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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.
Genetic Approaches to Understanding the Keratinopathies

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In the past half-decade, the tools of genetics have been used very successfully toward understanding hereditary skin disorders. One of the most exciting achievements has been the discovery that several inherited epidermal disorders are caused by mutations in genes for specific keratins (Table 1). This knowledge has already led to greater understanding of the pathobiology of these epidermal disorders and should eventually result in greater understanding of the structure-function relationships within the skin and how they influence health and disease.

In this chapter we will review the basic genetic methods used to identify the molecular basis of several keratinopathies. We will review each of the disorders shown to be caused by a keratin abnormality, including a clinical description and the current state of knowledge about the molecular basis of the disease.

GENETIC METHODS

LINKAGE ANALYSIS

Linkage analysis is a powerful tool for probing the genetic basis of a disease. Using a linkage analysis approach to mapping disease genes requires

<table>
<thead>
<tr>
<th>TABLE 1. Keratin Gene Clusters</th>
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<tr>
<td>Type I keratins (acidic keratins)</td>
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<tr>
<td>Examples include keratins 10, 13, 14, 16, and 17</td>
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<tr>
<td>Type II keratins (basic keratins)</td>
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<tr>
<td>Examples include keratins 1, 2, 4, 5, and 6</td>
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collection of family data. A variety of types of information must be collected, including the disease status of each individual, exact biological relationships of the family members, and some source for DNA (e.g., blood, buccal cells, fibroblasts) from each participant. The family structure most suitable for a linkage study depends on the inheritance pattern of the disorder of interest. For example, in an autosomal dominant disorder such as epidermolysis bullosa simplex (EBS), large families of several generations with multiple affected family members are ideal. In autosomal recessive disorders (e.g., lamellar ichthyosis), the most power is derived from many families in which multiple children in a sibship are affected. In addition, offspring of consanguineous unions (e.g., first-cousin marriages) can be very informative for identifying the location of recessive disease-causing genes.

In brief, linkage analysis is a statistical method used to define the chromosomal location of a genetic locus. The method involves estimating the genetic distance (usually denoted as \( \theta \)) between 2 loci (i.e., sites on chromosomes). Loci that are separated from each other by a large distance are likely to recombine (crossover) during meiosis. The closer together they are, the less likely recombination will occur. The parameter, \( \theta \), is measured in terms of frequency of meiotic recombination between a marker locus and a disease locus. The estimate of distance between loci (\( \theta \)) is dependent on the family structure, the model of inheritance, the frequency of the disease in the population, and the frequency of the different alleles at the marker locus. A statistic known as the LOD (logarithm of odds) score* is used to measure the significance of the linkage result. A LOD score of 3.0, giving odds in favor of linkage of 1,000:1, is generally considered “proof” of linkage. Conversely, a LOD score of –2 (odds against linkage of 100:1) is considered to exclude linkage between 2 loci for the particular value of \( \theta \) at which the LOD score was calculated.

Different types of markers can be used in a linkage analysis. In the early days of human gene mapping, useful polymorphic markers (loci with multiple alleles) were limited to blood group loci (including ABO and Rh blood groups and HLA) and serum or plasma protein loci (e.g., haptoglobin or glyoxalase). With the advent of DNA-based markers, new types of genetic polymorphisms became available for gene mapping. Restriction fragment length polymorphisms (RFLPs) were the first of these. An RFLP occurs when a stretch of DNA in some individuals contains a nucleotide sequence that is recognized by a restriction enzyme that cuts the DNA at that site but other individuals lack this DNA recognition sequence. Most genes in humans contain DNA sequences that are transcribed (exons) into messenger RNA separated by regions that are not (introns); RFLPs usually occur in introns. Because they occur regularly throughout the genome, they were a tremendous advance over biochemical markers. They were, however, still relatively uninformative because the only variation possible was the presence or absence of the recognition site (i.e., only 2 alleles exist in the human population). The next generation of genetic markers were the microsatellites, and the development

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*The LOD score is defined as the logarithm (to base 10) of the odds in favor of linkage at a given value of \( \theta \) compared with the odds that the 2 loci are not genetically linked.
of these was an even greater advantage to gene mappers. Microsatellites are identical units of 2, 3, or 4 nucleotides repeated many times. Microsatellites are easily detected using polymerase chain reaction (PCR) technology, which is quick and direct. The highly polymorphic microsatellite markers usually occur in introns, and the number of repeats varies greatly among individuals in a population. More than 5,000 microsatellite markers have been mapped in the human genome.

Microsatellites and RFLPs are primarily variations in our so-called junk DNA (e.g., intronic sequences), which is DNA that is not usually transcribed and that does not code for products used by the cell. However, genes whose product and function we know can also be used as marker loci for gene mapping. This type of marker is the “candidate gene.” If one suspects that an abnormality in a particular gene is the cause of a disorder, and if there are polymorphisms in that gene (usually in the introns), it can be used the same way any other polymorphic genetic marker is used. For example, polymorphisms in the keratin genes can be used as genetic markers in a linkage study.

**DISEASE GENE IDENTIFICATION AND MUTATION DETECTION**

Once a disease gene has been shown by linkage analysis to lie on a particular chromosome or in a particular chromosomal region, the next challenge is to identify the specific disease gene itself. This often requires collecting additional families, so that more meiotic events can be observed. If loci are close together, many meioses may occur before a recombination that narrows the disease location is found. It is also possible that a search of genome databases will identify genes that are good candidates for the disorder and that have been mapped to the chromosomal region to which the disease gene was mapped. If the candidate gene happens to have a polymorphism, a linkage analysis can be performed with the candidate gene itself being used as a marker. If the candidate gene is, in fact, the disease-causing gene, linkage analysis should produce an estimate of 0 equal to zero. In other words, all affected individuals in the family will have inherited one allele of the candidate gene, whereas none of the unaffected individuals will have inherited that allele.

Finding linkage of a candidate gene in a family still does not prove that the gene actually causes the disease. It is possible that the true disease gene is just extremely close to the candidate gene and no recombination between the candidate gene and the true disease gene has occurred.

Therefore, the next step is to test the candidate gene for actual involvement in the disease process. The proof that an abnormality in a candidate gene is truly the underlying cause of an inherited disease can be provided in several ways. The complete genomic or complementary DNA sequence of the candidate gene can be determined in healthy individuals and diseased persons. Then the coding region of the genes can be compared for differences. Within a family, all affected persons should be shown to have this change, and all unaffected persons should be shown to have the normal sequence. It is also necessary to confirm that this change is not a simple polymorphism but is indeed a disease-causing gene mutation. This can be done in several ways, including (but not limited to) (1) demonstrating that the mutation is not present in a large series of
normal control individuals, (2) showing that the mutation is expected to disrupt the normal function of the gene (e.g., a premature stop codon that produces truncated protein), (3) using in vitro functional assays to show that the mutated gene behaves abnormally, or (4) introducing the gene into an animal model (e.g., transgenic mouse) and showing that an abnormal phenotype is produced.

Often direct sequencing of a large gene is difficult and time-consuming. Other methods of mutation detection are used, and new ones are constantly being developed. An excellent review was provided by Grompe. One of the most widely used methods is the single-strand conformational polymorphism assay. It involves electrophoresis of PCR-amplified DNA fragments from the candidate gene on a nondenaturing polyacrylamide gel. The two single strands of DNA from each PCR product take on a three-dimensional conformation that depends on their primary nucleotide sequence. Differences between the normal DNA sequence and the sequence in the candidate gene (the purported mutation) will result in differential migration of the fragments on the gel. Subsequent direct sequencing of the abnormally migrating fragment will detect the specific mutational change. Other methods, including denaturing gradient gel electrophoresis, heteroduplex analysis, RNase A cleavage, chemical mismatch cleavage, and dideoxy chain termination sequencing technology, can be used to identify gene mutations.

EPIDERMAL KERATINOPATHIES

EPIDERMOLYSIS BULLOSA SIMPLEX

The earliest hereditary disease found to be associated with defects in a keratin gene was EBS. An autosomal dominant trait, EBS is the most common and least severe form of the epidermolysis bullosas. It is characterized by the development of skin blistering on trauma, generally without resultant scarring, and has been divided into several subtypes. The disease is often worse in warm weather. On histologic examination, blistered skin from patients with EBS shows fragility of the keratinocytes, with cleavage occurring through the basal cells. Tono-filament clumping is associated with cell cytolysis, as shown on electron microscopic examination.

Two research teams, each using a different approach, determined that keratin abnormalities underlie the clinical features seen in EBS. Bonifas et al. had noticed that the cellular fragility of EBS basal keratinocytes resembled the fragility of red blood cells in a group of hereditary anemias characterized by poikilocytosis. Those anemias were known to be caused by mutations in the genes encoding the red blood cell cytoskeletal proteins. The fact that both of these groups of disorders shared temperature-sensitive cell fragility led the investigators to hypothesize that abnormalities of the cytoskeleton of keratinocytes caused EBS. Using linkage analysis, Bonifas et al. investigated two large EBS families, one with the Weber-Cockayne type and another with the Koebner type. They showed that EBS in the Weber-Cockayne family was linked to the cluster of type II keratin loci on chromosome 12. The disorder in the Koebner family was linked to markers on chromosome 17 in the region of the type I keratins. Because keratins 5 and 14 are the keratins expressed pre-
dominantly in the basal keratinocyte layer where the histologic abnormalities in EBS occur, these were prime candidate loci. DNA sequence analysis identified a single base change in KRT14 (the official nomenclature for the gene for keratin 14) in affected family members. This was the first keratin mutation (T to C at base pair 3542 in exon 6) to be shown to cause clinical disease in humans.

The second laboratory that independently discovered the involvement of keratins in EBS was not attempting to study the human disorder but was interested in the function of keratins in general. They knew that mutated keratins introduced into cultured cells caused disruption of keratin networks. To investigate the effect of keratin mutations on living organisms, they engineered transgenic mice with a mutant keratin 14 gene. The mice exhibited blistering on the paws with histologic and ultrastructural abnormalities reminiscent of EBS.

Since these initial reports in 1991, 25 mutations in keratin 5 and 14 have been reported in patients with autosomal dominant EBS including Weber-Cockayne, Koebner, and Dowling-Meara types (Compton JC: Personal communication, 1996). In addition, an individual with a rare autosomal recessive form of EBS was shown to have a point mutation in the first a-helical segment of the rod domain in KRT14. Another patient with a severe case of EBS (generalized bullae, especially on extremities and face, present at birth and continuing postnatally, and without scarring) had a homozygous mutation in the KRT14 gene leading to a premature termination codon. Essentially this patient is keratin 14 null as a result of complete ablation of the keratin 14 protein.

**EPIDERMOLYTIC HYPERKERATOSIS**

Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma, or EH) is an autosomal dominant ichthyosis that occurs in approximately 1 in every 200,000 to 300,000 individuals. However, as many as half the cases of EHK represent new mutational events, where both parents are unaffected. The disease is manifest at birth, usually with blistering, redness, and peeling. Over time patients may have a generalized hyperkeratosis with or without erythroderma develop. Epidermolytic hyperkeratosis presents striking clinical heterogeneity between families, particularly regarding extent of body surface involvement, quality of scale, presence or absence of erythroderma, and palmoplantar involvement.

Information derived from a variety of approaches, including histology, ultrastructure, and molecular genetic studies in mice and humans, has led to the identification of the underlying defects in EH. In contrast to most other ichthyoses, the histopathologic picture of EH is distinctive. The stratum corneum is tremendously thickened, and there is vacuolar degeneration of the upper epidermis, leading to the histologic term “epidermolytic hyperkeratosis.” Granular cells exhibit dense, enlarged, irregularly shaped masses that appear to be keratohyalin granules. Electron microscopic examination illustrates that clumping of filaments begins in the first suprabasal layer. These aggregated filaments are clumps of keratin intermediate filaments (KIFs) that contain the terminal differentiation-specific keratins 1 and 10.

These light and electron microscopic studies suggested that a defect
in a terminal differentiation-specific epidermal gene product might underlie EHK, causing KIF disorganization, increased numbers of keratohyalin granules, and vacuolated granular cells. Another clue came from the similarity observed in the filament clumping in EHK and EBS. The discovery that EBS could be caused by a defect in either of the basal specific keratins (keratin 14 or keratin 5\textsuperscript{29}) suggested that the keratins expressed suprabasally (keratins 1 and 10) were particularly good candidates for EHK.

Compton et al.\textsuperscript{21} used a large family in which EHK was segregating through three generations to test for genetic linkage of the gene causing EHK to several candidate loci, including transglutaminase K, loricrin, profilagrin, and keratins 1 and 10. Each of these candidates could be excluded as the disease causing gene except for the locus for keratin 1, a member of the group of neutral-basic (type II) keratins. The type II keratin genes reside in a cluster located on the long arm of chromosome 12.\textsuperscript{22-24} Use of several microsatellite markers located in the region of the type II keratin loci confirmed linkage to this locus. Multilocus linkage analysis further supported this location, implicating a type II keratin gene, very probably K1, as the site of the molecular defect causing EHK in this family.

Fourteen affected individuals from three other EHK families studied by Bonifas et al.\textsuperscript{25} provided some evidence for linkage to markers on chromosome 12q. Linkage to markers on chromosome 17q, in the region of the type I keratins (the acidic keratins that include keratin 10) was strongly excluded in these families.

Chipev et al.\textsuperscript{26} sequenced the coding regions of both keratin 1 alleles of one patient in the family reported by Compton et al.\textsuperscript{21} A single base pair substitution in one allele was identified that caused a nonconservative amino acid change from leucine to proline in one residue of the H1 subdomain of the keratin 1 gene. One keratin 1 allele of every affected member in this family had the proline substitution, whereas all unaffected members had two unsubstituted (normal) alleles. To confirm that the proline substitution was not merely a polymorphism that by chance was segregating with EHK in this family, Chipev et al.\textsuperscript{26} tested another 100 alleles (from 50 normal control individuals). None was found to have the mutant allele.

To demonstrate that the mutation altered keratin 1 gene function, Chipev et al.\textsuperscript{26} developed a functional assay to study the effect of mutated keratin peptides on preformed KIFs. It had previously been shown that synthetic peptides with amino acid sequences corresponding to the principal overlap regions of keratin 1–keratin 10 KIF can disassemble preformed KIF in vitro.\textsuperscript{27-28} When the synthetic peptides representing either the normal or proline-substituted keratin 1 sequence were tested for their effect on the stability of preformed KIF, the normal peptide caused rapid disassembly. However, the proline-substituted peptide did so much more slowly. This abnormal interaction of mutated peptide with filaments observed in vitro could be extrapolated in vivo into diminished stability of intermediate filaments containing mutant keratin 1 chains.

Direct sequence analysis of the gene has been used to identify other mutations in keratin 1 in several small families and sporadic cases.\textsuperscript{29, 30}
FIGURE 1.
Relationship between gene and protein structure of type I and II keratins. *Shaded boxes* (labeled with large numbers) on gene structure represent exons. *Lines* (small numbers) between shaded boxes represent introns. Protein structure subdomains are also labeled (e.g., E1, V1). *Dotted lines* in the protein structure represent linker regions between domains. Regions 1A through 2B make up the central α-helical rod domain of the keratin protein. Offset in 2B represents the "stutter," or reverse of the regular heptad amino acid repeat motif. *Asterisks* denote mutation hot spots in keratin diseases. For review of keratin protein structure see Steinert. 63
Keratin 10 is the coexpressed partner of keratin 1, both of which are required to form KIF in the cells of the suprabasal layers of the epidermis. It is not surprising then, that abnormalities in keratin 10 were also found associated with EHK. To date, a number of EHK families have been studied and found to have mutations in keratin 10. Many mutations have been identified at the beginning of the 1A and end of 2B rod domain segments (Fig 1). These preferential sites for disease-causing mutations might facilitate the development of prenatal diagnostic testing and biologically based therapies.

Subtypes
In his original article in 1902, Brocq described EHK as “bullous ichthyotic erythroderma” and distinguished this condition from nonblistering congenital ichthyotic erythroderma. The original description included three unrelated patients with a blistering ichthyosis whose clinical manifestations varied by the presence of palmoplantar hyperkeratosis, quality of scale, and persistence of erythroderma into adulthood. Although clinical heterogeneity in EHK has previously been observed, the distinctions have not been clear. In an effort to better define and characterize the specific clinical features of this disorder, DiGiovanna and Bale examined 52 patients with histologically confirmed EHK from 21 families. Patients were evaluated and graded for involvement of the palms and soles, scalp, extensor and flexor areas, erythema, infection, and blisters. Within this group of patients, 6 clinical phenotypes were distinguished. Several features were useful for separating patients into clinical subtypes. The most distinctive characteristic was presence or absence of severe palmoplantar hyperkeratosis. Twenty-nine patients in 6 families had palmoplantar involvement. These patients were grouped into the PS (palm-sole hyperkeratosis) types. The remaining 15 families (23 patients) were classified as NPS (no palm-sole hyperkeratosis) types. On the basis of additional clinical characteristics, 3 distinct PS types and 3 distinct NPS types were identified, distinguished by the presence or absence of erythroderma, quality of scale, extent of involvement, presence of digital contractures, and gait abnormality. In an effort to correlate the clinical disease subtypes with specific mutations, the authors identified mutations in 11 of the 21 families. When keratin mutations were implicated in the pathogenesis of the disease, all families with severe palmoplantar hyperkeratosis have had abnormalities in keratin 1, whereas the NPS types had abnormalities in keratin 10 (Table 2). Further correlation of the clinical disease subtypes with the specific mutations should lead to a better understanding of the relationship between keratin structure and function in normal and diseased epidermis.

Table 2
<table>
<thead>
<tr>
<th>Important Correlations in Epidermolytic Hyperkeratosis</th>
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<tbody>
<tr>
<td>EHK with severe palmoplantar hyperkeratosis</td>
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<td>EHK without severe palmoplantar hyperkeratosis</td>
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Abbreviation: EHK, epidermolytic hyperkeratosis.
Palmoplantar Keratodermas

The palmoplantar keratodermas (PPKs) are a heterogeneous group of disorders distinguished by clinical and histologic features and pattern of inheritance.

Epidermolytic Palmoplantar Keratoderma

Palmoplantar keratoderma of Vörner, originally described in 1901, is characterized clinically by blistering and hyperkeratosis limited strictly to the palms and soles. In this condition, which is inherited in an autosomal dominant pattern, the histology is characteristic, showing hyperkeratosis with a ballooning degeneration of the suprabasal epidermis. These histologic features have been termed epidermolytic hyperkeratosis. Because of the clinical and histologic features, this disease has been called palmoplantar EHK and epidermolytic PPK (EPPK). As previously discussed, there is a generalized skin disease known as EHK. Generalized EHK may be both clinically and genetically heterogeneous. Several types of EHK distinguishable from each other on the basis of clinical features have been described, and the disease is often caused by mutations in either keratin 1 or keratin 10. Because keratins 1 and 10 are expressed in the skin over most areas of the body, it is not unexpected that their mutated variants would lead to generalized skin disease. Conceptually, the disease described by Vörner, palmoplantar EHK, is similar both histologically and clinically ( blistering and hyperkeratosis) to the generalized types except for distribution. Keratin 9 is a type I keratin expressed in the suprabasal cells of palm and sole epidermis. Keratin 9 was initially implicated in EPPK by identifying genetic linkage of the disease to the type I keratin gene cluster at chromosome 17q12–21. Subsequently several laboratories have identified mutations in keratin 9 in association with EPPK. All nine of the different amino acid substitutions that have been identified in EPPK to date have been in the 1A segment of the rod domain of keratin 9. This reflects the importance of this region of the protein to the alignment of heterodimers in the formation of intermediate filaments.

Nonepidermolytic Palmoplantar Keratoderma

Nonepidermolytic palmoplantar keratodermas (NEPPKs) have been classified clinically into diffuse, punctate, and focal forms. Unna-Thost disease is a diffuse PPK inherited in an autosomal dominant pattern. Although this disease may appear similar to EPPK because of the presence of hyperkeratosis, there is usually no blistering. Areas of hyperkeratosis may not be confined strictly to palms and soles but may involve other limited areas, such as the elbows, knees, areolae, and umbilicus. Histologically this disease does not have the distinctive pattern of EPPK but shows only orthokeratotic hyperkeratosis (thickened stratum corneum) and acanthosis (epidermal hyperplasia).

In a family with NEPPK studied by Kimonis et al., linkage with the type II keratin region on chromosome 12q was found. A single base change in the amino-terminal V1 variable subdomain of keratin 1 was found that completely cosegregated with the disease. This base change occurred in a window in the V1 subdomain that is conserved among most type II keratins. The observation that a mutation in this region is not as-
associated with epidermolysis suggests that the amino-terminal domain may be involved in KIF interactions with other cellular molecules rather than in stability of the KIF.

Rogaev et al. studied a large pedigree from Uzbekistan with a diffuse, nonepidermolytic type of PPK and identified linkage with genetic loci on chromosome 17. In a study of the striated form of PPK (type Brünauer-Fuhs-Siemens), linkage was excluded to both the type I and II keratin gene clusters but was found on chromosome 18q12, near a cluster of desmosomal cadherin genes. Shamsher et al. studied 2 families with a focal type of NEPPK. In addition to the palms and soles, these families had follicular, oral, and genital hyperkeratosis. After linkage of these families to the cluster of type I keratin genes on chromosome 17, mutations were found in keratin 16. In normal epidermis, keratin 6 and 16 are coexpressed and are present in the upper outer hair root sheath and nail bed, palm and sole skin, and suprabasal oral and genital mucosal keratinocytes. However, they may be induced in interfollicular epidermis by wounding or inflammation. This diverse heterogeneity within NEPPK is further demonstrated by the finding of linkage in a family with PPK (tylosis) and esophageal cancer, with the 17q23–qter region, excluding keratins 6, 9, 16, and 17.

ICHTHYOSIS BULLOSA OF SIEMENS

Ichthyosis bullosa of Siemens (IBS) is an autosomal dominant genodermatosi similar in clinical appearance to EH. Patients are born with redness and blistering, and hyperkeratosis develops over a period of weeks to months, particularly over flexural areas. In some areas the skin may have a shiny or lichenified appearance. The epidermis is fragile in IBS, and denudation of the superficial epidermal layers may result in the appearance of "molting." Histologically the epidermis shows hyperkeratosis and vacuolization of the granular cells, similar to EH, but is restricted to the uppermost living layers of the epidermis. Rothnagel et al. studied 4 families diagnosed with IBS and two originally diagnosed with EH but who lacked KRT1 or KRT10 mutations. In all of these families mutations were found that affected the same codon in the conserved helix termination motif at the end of the 2B segment of KRT2e. Subsequently other authors have identified KRT2e mutations in IBS.

WHITE SPONGE NEVUS

White sponge nevus (WSN) is a relatively benign, autosomal dominant disorder that affects noncornifying epithelia. Patients have white, spongy plaques of the oral mucosa. In some individuals the esophagus, nose, genitalia, and rectal epithelia are also involved. Histopathology of WSN shows epithelial thickening, parakeratosis, and extensive vacuolization of the suprabasal keratinocytes. The ultrastructural features include compact aggregates of KIFs in the upper spinous layers, showing a striking resemblance to those found in other epidermal disorders due to keratin defects. Keratins 4 (type II) and 13 (type I) are expressed primarily in noncornifying epithelia and have expression patterns that parallel the clinical and histologic features of WSN. Rugg et al. sequenced the
regions of the genes for keratins 4 and 13 that code for the peptides at the ends of the rod domains of these keratin proteins. These regions are hot spots for mutations in other keratinopathies. In 2 families they identified a mutation in the gene for keratin 4 that encodes the helix initiation peptide. The mutation was a three-base pair in-frame deletion. Using genetic linkage analysis in a third family, Richard et al. excluded the type II keratin cluster on chromosome 12 but found evidence for linkage to chromosome 17. Deoxyribonucleic acid sequencing identified a single base change resulting in a proline for a normal leucine at residue position 15 of the 1A subdomain of keratin 13.

PACHYONYCHIA CONGENITA

Pachyonychia congenita (PC) is a rare, autosomal dominant condition in which patients have onychogryphosis, hyperkeratosis of the palms, soles, knees, and elbows, and follicular hyperkeratosis (cutaneous horn). Individuals with the Jadassohn-Lewandowsky type have oral leukokeratosis. Those families with the rarer Jackson-Lawler type lack oral leukokeratoses but have natal teeth, hair anomalies (pili torti), and cutaneous cysts (steatocysts). Affected persons of families with PC who also had laryngeal lesions have been reported. A third, possibly related syndrome, but without the hyperkeratotic features of PC, is steatocystoma multiplex. This disease is characterized by hundreds of cystic tumors distributed along the back, anterior trunk, scrotum, and extremities. Histologic examination of involved skin in PC shows evidence of an abnormal keratin filament network, including perinuclear inclusions in spinous and granular cells, and ultrastructural analysis shows dense keratin aggregates in a perinuclear distribution. These characteristics suggest that PC is a keratinopathy. The clinical features of PC also correlate well with the expression pattern of keratins 16 and 17, keratins that are often associated with epidermal hyperproliferation. McLean et al. identified a heterozygous missense mutation in the helix initiation motif of keratin 17 in a family with Jackson-Lawler type of PC and a keratin 16 mutation (Leu130Pro) in another family with Jadassohn-Lewandowsky type of PC. Because keratin 6 is the expression partner of keratin 16, it is not surprising that Bowden et al. found a mutation in the gene for keratin 6a (one isoform of keratin 6) in a family with Jadassohn-Lewandowsky type of PC.

SUMMARY

Genetic methods (both statistical and laboratory based), along with close clinical scrutiny, have led to the recent discovery that abnormal keratin genes underlie several disorders of cornification (Table 3). The ability to classify diseases based on the specific underlying gene mutation has now become a reality (e.g., the ability to distinguish IBS from EHKS and to correlate palmoplantar hyperkeratosis in EHKS with keratin 1 mutations vs. the lack of palmoplantar hyperkeratosis with keratin 10 mutations). Understanding how specific keratin mutations cause their associated clinical phenotypes will lead to better appreciation of the function of KIFs in epidermis in normal and disease states.
TABLE 3.
Diseases Characterized by Mutations in Keratin Genes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Keratin Involved</th>
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<tr>
<td>Epidermolysis bullosa simplex</td>
<td>Keratin 5, keratin 14</td>
</tr>
<tr>
<td>Epidermolytic hyperkeratosis</td>
<td>Keratin 1, keratin 10</td>
</tr>
<tr>
<td>Epidermolytic palmoplantar keratoderma</td>
<td>Keratin 9</td>
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<tr>
<td>Nonepidermolytic palmoplantar keratoderma</td>
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<tr>
<td>Focal nonepidermolytic palmoplantar keratoderma</td>
<td>Keratin 16</td>
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<tr>
<td>Ichthyosis bullosa of Siemens</td>
<td>Keratin 2e</td>
</tr>
<tr>
<td>White sponge nevus</td>
<td>Keratin 4, keratin 13</td>
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<tr>
<td>Pachyonychia congenita</td>
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<tr>
<td>Jadassohn-Lewandowsky type</td>
<td>Keratin 6a, keratin 16</td>
</tr>
<tr>
<td>Jackson-Lawler type</td>
<td>Keratin 17</td>
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ACKNOWLEDGMENT
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REFERENCES


Editor's Comment

Keratins represent the predominant proteins produced by keratinocytes. During the past 20 years, much has been learned about the biochemical and molecular character of these important cytoskeletal proteins. An outgrowth of these basic studies has been the development of an understanding of how inherited abnormalities in these proteins result in human disease phenotypes ranging from intraepidermal blisters in patients with epidermolysis bullosa simplex to epidermolytic hyperkeratosis in patients with bullous congenital ichthyosiform erythroderma. Drs. Bale and DiGiovanna present an excellent overview of investigative methods used to identify the molecular basis of inherited diseases, review the clinical features of various keratinopathies, and summarize current knowledge regarding mutations in keratin genes that result in such chronic and debilitating disorders.

Kim B. Yancey, M.D.