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Cyclic Ichthyosis with Epidermolytic Hyperkeratosis: A Phenotype Conferred by Mutations in the 2B Domain of Keratin K1

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Summary

Bullous congenital ichthyosiform erythroderma (BCIE) is characterized by blistering and erythroderma in infancy and by erythroderma and ichthyosis thereafter. Epidermolytic hyperkeratosis is a hallmark feature of light and electron microscopy. Here we report on four individuals from two families with a unique clinical disorder with histological findings of epidermolytic hyperkeratosis. Manifesting erythema and superficial erosions at birth, which improved during the first few months of life, affected individuals later developed palmoplantar hyperkeratosis with patchy erythema and scale elsewhere on the body. Three affected individuals exhibit dramatic episodic flares of annular, polycyclic erythematous plaques with scale, which coalesce to involve most of the body surface. The flares last weeks to months. In the interim periods the skin may be normal, except for palmoplantar hyperkeratosis. Abnormal keratin-filament aggregates were observed in suprabasal keratinocytes from both probands, suggesting that the causative mutation might reside in keratin K1 or keratin K10. In one proband, sequencing of K1 revealed a heterozygous mutation, 1436T→C, predicting a change of isoleucine to threonine in the highly conserved helix-termination motif. In the second family, a heterozygous mutation, 1435A→T, was found in K1, predicting an isoleucine-to-phenylalanine substitution in the same codon. Both mutations were excluded in both a control population and all unaffected family members tested. These findings reveal that a clinical phenotype distinct from classic BCIE but with similar histology can result from K1 mutations and that mutations at this codon give rise to a clinically unique condition.

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Introduction

Keratins are polymeric proteins that form the intermediate-filament cytoskeleton of epithelial keratinocytes. Mutations in keratins have been identified in a variety of inherited disorders of skin and other epithelia, all of which share in common fragility of the skin and hyperkeratosis. These disorders vary in severity and in the relative proportion of blistering to scaling. Mutations in K5 and K14, the basal keratins, result in the epidermolysis bullosa simplex disorders (Bonifas et al. 1991; Coulombe et al. 1991; Lane et al. 1992). Mutations in suprabasal keratins K1 and K10 are causal in bullous congenital ichthyosiform erythroderma (BCIE), also known as "epidermolytic hyperkeratosis" (Cheng et al. 1992; Chipev et al. 1992; Rothnagel et al. 1992). Mutations in K2e, a protein expressed in the upper layers of the epidermis, are responsible for ichthyosis bullosa of Siemens, a condition marked by superficial peeling or molting of the skin (McLean et al. 1994*b;* Rothnagel et al. 1994). Mutations in K9 have been found in palmoplantar hyperkeratosis with epidermolytic hyperkeratosis (Bonifas et al. 1994).

In its classic form, BCIE is characterized by blistering, erythroderma, and hyperkeratosis evident at birth. Gradually, blistering improves and erythroderma lessens, but the hyperkeratosis persists and may worsen. Usually the condition is generalized and relatively stable in its expression in a given individual. Suprabasal clumps of keratin filaments and cytolysis are seen on light microscopy and are confirmed by electron microscopy. These features give the condition one of its names, "epidermolytic hyperkeratosis," although this histological finding is not limited to this disorder. We present two families with a distinctive phenotype of cyclic ichthyosis (Francis et al. 1996), with histological evidence of epidermolytic hyperkeratosis, in whom we have identified mutations in the same codon of K1.

Subjects, Material, and Methods

Clinical Summaries

TH, the only person in his family to be affected, presented with blisters and erosions at age 12 h. A provi-

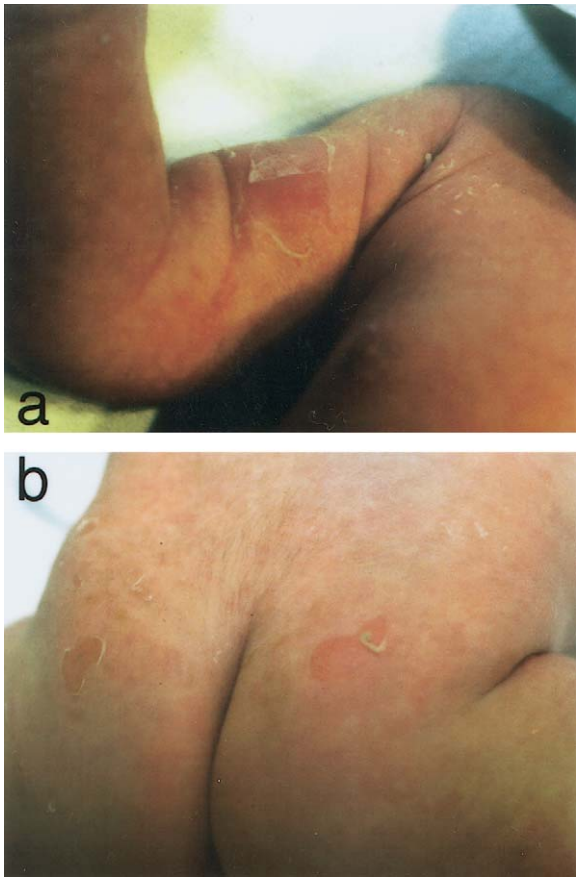

Figure 1 *a* and *b,* Patient TH at age 10 d. Scattered blisters, erosions, and peeling, along with patchy erythema, are evident.

sional diagnosis of and treatment for staphylococcal scalded skin was given. Blisters recurred at day 10; a diagnosis of epidermolysis bullosa simplex was entertained (fig. 1). At age 1 mo, the individual developed thickening of the palms and soles and patchy erythema. By the age of 2 years, he had experienced occasional blistering of the skin, hyperkeratosis of the palms and soles, and explosive bouts of generalized erythroderma (fig. 2). By age 3 years, plaques of thickened, sharply demarcated erythema and hyperkeratosis had appeared on his chest, groin, back, axillae, and flexures. Now almost 5 years of age, he has experienced one additional episode of explosive erythroderma necessitating hospitalization.

The phenotype of patient TH was recognized to be identical to that of a second proband, BM (fig. 3), who had been examined 10 years earlier. The second proband had migratory, erythematous, thickened plaques over his body and palmar and plantar hyperkeratosis. The features of the condition varied greatly among his affected relatives. His mother had involvement of her palms and soles and very subtle changes in her axillae at the time of our initial evaluation of patient BM. She reported intermittent involvement of the volar aspects of her forearms. His aunt, patient JS, was most severely involved, with episodic dramatic bouts of widespread erythema, vesicles, and pustules and had been given a misdiagnosis of pityriasis rubra pilaris and pustular psoriasis prior to biopsy confirmation of BCIE. Between the bouts of erythrodermic flare, she had palmar and plantar hyperkeratosis and plaques of mild erythema and scale in her folds (fig. 4). Her two affected children had only palm and sole involvement. Other family members identified by the index case's mother as being affected had involvement limited to the scalp, the palms and soles, or the abdomen (fig. 5).

Light and Electron Microscopy

Skin biopsies were obtained, with appropriate consent, from three affected individuals and from unaffected control subjects. Tissue was fixed in 10% neutral buffered formalin, processed into paraffin for routine histological analysis, and stained with hematoxylin and eosin. Samples were fixed in sodium cacodylate buffer containing 2.5% glutaraldehyde and 2% paraformaldehyde, postfixed in osmium tetroxide, en bloc stained in aqueous uranyl acetate, dehydrated through a graded series of ethanol and propylene oxide, and embedded in epoxy resin. One-micron-thick sections were stained with Richardson's blue, for light microscopy. Ultrathin sections were sequentially stained with uranyl acetate

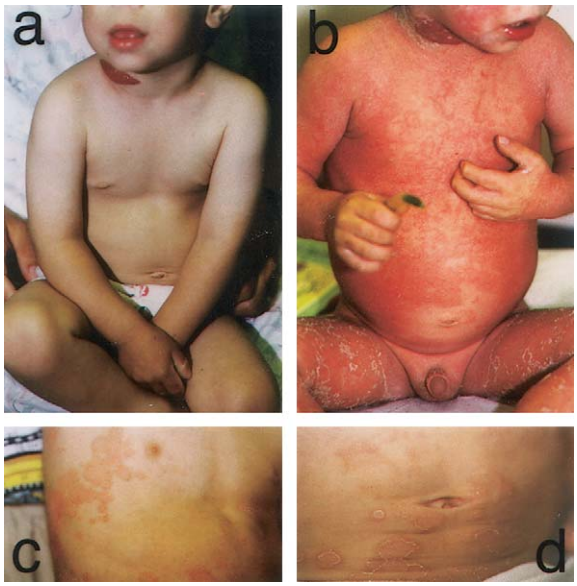

Figure 2 *a,* Patient TH at age 22 mo. The skin is almost entirely clear. The hemangioma on the neck is an unrelated finding. *b,* Explosive gyrate erythema and peeling in patient TH at age 30 mo. *c* and *d,* Patient TH at age 2 years 9 mo. Patchy circinate lesions reminiscent of EKV are present.

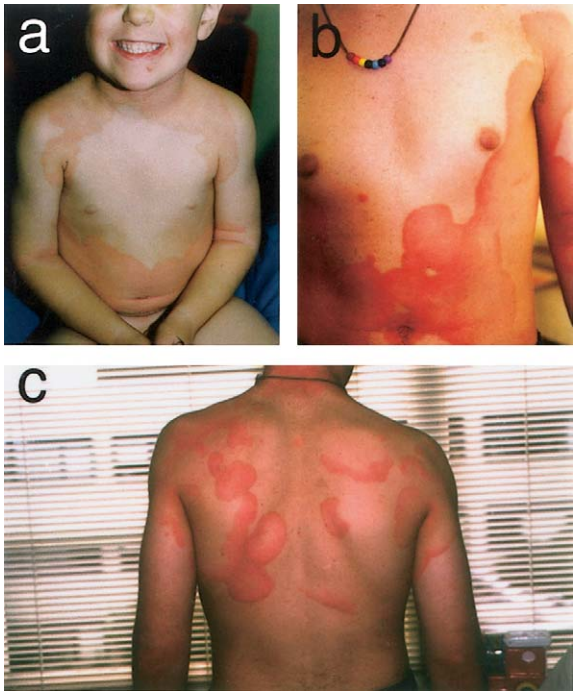

Figure 3 *a*, Patient BM at age 3 years, with sharply demarcated plaques. *b* and *c*, Patient BM at age 18 years. There has been migration of areas of involvement.

and lead citrate and were viewed by means of a Philips 420 transmission-electron microscope.

Immunofluorescence and Immunoperoxidase Microscopy

Unfixed skin-biopsy samples were submerged in OCT (optimal cutting temperature) and quick frozen in a slush of alcohol and dry ice. Sections 6 μm thick were mounted on glass slides and were immunolabeled according to standard protocols. Epidermal staining using monoclonal antibodies AE1, AE3, and AKH2 and the polyclonal antibody to keratin K2e was performed according to methods described elsewhere (Holbrook et al. 1987; McLean et al. 1994*b*).

Mutational Analysis

DNA was extracted, by standard methods, from peripheral blood lymphocytes from both probands, the affected aunt and mother of patient BM, the unaffected parents and brother of patient TH, and 50 normal, unrelated white individuals. cDNA was prepared from cryosections of snap-frozen skin-biopsy material obtained from patient TH, as described elsewhere (McLean et al. 1995). Near-full-length K1 cDNA was amplified by primers K1p1 (5′-TTC CGG GTC TGG GTA CCG AAG-3′) and K1p6 (5′-CTT ACT CAC ACT CAC GTT CGG GGC-3′), under the following PCR conditions: 1 cycle at 94°C for 5 min; 35 cycles at 94°C for 45 s, 56°C for 1 min, and 72°C for 2 min; and, last, 1 cycle at 72°C for 10 min. PCR buffer containing 1 mM of $MgCl_2$, 10% (v/v) dimethylsulfoxide, and 1 U of Ampli*Taq* polymerase (Perkin-Elmer) was used in a 50-μl reaction volume. The mutation 1436T→C creates a new *Bsm*AI site. For genomic confirmation, forward primer K1p5 (5′-TCC ATC AGT GAT GCA GAG CAG CGA-3′) was used in combination with K1p6 (above). PCR products (20 μl) were digested overnight with 4 U of *Bsm*AI in a total volume of 30 μl and were analyzed on 2.5 NuSieve agarose minigels.

The mutation in patient BM was identified in a PCR product amplified from genomic DNA by means of the HK1 primers and reaction conditions described elsewhere (Rothnagel et al. 1992). The PCR product was sequenced directly (Kogan and Gitschier 1989) by means of the forward HK1 primer. Ninety-two normal keratin 1 alleles were tested for the 1435A→T mutation, by al-

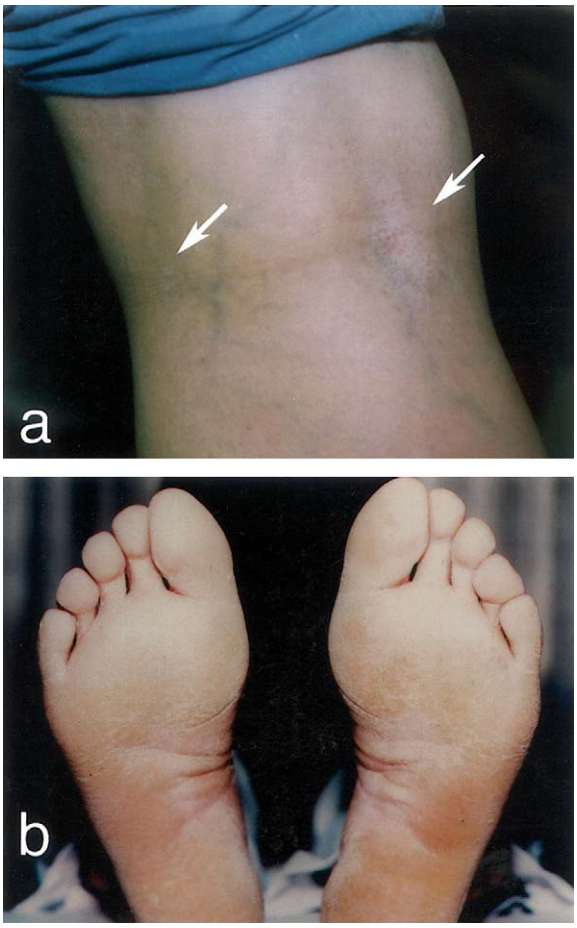

Figure 4 Patient JS, the aunt of patient BM. *a*, Minimal involvement of popliteal fossa, with mild lichenification and scaling. *b*, Hyperkeratosis of soles.

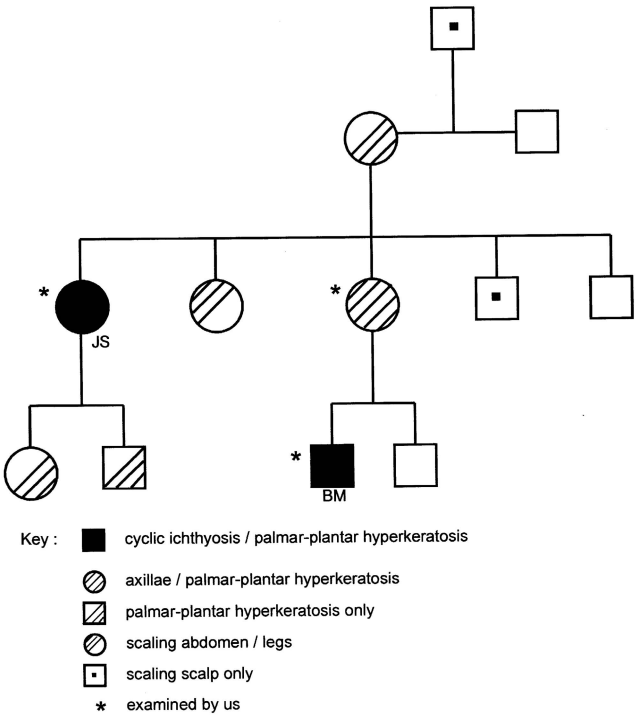

Figure 5 Pedigree of patient BM

lele-specific hybridization of PCR products, amplified from genomic DNA of 46 unaffected, unrelated individuals, with primers HK1. Samples were hybridized as described elsewhere (Stephens et al. 1997), with the oligonucleotides 5′-TGG ATC TGG AG[A/T] TTG CCA CCT A-3′, where the square brackets enclose the wild-type and mutant base that varied between the two allele-specific oligonucleotides. Blots were washed at 70°C.

Results

Keratin-Filament Abnormalities Revealed by Histological and Ultrastructural Analysis

Light microscopy (fig. 6*A*) of a skin-biopsy sample from patient TH showed an intraepidermal vesicle, epidermal spongiosis, eosinophils and neutrophils in the epidermis, and a superficial and deep perivascular infiltrate in the dermis. Immunofluorescence staining for IgA, IgE, IgG, IgM, C3, C1q, C4, and fibrinogen was negative. On electron microscopy (fig. 6*C*), cytolysis and circumscribed clumps of keratin filaments, some associated with desmosomes, and dense whorls of keratin filaments were seen in the lower and middle spinous layers. There appeared to be some dissolution of basal cells and some dyskeratosis. Results of immunohistochemical staining with keratin antibodies AE1, AE3, and AKH2 appeared to be essentially normal, although AE1 staining was noted in the spinous and cornified layers, and positive staining with polyclonal antibody to K2e was seen in the lower and upper spinous cells (not shown). Examination of skin-biopsy material derived from patient BM (data not shown) and his aunt, patient JS, revealed cytolysis and dense aggregates, on light microscopy (fig. 6*B*). Keratin-filament aggregation in suprabasal keratinocytes was confirmed by electron microscopy, consistent with the presence of BCIE (fig. 6*D*).

Although the clinical phenotype in both these families was observed to be markedly different from that typically seen in patients with BCIE, the presence of overt keratin-filament abnormalities in the suprabasal keratinocytes of affected members in both kindreds led us to postulate that mutations in either K1 or K10 might underlie this disorder. Since palmoplantar keratoderma was seen in both families, and since this aspect of the BCIE phenotype has been reported to be more severe in individuals carrying K1 mutations (DiGiovanna and Bale 1994), this gene was selected for initial analysis, in preference to K10.

Mutations in Codon 479 of K1 in Two Kindreds with Cyclic Ichthyosis

Direct sequencing of the PCR-amplified K1 rod domain of patient TH revealed a heterozygous transition mutation, 1436T→C, in the K1 gene, predicting the amino acid change of isoleucine to threonine in codon 479, I479T (fig. 7*b*). This alteration is in the highly conserved portion of helix 2B of K1, known as the "helix-termination motif." The mutation creates a new recognition site for the restriction enzyme *Bsm*AI, which was used to confirm the mutation in the proband and to exclude it from 50 normal unrelated individuals, by *Bsm*AI digestion of K1 genomic PCR fragments. Neither TH's parents nor his healthy sibling carried the mutation.

Direct sequence analysis of the PCR-amplified carboxy terminus of the K1 rod domain of patient BM revealed a heterozygous mutation, 1435A→T (fig. 7*c*), that predicts a substitution of the isoleucine at codon 479 by a phenylalanine residue, I479F. As expected, the mutation was carried by the patient's affected mother and affected maternal aunt but was not found in a screen of 96 K1 alleles of unaffected unrelated individuals (data not shown).

Discussion

The keratins are the major structural molecules of the epidermis and constitute a group of >30 distinct intermediate-filament proteins (Corden and McLean 1996, and references therein). They are divided into two groups, type I acidic keratins (K9–K20), whose genes

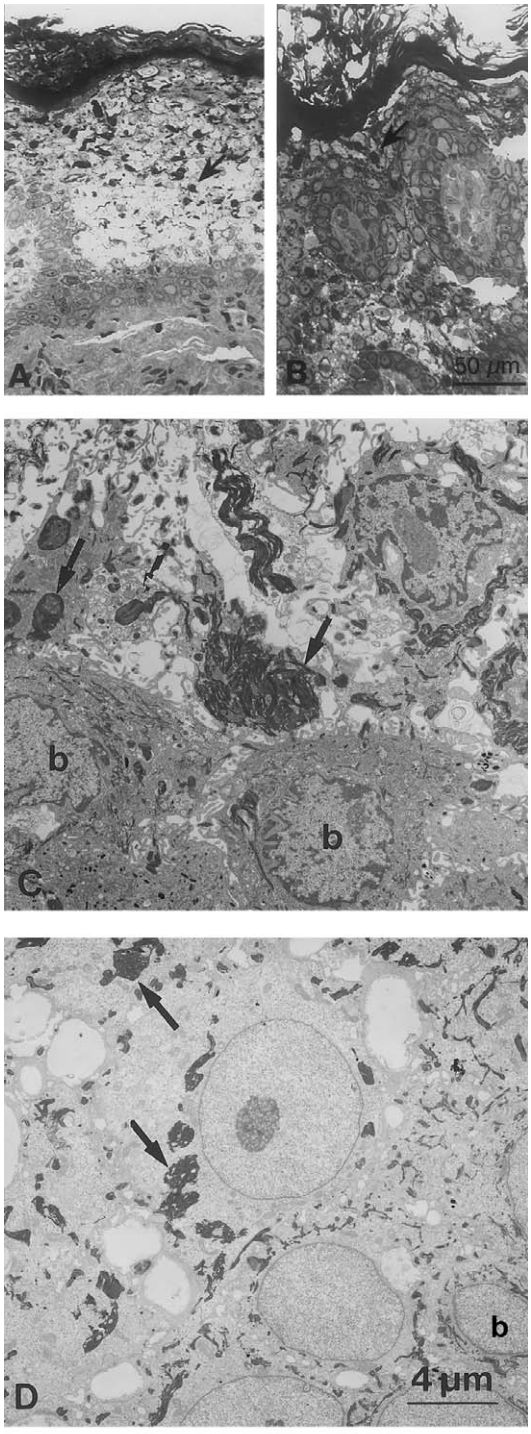

Figure 6 *A–D*, Light microscopy revealing intact basal cells and cytolysis of suprabasal keratinocytes in patient TH (*A* and *C*) and patient VS (*B* and *D*). Densely stained material is observed in the spinous layer (*arrows*). Electron microscopy of skin from patient TH (*C*) and patient VS (*D*) shows that basal keratinocytes (*b*) have evenly distributed keratin filaments, whereas in suprabasal cells there is abnormally dense keratin-filament aggregation including circumscribed clumps of keratin filaments (*arrows*).

reside at chromosome 17q12–q21, and type II basic keratins (K1–K8), localized to 12q11–q13. The acidic and basic proteins form dimers, which undergo higher-order polymerization to form 10-nm intermediate filaments that extend throughout and confer mechanical strength to epidermal keratinocytes. The expression of keratin protein pairs is specific for site and differentiation state. For example, K5 and K14 are the keratins of the basal epidermal keratinocytes; K1 and K10 are present in the suprabasal cells; and K2e is normally expressed in the upper spinous cells.

Keratins share the domain organization of all intermediate-filament proteins—a central coiled-coil rod domain containing four alpha-helical segments (1A, 1B, 2A, and 2B) separated by three nonhelical linker elements (L1, L12, and L2) (Quinlan et al. 1994). The rod domain is flanked by nonhelical head and tail domains. In the regions where the rod domain starts and finishes are two short, highly conserved sequences termed the "helix boundary motifs." The isoleucine residue that was found to carry the causative mutation in both families is fully conserved, not only in all type I and type II keratins but in all intermediate-filament proteins of all species cloned to date (Quinlan et al. 1994). Substitution within this protein motif, which has been implicated in molecular-overlap interactions (Steinert et al. 1993), is predicted to have a detrimental effect on keratin-filament assembly and/or the integrity in keratinocytes where K1 is expressed, consistent with the histological and ultrastructural findings in suprabasal keratinocytes. Mutations in nearby residues have been reported in several other keratin disorders in which filament aggregation is seen on electron microscopy (Corden and McLean 1996, and references therein; Irvine et al. 1997).

Mutations in the boundary-motif sequences of K1 and K10 have been reported in several families with the classic BCIE phenotype of severe, generalized epidermolytic hyperkeratosis (reviewed by Corden and McLean 1996). An unusual mutation in the VI variable domain of K1 has also been implicated in a family with nonepidermolytic palmoplantar hyperkeratosis (Kimonis et al. 1994). In individuals with BCIE, mutations in K1 have been reported to be more likely to result in palmar and plantar involvement than do mutations in K10 (DiGiovanna and Bale 1994). Palmoplantar keratoderma was observed in both families in the present study, a finding consistent with this reported correlation. Furthermore, a mutation in the 2B helical segment (R83E) of K10, the partner keratin of K1, resulting in a similar phenotype with blistering in childhood, accompanied with and followed by polycyclic erythematous hyperkeratosis but without palmoplantar involvement, has been reported (Joh et al. 1997).

The clinical picture in these two families and in the family studied by Joh et al. (1997) is quite distinct from

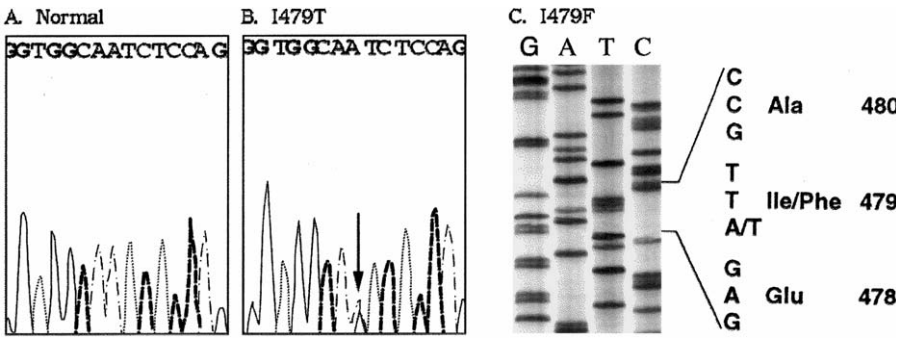

Figure 7 *A–C,* Direct sequencing of K1 genomic PCR fragments. *A,* Normal K1 sequence from the region of exon 7 encoding the helix-termination motif. The reverse strand is shown, complementary to bases 1443–1429 of the K1 cDNA (base 1 is assumed to be the A of the initiating methionine codon [Johnson et al. 1985]). *B,* K1 sequence equivalent to that shown in panel *A,* derived from patient TH. The arrow indicates the heterozygous mutation 1436T→C (the reverse strand A→G is shown). This mutation predicts the amino acid substitution 1479T. *C,* Sequence of the forward strand of K1, detailing bases 1432–1440, derived from patient BM, showing the heterozygous 1435A→T mutation, which predicts the amino acid substitution 1479F.

previous reports of BCIE. These distinctive features include recurrent explosive erythroderma, similar to erythrodermic psoriasis, and migratory erythematous scaling plaques, similar to erythrokeratodermia variabilis (EKV [MIM 133200]), along with palmar and plantar hyperkeratosis and mild ichthyotic changes in flexures and scalp. Nonetheless, the ultrastructural findings in skin are identical to those in BCIE.

The cyclic nature of the disorder and the marked variability in expression within patient BM's family are not readily explained. The positive staining for K2e in the lower spinous cells, where it is usually not present (Collin et al. 1992), suggests the possibility that its premature expression might provide substitute functional keratin molecules that can aggregate normally and mitigate disease expression. Our proposal of a distinct cyclic ichthyosis phenotype associated with alterations in this specific codon is supported by the recent report (Michael et al. 1997) that a family with episodic psoriasiform plaques on the body, with chronic and severe palmoplantar keratoderma, had the same mutation as we found in patient BM.

The cyclic ichthyosis disorder described here might be confused with EKV, a distinct autosomal dominant skin disorder, also characterized by migratory geographic plaques of erythema. The major ultrastructural feature of EKV is a reduction in the number of keratinosomes in the granular layer. Clumping of tonofilaments is an inconstant finding. The EKV phenotype has been linked to a locus on chromosome 1p (van der Schroeff et al. 1988), and mutations in connexin 31 (GJB3) have been implicated (Richard et al. 1998). The possibility of mutations in either K1 or K10 should be considered in families that present with EKV but do not show linkage to the 1p locus where connexin 31 resides.

In summary, we have described a distinct autosomal dominant disorder of keratinization characterized by marked variability in severity among affected relatives and, over time, in an individual. It is easily recognizable and is differentiated from other keratinizing disorders by bouts of polycyclic, geographic plaques of sharply demarcated erythema and hyperkeratosis, along with palmar and plantar hyperkeratosis. Different base changes in the same codon of K1 are responsible for the disorder in the two unrelated families reported here and in a third family recently presented in an abstract (Michael et al. 1997).

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Electronic-Database Information

The accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for EKV [MIM 133200])

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