BCIE is another autosomal dominant disorder characterized by epidermolytic hyperkeratosis: cell breakdown, leading to gross thickening of the outer layers of the epidermis, which is also a symptom of other skin disorders unrelated to keratin mutations. The ultrastructural changes in suprabasal filament aggregation were shown to specifically involve suprabasal keratins 1 and 10 [20] and transgenic mouse experiments again mimicked the BCIE phenotype [21]. The first mutations to be characterized included some in the helix boundary sequences of K1 and K10 [22], a proline mutation in the H1 subdomain of K1 [12], and the same amino acid change (of Arg125) in the 1A domain of K10 as described in K14 as a cause of EBS-DM [23]. Thus the same type of mutation in different genes is responsible for different sets of clinical phenotypes. Other mutations have been characterized subsequently [24–29], including the first mutations found in the 1A domain of a type II keratin, seen in BCIE patients in K1 [26]. The fact that mutations outwith the helix boundary peptides of the rod domains of K1 and K10 have not been found in patients suggests that such mutations are non-pathogenic, possibly because these are secondary keratins and the presence of K5/K14 may reinforce a faulty K1/K10 network.

**Body site specific keratin disorders: K9 and K2e**

Epidermolytic palmoplantar keratoderma (EPPK) is similar to BCIE except that the epidermal hyperkeratosis is confined to palm and sole epidermis. Mutations causing EPPK were found in the K9 gene (Table 3; [30**,31]), which is expressed specifically in palm and sole skin. Like K10 and K14, the arginine at residue 10 of the 1A domain of K9 (in the HIP) was again found to be a common target for mutation, although other mutations in the critical region also result in EPPK.

Icthyosis bullosa of Siemens (IBS; Table 3) is a mild type of epidermolytic ichthyosis similar to BCIE, but largely limited to the flexure surfaces and with no palmoplantar involvement. Lesional epidermis from IBS
patients revealed that tonofilament aggregation and cytolyis were present only in the upper suprabasal layers, unlike the situation in the K1 and K10 disease, where all suprabasal cells are affected [32**]. The keratin K2e is a recently characterized keratin which is expressed in outer suprabasal layers [33], in parallel with the IBS phenotype, and we identified a mutation (Glu493→Lys) in the K2e HTP in two cases of IBS [32**]. Kremer et al. [34**] found two more identical and two different mutations, only one of which was in helix 1A. Rothnagel et al. [35**] reported mutations in six families with IBS, all again in codon 493, and five of these were also Glu493→Lys.

**Double trouble: hypermutability in DNA coding for vital protein motifs**

EBS–DM, BCIE, EPPK and IBS mutations produce aggregation of tonofilaments that leads to dysfunction of the keratin cytoskeleton and consequently to cell lysis. The vast majority of mutations found so far occur in the helix initiation or termination motifs of the appropriate proteins. These are the most highly conserved motifs in keratins, indicative of their functional significance. Studies with chemical cross-linking, protolyis and peptide sequencing of keratins [36] indicate that the helix boundary motifs are in close association in filaments; Steinert et al. [36] suggest an overlap between these motifs is essential for correct filament assembly. Transfection studies and in vitro polymerization experiments with keratins that carry mutations in these motifs again show their importance [4].

The predominant EBS–DM mutations are Arg125→Cys and Arg125→His in the HIP of K14 (Table 2). Analogous mutations have been found in K9 and K10, causing EPPK and BCIE, respectively (Table 3). In most human type I keratins, the codon for this arginine contains a Cpg dinucleotide, and the common K14 mutations represent the two possible products of deamination mutation of methylated cytosine in this codon. These mutations have been reported in many families and it seems likely that this Cpg is methylated in K9, K10 and K14 and is therefore hypermutable [37]. The prevalence of HIP mutations in type I keratins has been somewhat offset by the mutations in IBS, which are nearly all in the HTP: the Glu493→Lys mutation accounts for 9 out of 12 K2e mutations known to us (Table 3). Two of these were sporadic cases (new mutations), indicating the mutability of this codon. This is another possible Cpg mutation and is therefore a 'hotspot' analogous to the arginine in the HIP of type I keratins. The codon usage in this motif is different in K1 and there is no Cpg at this location, however K5 does have this Cpg, so it is perhaps surprising that this Glu→Lys transition has not been seen in EBS–DM. Cpg-mediated mutation depends on methylation of the cytosine and therefore it may be that this sequence is unmethylated in K5.

**More keratins, more mutations, more diseases?**

More than 30 keratin genes are expressed in specific epithelial structures and more keratin genes will undoubtedly be linked to human genetic disorders before the end of 1995. A recent report has described close linkage of pachyonychia congenita to markers within the type I keratin locus on chromosome 17 [38]. This is a collection of autosomal dominant ectodermal dysplasias of which the major diagnostic feature is hypertrophic nail dystrophy, plus other ectodermal aberrations including palmoplantar keratoderma, hair abnormalities, natal teeth, buccal and lingual lesions. The many candidate genes at this locus include those encodiing the trichocyte keratins (the 'hard' keratins of hair and nail) and K16, K17 and K19, which are all expressed in hair follicles and the nail bed.

There have also been reports of linkage of various types of dominant non–epidermolytic palmoplantar keratoder-
mas to both keratin loci on chromosomes 12q and 17q (PE Purkis et al., abstract in J Invest Dermatol 1994, 103:427a; HP Stevens et al., abstract in J Invest Dermatol 1994, 103:428a). Those keratodermas which are linked to 17q have an obvious candidate in K9, where mutations outside the helix boundary peptides might result in the non-epidermolytic phenotype. Other good candidate genes are K1, K2e and K10, which are all abundant in palmpoplantar epidermis. There is one report in press of a mutation in the head of K1 in NEPPK (V Kimonis et al., abstract in J Invest Dermatol 1994, 102:545a). K6 and K16 are also expressed suprabasally in palmpoplantar epidermis and must be good candidates, although they might be expected to produce a more widespread phenotype as they are also expressed in many other tissues.

Transgenic studies have contributed a lot to understanding structural proteins, and mouse models have already been described for some of the keratin disorders described here (see review by Klymkowsky, this issue, pp 46–54) [6,21]. Defects in expression of the neurofilament proteins NF-L [39*] and NF-H [40*,41*] can produce phenotypes similar to those of motor neuron diseases. Some mouse models of defective intermediate filament expression are, however, currently under parallel in human diseases: a K8 knockout [42*] and a vimentin knockout [43**]. Finding the diseases that match these should be a high priority now in many laboratories.

**Conclusions**

We now know what the keratin cytoskeleton does in stratified squamous epithelia: it provides resistance to mechanical stress in epithelial cells. In the absence of an effective keratin cytoskeleton, epidermal cells are unable to resist the physical stresses of normal wear and tear, and they break down under physical pressure.

The clustering of the mutations has also highlighted regions of special importance in the intermolecular assembly interactions of keratins. A less obvious question emerging from this work is one of mutations with no phenotype. No deleterious mutations have been seen in most of the central rod domain which forms the basic coiled-coil structure, yet mutations must arise in these locations in the human population: are these really selectively neutral mutations? Asymptomatic genetic variation falls within the range of polymorphism, and the range and nature of polymorphisms within these important structural proteins are themselves going to produce interesting information.

It is probable that non-keratin intermediate filament cytoskeletons perform similar structural roles in other cells, each cell with its own specific mechanical requirements or additional functions. It is unlikely that primary intermediate filament disorders will be limited to the keratins for much longer. The newly discovered beaded filament proteins of the eye lens, found to be intermediate filament proteins (albeit rather distantly related ones) may, for example, be involved in cataract formation. In some intermediate filament proteins, defects may be expected to be lethal (e.g. type V proteins, the nuclear lamins), or may only ever show mildly disruptive mutations as viable phenotypes. This would be the opposite of the epidermal keratins, for which the short half-life of the cell and the other coexpressed cytoskeleton filaments mean that marginally disruptive mutations may never be detected. There will be some exciting discoveries to be made in the near future once the pathological consequences of cell fragility in other body sites are recognized for what they are.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest


One of the initial reports of mutations in the H1 subdomain of K5 responsible for the EBS-WC phenotype.


One of the first reports of mutation in the L12 linker domain. These mutations are surprising, as this domain is not known to be directly involved in filament assembly.


Mutations in the linker L12 domain of both basal keratins K5 and K14 cause EBS-WC. This paper presents data which suggest that these mutations are acting to increase the tendency of the linker to form helical structures and implies that lack of flexibility in this domain weakens the filament. This report therefore sheds light on the function of this and other linker domains in intermediate filaments.


The first report of a small in-frame deletion in a keratin gene in an EBS-WC family. The deletion has important structural implications as the mild phenotype indicates that this mutation does not grossly interfere with coiled-coil formation, as one would have expected.


The first report of the mutation in a rare recessive form of EBS. This point mutation in the less well conserved part of the 1A domain produces a mild phenotype in homozygotes and has no noticeable effect in heterozygotes.


The first demonstration that ablation of an epidermal keratin, K14, leads to a severe recessive form of epidermolysis bullosa simplex. The discovery of a natural "knockout" precedes the analogous transgenic experiment in this case. We show that it is absence of functional filaments and not presence of aggregates that leads to the disease phenotype in keratin disorders. We also show that one K14 allele is sufficient for normal function in the normal heterozygous parents, which has major implications for gene therapy. Suprabasal keratin filaments are present but are slightly abnormal, demonstrating that interactions occur between these filament systems.


One of the first two reports of a natural "knockout" of K14 causing a severe recessive form of EBS. These findings are of particular interest because the mutation might be expected to produce dominant-negative effects in the heterozygotes. However, this is not the case, apparently due to instability of the mutant mRNA and also possibly of the truncated protein.


This is the initial report of the cause of EPPK: mutations in the palmoplantar-specific keratin gene, K9. Again, mutations were found in the same arginine residue of the helix initiation peptide as in K10 and K14, showing that this residue is subject to CpG hypermutability (methylation of a CpG dinucleotide followed by deamination and mismatch repair).


This paper describes for the first time the molecular basis of IBS mutations in the K2e gene, in two British families. A new mutation was demonstrated in one kindred and identical mutations have now been reported in a total of 9 families worldwide, indicating that this is a CpG mutational hotspot in K2e.


One of the first papers describing mutations in K2e. This paper describes the causative mutations in IBS families, including the descendents of the families in which Siemens first described the disease. One family was diagnosed originally as having ichthyosus exfoliativa, but has a mutation identical to the most common IBS mutation, showing that this classification is probably false.

A report of K2e mutations in six IBS families, all in the same codon. Some of these patients have a severe IBS phenotype and were initially misdiagnosed as bullous congenital ichthyosiform erythroderma. This phenotypic heterogeneity is a common feature of all keratin diseases and often leads to false clinical classification. The cause of this variation is unknown.


This transgenic study shows that aberrant expression of the neurofilament protein NF-L produces a phenotype similar to human neurodegenerative disease. There might therefore, be a role for neurofilaments in this major clinical area. This role remains to be demonstrated conclusively in humans.


Further evidence of the involvement of neurofilament proteins in neurodegenerative diseases by production of transgenic mice aberrantly expressing NF-H.


NF-L fusion protein failed to enter axons and trapped all other neurofilament proteins in the cell body, yielding neurofilament-free axons. The resulting phenotype was reminiscent of some human neurodegenerative diseases.


This report shows that knocking out K8, which is expressed in simple epithelia, produces a lethal phenotype in mice. Most K8-null mice died in mid-gestation as a result of liver haemorrhage; surviving homozygous-null females were sterile.


Mice lacking expression of the type III protein vimentin were reported to have no phenotype. Despite this result, it is possible that vimentin mutations might have effects in humans where the physical size of the organism leads to greater stresses on cells than in mice, analogous to the phenotypic differences between mdx mice versus Duchenne muscular dystrophy in humans.


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