Epidermolysis Bullosa Simplex in Israel

Clinical and Genetic Features

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Background: Epidermolysis bullosa simplex (EBS) is the most common form of epidermolysis bullosa. The disease is characterized by intraepidermal blistering due in most cases to mutations in cytokeratin genes 5 (K5) or 14 (K14). Extensive studies in the United States and Europe have shown that EBS is almost always inherited in an autosomal dominant fashion.

Objective: To assess the possibility that the molecular features of EBS may differ according to the type of population studied.

Design: We assessed 10 Israeli families diagnosed as having EBS and compared their clinical and genetic features with previous observations. Affected individuals underwent complete clinical evaluation. DNA from all family members was assessed for mutations in K5 or K14 using polymerase chain reaction amplification, direct sequencing, and subsequent mutation verification. In addition, specific cases were genotyped using a panel of microsatellite markers spanning the K14 locus.

Results: Eight distinct pathogenic mutations in K5 (3 mutations) and K14 (5 mutations) were identified. Six of these mutations are novel. The mutations included 2 nonsense mutations and 6 missense mutations. A third of the affected families inherited EBS in a recessive fashion, in contrast with previous observations in Europe and the United States. In addition, we identified a unique case that resulted from compound heterozygosity for a missense and a nonsense mutation in K14. Homozygous nonsense mutations were strongly associated with a severe phenotype.

Conclusion: The present study demonstrates a unique mutation spectrum and a strikingly different pattern of inheritance for EBS in a series of Israeli families compared with families of European or US extraction.

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to friction forces. Despite marked advances in our understanding of EBS during the last decade, little is currently known about the molecular genetics of the disease in geographic areas outside the United States and Europe. The present study was performed to elucidate the clinical and genetic features of a series of Israeli families affected with EBS.

METHODS

PATIENTS

We identified 20 families diagnosed as having EBS during the past decade at Rambam Medical Center, Haifa, Israel. The diagnosis of EBS was established on the basis of clinical, immunohistochemical, and electron microscopic criteria as previously described. Three of these families gave their informed and written consent to participate in this study according to a protocol reviewed and approved by the local Helsinki Committee. Each family received a thorough explanation of the disease, the current status of knowledge regarding EBS, and a detailed description of the genetic analysis to be performed. All patients were asked to fill out a standard questionnaire and underwent a thorough physical examination. Fifteen milliliters of blood was drawn from each individual and processed for DNA extraction and genetic analysis.

MUTATIONAL ANALYSIS

Genomic DNA was isolated from blood samples using the salt chloroform extraction method. Primer pairs used for K5 amplification have been previously described. Primer sequences for amplification of the full-length functional K14 gene were provided by P. W. D. Bary, E. B. Lane, W. H. I. McLean, Epithelial Genetics Group, Human Genetics Unit, University of Dundee, Dundee, Scotland. K14 exon 1 was further amplified using the following nested primers: 5'-CCAGACACCTCTCCTCAGT-3' and 5'-CAGTGATCAGAAGCTGGTCTG-3'. Polymerase chain reaction (PCR) amplification of genomic DNA was performed using Taq polymerase (Qiagen, Valencia, Calif) and Q solution (Qiagen) according to the manufacturer's instructions. Cycling conditions were as follows: 5 minutes at 94°C followed by 30 cycles for 30 seconds at 95°C, 45 seconds at 58°C, 90 seconds at 72°C, and a final extension step at 72°C for 7 minutes. The PCR amplification of exon 1 of K14 was performed using the following cycling conditions: 5 minutes at 94°C followed by 10 cycles for 1 minute at 94°C, 1 minute at 59°C, 90 seconds at 72°C, and a final extension step at 72°C for 5 minutes. This was followed by a nested PCR using the same cycling conditions for 30 cycles. Amplified products were electrophoresed on a 1.5% agarose gel and gel purified using QIAquick gel extraction kit (Qiagen) according to the manufacturer's instructions. Cycling conditions were as follows: 4 minutes at 95°C followed by 35 cycles for 30 seconds at 95°C, 45 seconds at 58°C, 90 seconds at 72°C, and a final extension step at 72°C for 7 minutes. The PCR amplification of exon 1 of K14 was performed using the following cycling conditions: 5 minutes at 94°C followed by 10 cycles for 1 minute at 94°C, 1 minute at 59°C, 90 seconds at 72°C, and a final extension step at 72°C for 5 minutes. This was followed by a nested PCR using the same cycling conditions for 30 cycles. Amplified products were electrophoresed on a 1.5% agarose gel and gel purified using QIAquick gel extraction kit (Qiagen) according to the manufacturer's instructions. Finally, PCR products were subjected to bidirectional sequencing using the Big Dye terminator kit (PE Applied Biosystems, Foster City, Calif) and the sequenced products were analyzed on an ABI Prism 3100 analyzer (PE Applied Biosystems).

Where required, PCR amplicons were digested using restriction enzymes as detailed in the text. Mismatched primers were designed to create recognition sites for restriction enzymes by in vitro mutagenesis in specific cases:

Family 2: forward, 5'-CGATTCACGGCCTAAGGAAACA-3'; reverse, 5'-CCTGGCGGTCCCTGCAGACGCAGCGC-3'.

Family 3: forward, 5'-CGCACAGCCTGTGTCACTACCT-3'; reverse, 5'-CAATCCTTAGTGTCGTACTGG-3'.

MICROSATELLITE ANALYSIS

We selected 6 polymorphic microsatellite markers derived from the Genome Database (GDB) database (http://www.gdb.org) spanning 31 cM on 17q and encompassing the K14 locus. Genotypes were established by PCR amplification of genomic DNA using fluorescently labeled primers (Research Genetics; Invitrogen, Carlsbad, Calif) and Taq polymerase (Eisenberg Bro. Co, Givat Shmuel, Israel) according to the manufacturer's recommendations. The PCR products were separated by polyacrylamide gel electrophoresis on an ABI 310 sequencer system (PE Applied Biosystems), and allele sizes were determined with computer software (Genescan 3.1 and Genotyper 2.0; PE Applied Biosystems).

IMMUNOHISTOCHEMISTRY

Immunohistochemical analysis was performed on formalin-fixed, paraflin-embedded sections. The sections were treated with 3% hydrogen peroxide in methanol for 15 minutes at room temperature, warmed in a microwave oven in citrate buffer for 15 minutes at 90°C, and stained with a monoclonal antibody directed at KRT14 (BioGenex Laboratories, San Ramon, Calif). After extensive washings in phosphate-buffered saline, the antibody was revealed using the ABC technique (Zymed, San Francisco, Calif) and the slides were counterstained using hematoxylin.

RESULTS

DEMOGRAPHIC AND CLINICAL FEATURES OF THE STUDY POPULATION

Among the 10 families who participated in this study, one presented features characteristic of Kindler-Weary syndrome, which were not apparent at the time of the proband's initial assessment. This family was excluded from subsequent molecular analyses. A total of 13 individuals affected with EBS, aged 5 months to 50 years, were identified (8 males and 5 females). All families lived in Israel; 5 were of Jewish origin, 1 (family 2) was Druze, and 3 (families 3, 5, and 6) were of Arab-Muslim descent. Two families were consanguineous. All patients presented with features typical of EBS. Mucosal involvement was noticed in families 1 and 5 only. Two families presented with features characteristic of Koebner subtype, one family was diagnosed as having the Dowling-Meara subtype, and the rest were considered as presenting features consistent with the diagnosis of Weber-Cockayne EBS subtype. Clinical and ultrastructural findings are summarized in Table 1.

MUTATION SPECTRUM

Overall, pathogenic mutations were identified in all EBS families except in family 6. A total of 8 distinct mutations were identified in 8 families. Three mutations were found in K5, and 5 mutations were identified in K14. Table 2 presents a summary of the mutational spectrum. The distribution of the mutations along the various keratin domains is shown in Figure 1. Six of 8 mutations are novel and 2 are recurrent. Six of 8 mutations were missense mutations and 2 were nonsense mutations. All novel mutations were verified by PCR—
restriction fragment length polymorphism assays (Table 2) and excluded from a panel of 100 chromosomes derived from healthy, unrelated individuals of Israeli-Jewish, Druze, or Israeli-Muslim ascendance. Where family members were available for molecular analysis, segregation of the mutation throughout the family was confirmed.

**MISSENSE MUTATIONS**

Consistent with previous data, most disease-causing mutations in the present series resulted in single amino acid substitutions. R125 has previously been shown to represent a “hot spot” for EBS-causing mutations. The proband of family 3 was shown to carry R125H in a heterozygous state (Table 2). This patient presented with severe blistering at birth associated with characteristic tonofilament clumping on EM (Table 1). Curiously, follow-up of the patient revealed marked attenuation of the disease course at the age of 20 years, with only occasional blisters developing over the palms and soles.

Two additional mutations in K14 (Y415C and R388H) were found to affect protein positions previously associated with different amino acid changes (Table 2). Y415C was not found in the parents of the only affected child of family 2. Using microsatellite analysis, we confirmed parenthood (not shown), suggesting that Y415C occurred de novo.

Three missense mutations in K5 were shown to result in a mild phenotype (Table 2). E167K and V324D affect regions previously shown to be mutated in Weber-Cockayne cases of EBS. L311P occurred in the IB domain, at a highly unusual site for mutations in EBS. This region is considered less critical for normal KRT5 function during KIF assembly. However, the leucine residue at position 311 is conserved among various type II keratins, including KRT1, KRT6a, and KRT5.

**NONSENSE MUTATIONS**

In three families (1, 5, and 6), we identified nonsense mutations in the K14 gene. The proband in family 1 displayed widespread blistering at birth, including the buc-
cal mucosa, and complete skin denudation over the palms and feet. Similar features accompanied by failure to thrive and severe anemia persisted during the first year of life. A homozygous C→T transition at position 1186 of the K14 gene was found in the proband (Figure 2A). Each healthy parent was found to carry the mutation in a heterozygous state, indicating recessive inheritance. This mutation results in the substitution of a glutamine residue by a stop codon (Q396X) and is therefore predicted to cause premature termination of the KRT14 protein translation with associated nonsense-mediated messenger RNA decay. The absence of tonofilaments on EM (Figure 2B) and of immunostaining for KRT14 (Figure 2C) is consistent with these predicted effects of the mutation. The unexpected identification of a nonsense mutation in K14 in 2 apparently unrelated parents raised the possibility that they may have inherited Q396X from a common ancestor. Reassessment of the family history revealed that all 4 grandparents emigrated to Israel from the Transylvania region at the border between modern Hungary and Romania (Figure 2D). Using a panel of polymorphic markers, we found that both parents share a 16-centimorgan-long chromosomal segment, encompassing the K14 gene, suggesting a founder effect for Q396X within this family (Figure 2E).

Another homozygous nonsense mutation in K14 that led to the substitution of a tryptophan residue by a stop codon at position 305 of the amino acid sequence (W305X) was identified in an affected child in family 5 (Table 2). The parents are first-degree cousins and were found to carry the mutation in a heterozygous state. W305X resulted in a severe phenotype with widespread blistering over palms, soles, and oral and genital mucosae. The same mutation has previously been described in a consanguineous family from Qatar with a similar phenotype.15

Family 4 comprises 2 apparently unrelated parents with 4 children, 2 of whom presented at birth with blis-
Recent reports\textsuperscript{16-18} have emphasized the importance of ethnic and geographic features in the study of other subtypes of EB and their relevance to the implementation of diagnostic strategies in specific regions of the world. The present study was aimed at assessing the possibility that EBS may present specific features in the Israeli population compared with the US and European populations. In this report, we identified pathogenic mutations in 8 of a series of 9 families with EBS. Mutations located in non-coding regions (promoter, introns, 3'-untranslated region) may account for our inability to identify a pathogenic mutation in family 6. Another possibility is that the patient represents a phenocopy of EBS. In this regard, dominant mutations in the plectin gene and in the BPAG2 gene have recently been shown to result in a phenotype resembling EBS.\textsuperscript{19,20}

Several general principles have been derived during the last decade from mutation analyses mainly conducted in Europe and the United States on large numbers of EBS cases.\textsuperscript{3} Our results, obtained in a series of Israeli patients, are in part at odds with several of these principles presented below:

\textbf{MUTATION SITE CAN FAIRLY PREDICT CLINICAL SEVERITY IN EBS}

Mutations in 19 distinct keratins have been identified as causing diseases of the skin, nails, hairs, mucosae, cornea, and liver.\textsuperscript{4} Mutations in K5 and K14 are considered to cause almost all cases of EBS. Pathogenic mutations result in the synthesis of an aberrant keratin protein with altered 3-dimensional structure, electrical charge, or protein stability that interferes with the normal functions of the protein during KIF assembly\textsuperscript{21-23}. Abnormal KIF formation affects the cell resilience. On exposure of the skin to friction, the cytoskeleton collapses, resulting in the formation of intracytoplasmic vacuoles and finally in intraepidermal dermoeipidermal separation. Mutations located at the helix initiating and termination motifs of keratin central \(\alpha\)-helical rod have been shown to be especially disruptive.\textsuperscript{24,25} The more severe types of EBS have recently been shown to result from mutations outside the helix boundary motifs.\textsuperscript{8,10,35-37} Nevertheless, the present study and several previous reports\textsuperscript{38,39} indicate that not only the site of the mutation at position 396 of the amino acid sequence (Q396X) is of note but also the nature of the mutation.
but also the type of amino acid substitution may be important in determining the clinical phenotype. For example, Y415C in K14 affects a highly conserved codon of K14. A mutation at the same position, Y415H, has previously been described in another Israeli family.\textsuperscript{32} Whereas Y415C was found to result in a relatively mild phenotype, Y415H was shown to cause widespread and unremitting blistering.\textsuperscript{10} This discrepancy may be explained by the type of amino acid substituting for the tyrosine residue at position 415. Y415C results in the replacement of a neutral tyrosine by a basic amino acid, histidine. In contrast, Y415H involves a change in electrical charge, since, in this case, histidine, a basic amino acid, replaces the neutral tyrosine. This is likely to interfere more seriously with KIF assembly and thus to lead to a more severe phenotype. Similarly, heterozygous R388H in the father of family 4 was shown to result in a normal phenotype, although another mutation at the same amino acid position, R388C, was reported to cause Weber–Cockayne–type EBS.\textsuperscript{8} R388C differs from R388H in that in the former case a basic amino acid is substituted for a neutral one, whereas in the later case a basic amino acid (arginine) is replaced by a basic amino acid (histidine), which may explain why heterozygous R388H is phenotypically silent.

Mutations at amino acid position R125 have been repeatedly reported to cause severe disease\textsuperscript{4,5} due to profound disturbance of KRT14 normal function.\textsuperscript{50} Interestingly, the disease course in the proband of family 3 affected with R125H significantly improved throughout the years, indicating that the nature of phenotype–genotype correlation should also be assessed over time. We speculate that reduced exposure to friction during adulthood may partly explain the milder course of the disease with time in this patient. Also, we cannot exclude compensatory mechanisms, such as the progressive development of exon skipping as shown in other forms of EB.\textsuperscript{41}

In contrast with the varying expression of the dominant mutations, all EBS cases due to homozygous nonsense mutations reported in this series were associated with a severe phenotype as previously reported in the literature.\textsuperscript{15,42-44} Thus, it seems that in these cases a severe course can be predicted with confidence during genetic counseling.

### Table 3. Summary of Recessive Mutations in EBS Without Extracutaneous Manifestations

<table>
<thead>
<tr>
<th>Consanguinity</th>
<th>Phenotype Severity</th>
<th>Gene</th>
<th>Mutation</th>
<th>Protein Expression</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+++</td>
<td>K14</td>
<td>p. W305X/W305X</td>
<td>Absent</td>
<td>15, Present study</td>
</tr>
<tr>
<td>+</td>
<td>+++</td>
<td>K14</td>
<td>c. 313_314del/313_314del</td>
<td>Absent</td>
<td>42</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>K14</td>
<td>p. T204X/T204X</td>
<td>Absent</td>
<td>43</td>
</tr>
<tr>
<td>+</td>
<td>+++</td>
<td>K14</td>
<td>g. 1842-2A→C/1842-2A→C</td>
<td>Absent</td>
<td>44</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>K14</td>
<td>p. E144A/E144A</td>
<td>ND</td>
<td>46</td>
</tr>
<tr>
<td>+</td>
<td>+++</td>
<td>K14</td>
<td>p. M119I/M119I</td>
<td>ND</td>
<td>47</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>K14</td>
<td>c. 92delT/92delT</td>
<td>Absent</td>
<td>48</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>K5</td>
<td>p. E170K/E418K</td>
<td>ND</td>
<td>49</td>
</tr>
<tr>
<td>+</td>
<td>+++</td>
<td>K14</td>
<td>p. D396X/D396X</td>
<td>Absent</td>
<td>Present study</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>K14</td>
<td>p. R388H/R388H</td>
<td>ND</td>
<td>Present study</td>
</tr>
</tbody>
</table>

Abbreviations: EBS, epidermolysis bullosa simplex; ND, not determined; +, involvement of palms and soles; ++, involvement of whole skin; ++++, involvement of skin and mucosae.

### RECURRENT MUTATIONS CAUSE A LARGE PORTION OF EBS CASES

Mutations that affect R125 are thought to account for 40% of EBS-causing mutations. R125 has been shown to be replaced most often by histidine (R125H) or cysteine (R125C) due to spontaneous deamination on the non-coding or coding strands, respectively.\textsuperscript{15} In the present series, only 1 of 8 cases was shown to be due to a mutation at position R125. A larger screening effort is needed to assess the exact prevalence of this type of recurrent mutation in our population.

### EBS IS MOSTLY A DOMINANT DISEASE

Most cases of EBS reported to date are due to dominant missense mutations in K5 or K14.\textsuperscript{4} Only 8 recessive cases have been described up to now, mostly due to nonsense mutations in K14 (Table 3).\textsuperscript{15,42-44,46-49} In the present study, EBS was inherited in an autosomal recessive fashion in 3 of 9 families. Although RNA from our patients was not available, previous studies have demonstrated that nonsense mutations in the K14 gene result in nonsense-mediated RNA decay with markedly decreased levels of KRT14 protein.\textsuperscript{43} Consistent with these observations, we did not observe tonofilament formation or KRT14 expression in the basal layer in biopsy specimens obtained from the proband in family 1 (Figure 2). Previous observations have shown similar results in a family originating from Qatar\textsuperscript{15} and carrying the same mutation as that identified in family 5 (W305X).

Recessive EBS is characterized by the absence of symptoms in carriers of the disease-causing nonsense mutations.\textsuperscript{15,44} Thus, haploinsufficiency for K14 seems to be compatible with normal KIF assembly. In contrast, in most cases of K14 deficiency, as in families 1 and 5, the disease course is severe, indicating the absence of efficient compensatory mechanisms. Nevertheless, improvement with age is noticed in most patients affected with recessive EBS. Although most reports depict the absence of tonofilaments on EM, fine “whisker” filaments have been observed to develop with time\textsuperscript{48} and have been suggested to reflect compensatory expression of K15, which may explain the progressive attenuation of the disease severity over time.
All children of family 4 were found to carry Q396X in a heterozygous state. A heterozygous R388H mutation was identified in the father of family 4. When carried in a heterozygous state, this mutation does not seem to result in an abnormal phenotype, since the father denied skin symptoms at any time since birth. The 2 affected children in this family were found to carry both Q396X (resulting in KRT14 haploinsufficiency) and R388H. This case is reminiscent of an earlier report in which a homozygous missense mutation in K14 caused EBS Weber-Cockayne type. Instead, in the present case, hemizygosity for the mutant R388H allele (due to Q396X-mediated K14 haploinsufficiency) was shown to cause EBS, suggesting that the presence of a normal K14 allele is sufficient to maintain KIF integrity in the face of R388H. This is the first report, to our knowledge, of an EBS case resulting from the combination of nonsense and missense mutations, thus further expanding the spectrum of pathogenetic mechanisms known to cause EBS.

The high incidence of recessive cases of EBS in the present series carries significant implications for future mutational analyses and genetic counseling of EBS in our region. For example, in the case of a single child with EBS born to nonrelated, healthy parents, assuming dominant inheritance (as commonly found in Europe and the United States) and excluding the rare possibility of germ-line mosaicism, one could assume that the disease-causing mutation occurred de novo in the affected child and that the chance for an additional affected child equals that of the general population. However, in a population characterized by a high inbreeding coefficient like the Israeli population, taking into account the present results, one should also consider the possibility of recessive inheritance. For example, based on molecular analysis, the chance for a second affected child in family 1 is 25%.

In conclusion, the present study demonstrates unique features of EBS in this series of affected Israeli families. These features include a unique mutation spectrum, expanding our understanding of the pathomechanisms underlying EBS; a varying phenotype-genotype correlation, suggesting that phenotypic severity is ultimately determined by a combination of variables that comprise the location of the mutation, the nature of the amino acid change, the mode of inheritance, and still poorly understood genetic modifiers; and a different pattern of inheritance for EBS in Israeli families, compared with families of European and US ascendency, characterized by a relatively high incidence of recessive cases possibly due to extensive inbreeding within closed ethnic groups.

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Primer sequences for amplification of the full-length functional K14 gene were provided by Pam Wood, PhD, Epithelial Genetics Group, Human Genetics Unit, University of Dundee, Scotland.

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22. Hatsfeld M, Weber K. A synthetic peptide representing the consensus sequence motif at the carboxy-terminal end of the rod domain inhibits intermediate fila-
later his skin and oral mucosa flared. His eyes, however, remained under control and he was able to discontinue the tacrolimus after using it 24 weeks.

Comment. There has been a pilot study using topical 0.06% tacrolimus 3 times daily in 15 patients with inflammatory conjunctival and corneal disease (atopic blepharoconjunctivitis, Mooren ulcer, ocular pemphigoid, Thygeson superficial punctate keratitis, nummular adenoviral keratitis, graft-vs-host reaction of the conjunctiva, and steroid-responsive glaucoma after penetrating keratoplasty). In this study with a follow-up of 26±15 weeks, improvement was noted in 5 of 15 patients and stabilization in 5 of the 15.

We speculate that topical tacrolimus acts in the blistering disorders by locally inhibiting activation of T cells. Although topical cyclosporine has been used for inflammatory conjunctival and corneal diseases with some success, tacrolimus may be more promising as it has better penetration into the conjunctiva. Although our experience is anecdotal, topical tacrolimus was well tolerated by both of our patients and both seemed to experience a good local response. There may be a role for this treatment in the management of ocular immune-mediated diseases.

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Correction

Error in Table. In the study titled “Epidermolysis Bullosa Simplex in Israel: Clinical and Genetic Features,” published in the April issue of the ARCHIVES (2003;139:498-505), two of the nucleotide changes were presented incorrectly in Table 2. The correct nucleotide changes (column 5) are as follows: C1186G should be C1186T, and T932G should be T932C. The mutations reported remain the same.