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Linkage of Autosomal Recessive Lamellar Ichthyosis to Chromosome 14q

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Summary

We have mapped the locus for lamellar ichthyosis (LI), an autosomal recessive skin disease characterized by abnormal cornification of the epidermis. Analysis using both inbred and outbred families manifesting severe LI showed complete linkage to several markers within a 9.3-cM region on chromosome 14q11. Affected individuals in inbred families were also found to have striking homozygosity for markers in this region. Linkage-based genetic counseling and prenatal diagnosis is now available for informative at-risk families. Several transcribed genes have been mapped to the chromosome 14 region containing the LI gene. The transglutaminase 1 gene (TGM1), which encodes one of the enzymes responsible for cross-linking epidermal proteins during formation of the stratum corneum, maps to this interval. The TGM1 locus was completely linked to LI ($\hat{Z}$=9.11), suggesting that TGM1 is a good candidate for further investigation of this disorder. The genes for four serine proteases also map to this region but are expressed only in hematopoietic or mast cells, making them less likely candidates.

Introduction

The recessive ichthyoses are a clinically heterogeneous group of disorders (Williams and Elias 1985). Attempts to classify these diseases on the basis of histologic, biochemical, and ultrastructural parameters have failed to yield a widely accepted, reliable classification (Williams and Elias 1985, 1987; Traupe 1989). However, a severe type of autosomal recessive lamellar ichthyosis (LI) can be recognized. LI is a rare, generalized disorder of epidermal cornification, with a prevalence of ~1/200,000 persons (Foundation for Ichthyosis and Related Skin Types 1987). The disease is evident at birth, when it frequently presents with a thick, shiny, and taut encasement of the neonate called a *collodion membrane*. Later, the skin develops large, brown, platelike scale covering the entire body (Williams and Elias 1987). Patients may have palmar and plantar hyperkeratosis and significant tautness of the facial skin, which may be associated with ectropion and eclabium (everted eyelids and lips). If left untreated, severe ectropion can lead to blindness. Many individuals exhibit scarring alopecia and secondary hypohidrosis. The histologic features of the epidermis in LI are nonspecific but characteristically include marked thickening of the stratum corneum (hyperkeratosis).

The pathogenesis of LI is unknown, although an error in terminal differentiation of the epidermis has been postulated (Hohl et al. 1993; Williams and Elias 1993). Formation of the stratum corneum (cornification) is characterized by terminal differentiation in the granular layer and transition to corneocytes, which consist of cornified envelopes filled with keratin matrix. During this process, cornified envelopes are produced by transglutaminase-catalyzed cross-linking of cellular proteins and attachment of fatty acids and ceramides derived from the lamellar bodies to the surface of the envelope (van Hooijdonk et al. 1991; Reichert et al. 1993). This forms the epidermal barrier to water loss and microbial invasion. The thickness of the stratum corneum reflects the balance between the rate of cornification and the loss of cells through desquamation.

Recently, a number of genes have been characterized that encode proteins involved in the formation of the stratum corneum and that are therefore candidates for the LI gene. Keratins 1, 2e, and 10 are synthesized in the suprabasal layers and are retained in corneocytes. Filaggrin, a protein formed from posttranslational processing of profilaggrin, aggregates keratin filaments as part of the production of the intracellular keratin matrix in cornified cells (Dale et al. 1978; Steinert et al. 1981). Loricrin (Hohl et al. 1991) and involucrin (van Hooijdonk et al. 1991; Reichert et al. 1993) are major structural proteins of the cell envelope that are cross-linked by transglutaminases. Both transglutaminase 1 and transglutaminase 3 are present in the granular layer cells where the transition to corneocytes occurs. (Transglutaminase 1 is the same as transglutaminase K. Transglutaminase 3 is transglutaminase E.)

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In light of the clinical heterogeneity in the recessive ichthyoses, only families having a clinically similar, severe phenotype of LI were selected for this study. Our approach to family collection was twofold: We chose families from the United States with two or more individuals with LI. In addition, because of the increased power for linkage analysis of recessive disorders by using inbred pedigrees, we sought both simplex and multiplex inbred families in an Egyptian population where the frequency of consanguineous marriages is nearly 30% (Hafez et al. 1983). These families were tested for linkage to the candidate genes described above. We have found conclusive evidence for linkage of LI to markers on chromosome 14 in the region of the transglutaminase 1 gene locus (TGM1) in both inbred and outbred families. In the inbred families, there was striking homozygosity of markers in the 14q11 region.

Subjects and Methods

Subjects

The families presented here are a subset of our collection of pedigrees ascertained as part of an ongoing study to identify the genetic basis of several different ichthyotic skin disorders. This subset consisted of all those families where affected persons exhibited the severe LI phenotype described above. All patients from both the United States and Egypt consented to examination by a dermatologist and provided detailed medical and dermatologic history. Patients ranged in age from 10 mo to 48 years at the time of ascertainment. DNA was obtained from each individual either from blood or buccal mucosa, with informed consent under a protocol approved by the institutional review board. Patient diagnosis was established through examination by a dermatologist and review of medical records. Egyptian families were ascertained from the clinic records of the Ain-Shams Medical Genetics Center in Cairo. Because of the heterogeneity of the autosomal recessive ichthyoses and in an effort to maximize the chance of identifying a single Mendelian locus, we selected a clinically homogeneous group of families from our data prior to performing any linkage analysis. The patients we selected all had a severe form of LI with brown, platelike scale covering the entire body surface (fig. 1). Seven families from the United States (37 individuals; 17 affected) (fig. 2*a*) and six Egyptian families (23 individuals; 10 affected) (fig. 2*b*) had this severe clinical phenotype and were included in our analysis. All patients had congenital onset of their skin disease. Of the 22 cases on whom this information was available, 21 had a history of collodion presentation at birth.

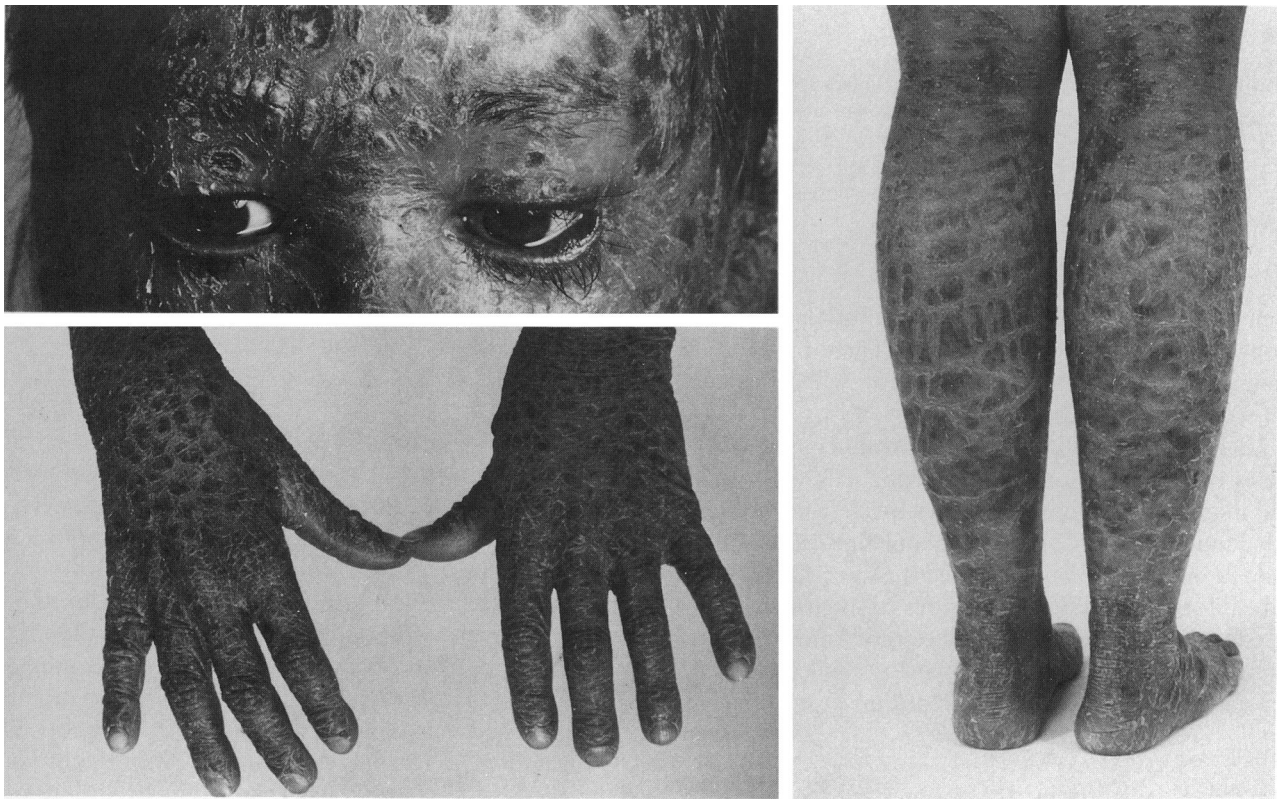

Figure 1 Individuals with autosomal recessive LI. *Top left panel,* Face of a young patient showing bilateral ectropion. *Bottom left panel,* Dorsum of hands. *Right panel,* Lower legs of an adult with large, brown, platelike scale.

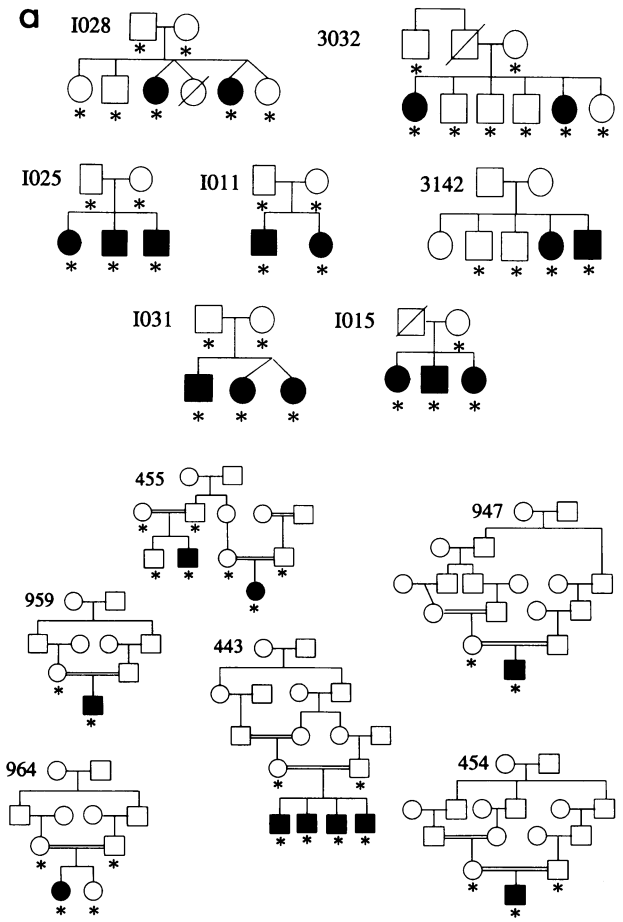

Figure 2 *a*, Pedigrees of the seven LI families ascertained in the United States. *b*, Pedigrees of the six inbred Egyptian families. Blackened symbols signify affected individuals; unblackened symbols signify unaffected persons. An asterisk (*) signifies an individual on whom DNA was obtained and analyzed. Double marriage lines identify consanguineous relationships.

Nineteen of 27 patients had ectropion (fig. 1), and half had alopecia with scarring of the scalp. Three patients were examined while on oral retinoid therapy, while the remainder were using only topical treatments.

All Egyptian families were consanguineous, with marriages between first cousins occurring in several families and more complex inbreeding in others. The families resided in the greater Cairo area (population 14–16 million) and Alexandria. No family shared the same surname. Pedigree information obtained for four to six generations antecedent of each proband failed to reveal any evidence of interrelatedness among the Egyptian families. All of the U.S. families were Caucasian and of European ancestry.

DNA Isolation

Standard isolation methods were used to purify DNA directly from patient blood cells. In some cases DNA was obtained by gently swabbing the buccal mucosa for 30 s by using a cytobrush (Richards et al. 1993). The cells obtained were placed directly in 50 mM NaOH. This solution was heated for 10 min to 95°C, neutralized with 1.0 M Tris-Cl pH 8.0, and stored at 4°C. Five-microliter volumes typically sufficed for PCR amplification.

DNA Marker Analysis

The microsatellite markers were amplified by PCR in 30-μl reaction volumes containing 200 ng genomic DNA prepared from whole blood or 5 μl DNA prepared from buccal mucosa. Reactions were performed with 100 nM of each primer; 200 μM each of dGTP, dATP, and dTTP; 25 μM dCTP; 0.1 μl ^{32}P dCTP(3,000 Ci/mmol); 1.5 U AmpliTaq DNA polymerase; and 1 × buffer containing 10 mM Tris-Cl, 50 mM KCl, 1.5 mM $MgCl_2$, and 1 mg gelatin/ml, pH 8.3. After an initial denaturing step of 5 min at 95°C, amplification was generally performed for 35 cycles at 94°C for 1 min, 55°C for 1 min, and 72°C for 1.5 min, followed by a final incubation for 10 min at 72°C. For D14S283 and D14S275, denaturation and annealing times were each reduced to 30 s and extension was omitted, as per the optimal PCR conditions for these markers (Gyapay et al. 1994). Amplified products were analyzed after 1:1 dilution with 100% formamide by electrophoresis of 4 μl on a 6% denaturing polyacrylamide gel. The gels were dried, and autoradiograms were exposed overnight at −70°C.

Linkage Analysis

LI was modeled as a fully penetrant autosomal recessive condition with disease allele frequency calculated from the reported prevalence of 1/200,000. Marker allele frequencies were estimated from 53 to 75 alleles of unrelated individuals in the study families and in other reference families without LI in our laboratory. Computations were performed using the LINKAGE package of programs (Ott 1985) on a VAX workstation.

Results

Linkage studies

We initially utilized seven polymorphic microsatellite markers to test for linkage to a number of candidate loci: the type I and type II keratin genes on chromosomes 17q and proximal 12q, respectively, the profilaggrin-loricrin-trichohyalin cluster on chromosome 1q, and the recently mapped locus for Darier disease (a dominant disorder of cornification) on distal chromosome 12q. Families were also genotyped for a marker within the gene encoding von Willebrand factor, because of a reported association between LI and von Willebrand disease (Capra et al. 1993). Obligate recombination was found between the LI locus and each of these marker loci, providing exclusions of 3 cM to 29 cM on either side of the candidate genes (data not shown).

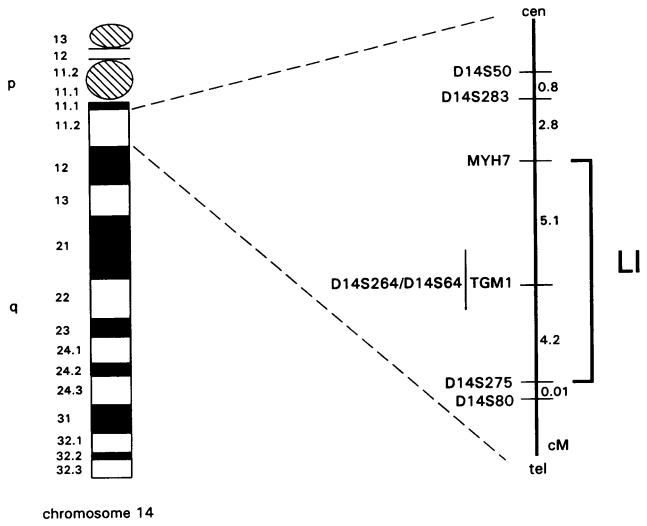

Figure 3 Map of chromosome 14q11, showing the LI region

We next tested linkage to the candidate locus TGM1 on chromosome 14q11 by using a dinucleotide repeat polymorphism within intron 14 of the gene (Kim et al. 1992). Complete cosegregation between LI and TGM1 was observed in all of the families tested, yielding a lod score of 9.11 at $\hat{\theta} = 0$.

To more precisely define the location of the LI gene, we analyzed our families with seven microsatellite markers flanking TGM1. The order and distances between these markers is illustrated in figure 3 (Gyapay et al. 1994; Buetow et al. 1994; O. W. McBride, personal communication). Our analysis showed no recombination with either D14S64 or D14S264, two markers tightly linked to each other and to TGM1. The results of linkage analyses for all eight chromosome 14q markers versus LI are shown in table 1.

Homozygosity in Inbred Families

Eight of the 10 inbred Egyptian LI patients (five families) were informative and homozygous at the TGM1 locus. The remaining two individuals were also homozygous at this locus, although in these two families either one parent was untyped or the parents were homozygous and therefore uninformative. Figure 4 shows haplotype analysis of two of the Egyptian families with extensive chromosome 14 homozygosity in affected individuals. In contrast to the Egyptian patients, only four persons with LI in seven U.S. families were informative and homozygous for TGM1 (data not shown). The results of the homozygosity mapping for the eight markers tested on chromosome 14q are shown in figure 5. All inbred individuals were homozygous for TGM1, D14S264, and D14S64. Two individuals were heterozygous for the three markers proximal to TGM1 (MHY7, D14S283, and D14S50), and one of these individuals was also heterozygous for D14S80, the most distal marker tested. Two additional persons were heterozygous for D14S50 and D14S275, respectively. No excess homozygosity was detected at six other loci on different chromosomes (data not shown). These results are consistent with the linkage data and define the candidate region as 9.3 cM on chromosome 14, flanked by MYH7 and D14S275.

Haplotype Analysis

Haplotype analysis of the markers completely linked to LI (TGM1, D14S64, and D14S264) in both the Egyptian and U.S. families revealed that 14 different haplotypes were present among 17 phase-known independent disease-carrying chromosomes. Of the two haplotypes that were represented twice, one (3-3-3) was present in one Egyptian family and two U.S. families. The other (3-2-3) was present in one Egyptian and one U.S. family. The "3" (~174 bp) allele at the TGM1 locus was the most frequent allele in each population (50% of U.S. chromosomes and 58% of Egyptian). The "3" and "2" alleles of D14S64 and the "3" allele of D14S264 were also common alleles in the general population.

Discussion

The recessive ichthyoses are a heterogeneous group of disorders whose classification has been problematic. The

Table 1

Maximum-Likelihood Estimates of Lod Scores and Recombination Fractions for Linkage of LI to Chromosome 14 Markers

Marker	Family Origin	$\hat{Z}$	$\hat{\theta}$
D14S50	United States	3.2	.05
	Egypt	3.19	.03
	Overall	6.37	.04
D14S283	United States	1.16	.08
	Egypt	4.11	.04
	Overall	5.21	.05
MYH7	United States	3.12	.04
	Egypt	2.93	.04
	Overall	6.05	.04
TGM1	United States	4.64	0
	Egypt	4.47	0
	Overall	9.11	0
D14S64	United States	4.86	0
	Egypt	5.43	0
	Overall	10.29	0
D14S264	United States	4.38	0
	Egypt	3.78	0
	Overall	8.16	0
D14S275	United States	1.89	.05
	Egypt	3.24	.03
	Overall	5.09	.04
D14S80	United States	1.21	.08
	Egypt	4.98	0
	Overall	5.85	.03

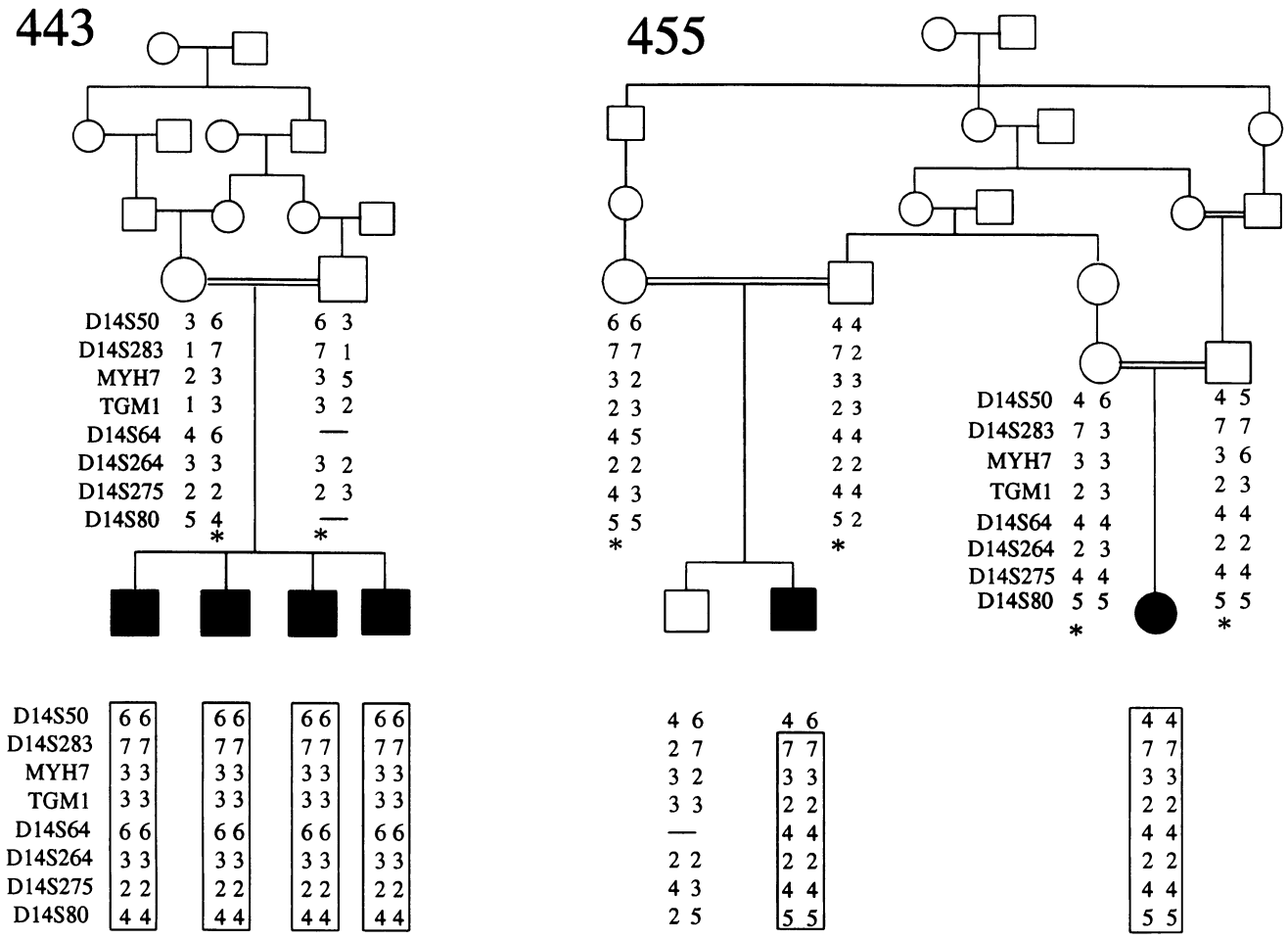

Figure 4 Haplotype analysis of chromosome 14 markers in two inbred Egyptian LI pedigrees. In family 443, all four affected children are homozygous at each of the eight markers tested, and the parental genotypes are informative. In family 455, two cousins share identical homozygous haplotypes from D14S283 to D14S80. An asterisk (*) signifies a chromosome carrying the LI gene.

term *lamellar ichthyosis* was originally used to include a spectrum of clinical phenotypes (Traupe 1989). Williams and Elias (1985) narrowed this spectrum by distinguishing LI with large, dark, and platelike scale from congenital ichthyosiform erythroderma with prominent redness of the integument and fine, white scale. Between these two extreme phenotypes, however, lies a gradation of clinical findings. Collodion membrane, ectropion, and alopecia may occur across the spectrum and are therefore not useful for classification. Attempts to refine the categorization of these disorders by using biochemical (Bergers et al. 1990) and ultrastructural parameters (Traupe 1989) have failed to yield consistent or replicable results to date. Given this clinical heterogeneity, we limited our analysis to a homogeneous group of patients exhibiting a severe, nonerythrodermic ichthyotic disease. This phenotype would be considered by most investigators as *classical lamellar ichthyosis*.

All of the families in this study showed complete linkage of the LI locus to TGM1, supporting the hypothesis that these patients represent a single genetic entity and providing the first evidence of gene localization for autosomal recessive LI. This result is further strengthened by the demonstration of complete linkage ($\hat{Z}$=10.29) to two anonymous markers that map <1 cM from TGM1. Five other markers tested gave lod scores >5.0 at close recombination distances.

In addition, all 10 affected individuals in the consanguineous Egyptian families were homozygous for TGM1 and the two closest markers, D14S64/D14S264, while 8 of the 10 were homozygous for MYH7, a marker proximal to TGM1. This is consistent with the expectation that the chromosomal regions adjacent to a recessive disease locus will be coinherited and homozygous by descent in inbred children, as proposed by Lander and Botstein (1987). Although the sample was small (N=17 independent disease-carrying chromosomes), haplotype analysis of the three loci completely linked to LI gave no evidence for linkage disequilibrium or a founder effect in either set of pedigrees. Based on available information about gene order and dis-

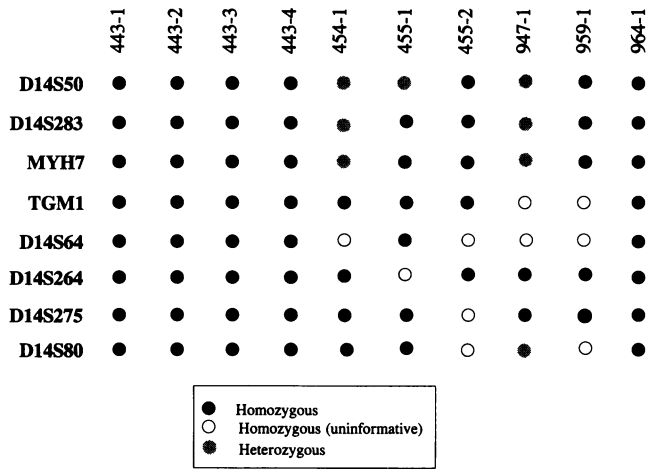

Figure 5 Evaluation of homozygosity at eight chromosome 14q markers in 10 individuals affected with LI who are the offspring of consanguineous marriages. Numbers across the top of each column identify the inbred individuals by pedigree number. Chromosome 14 markers are listed vertically. Blackened circles signify a marker that is homozygous in the affected individual, where at least one parent was a heterozygote at the locus. Unblackened circles identify markers that are homozygous, but where the parental mating was uninformative. Gray circles identify markers that were heterozygous in the inbred LI patient.

tance (Buetow et al. 1994; Gyapay et al. 1994; O. W. McBride, personal communication) the candidate region in our families is ~9.3 cM. Further delineation of the LI locus within this interval will require new polymorphic markers between MYH7 and D14S275. Analysis of recombinants between LI and MYH7 or D14S275 will then narrow the candidate region. Exact placement of D14S264/D14S64 with respect to TGM1 will also be helpful in delineating the LI region.

The genes for several cathepsins map within this 9.3-cM candidate region and are therefore potential candidates for the LI gene. The cathepsins are a group of intracellular proteases located predominantly in the lysosomes, where they play important roles in regulating intracellular protein degradation and turnover. Cathepsin G (CTSG) is a serine protease found in the azurophil granules of neutrophils (Hohn et al. 1989). Two similar serine proteases, CTSG-like 1 and 2 (CGL1 and CGL2), are closely linked to CTSG and are expressed only in activated cytotoxic T lymphocytes (Klein et al. 1989). A fourth serine protease, mast cell chymase, is expressed in mast cells of the dermis (Caughey et al. 1993). This family of genes forms a cluster of hematopoietic serine protease genes, which are linked to each other within the LI candidate region at chromosomal band 14q11.2 and to the genes for the T cell receptors A and D (Hanson et al. 1990), which map centromeric to the LI region. Although other members of the cathepsin family are expressed in the epidermis, those mapping to band 14q11.2 are expressed virtually exclusively in hematopoietic or mast cells, making them less likely to be candidates for the LI gene.

Transglutaminase 1, encoded by the TGM1 locus, is a prime candidate disease gene for LI in our families. Transglutaminase 1 plays a key role in the process of the terminal differentiation and formation of the stratum corneum. It was for this reason that we chose TGM1 in our initial selection of candidate loci to screen in LI. This enzyme is one member of a family of five transglutaminases, three of which (transglutaminases 1, 2, and 3) are expressed in a variety of stratified epithelia, including the epidermis. Transglutaminase catalyzes the calcium-dependent cross-linking of proteins through the formation of N^{ε}-(γ-glutamyl)lysine isodipeptide bonds. In the epidermis, involucrin and loricrin are known to be cross-linked by transglutaminases in the process of formation of the cornified envelope. In the case of transglutaminase 1, the newly synthesized protein undergoes postsynthetic fatty acid acylation, resulting in its anchorage in the plasma membrane (Hohl et al. 1993; Reichert et al. 1993). Interestingly, a literature search revealed two recent studies that have suggested the possibility that there may be abnormal expression of transglutaminase 1 in LI. van Hooijdonk et al. (1991) assayed transglutaminase 1 activity in scale from patients with autosomal recessive LI and demonstrated a striking and specific increase in activity of the enzyme relative to normal controls. In contrast, Hohl et al. (1991) used transglutaminase 1–specific antibodies on skin biopsies from three LI patients and found reduced or absent cytoplasmic staining in these specimens. They suggested several mechanisms that could account for their observations, including alteration of loricrin and involucrin cross-linking, which could interfere with formation of the cornified cell envelope in LI, perhaps through mutations in transglutaminase 1 or disturbed membrane anchorage.

These studies suggesting transglutaminase 1 in the pathogenesis of LI, in conjunction with our linkage of LI to the chromosomal region containing TGM1, furnish an exciting hypothesis for the role of this enzyme in the etiology of LI. In addition, these results provide the first opportunity for linkage-based genetic counseling for informative families at risk for LI. Localization of the LI gene serves as the springboard for the eventual identification of the LI gene product, which will enhance our understanding of the development of this disease and yield stimulating clues to the etiology of the large number of ichthyotic and scaling skin disorders.

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