Immunolocalization of βig-h3 Protein in 5q31-Linked Corneal Dystrophies and Normal Corneas

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Objective: To characterize the relation of the βig-h3 protein to the diagnostic corneal deposits in the hereditary corneal dystrophies recently shown to have mutations in the βig-h3 gene on chromosome 5q31.

Methods: Corneas with lattice, granular, mixed granular-lattice (“Avellino”), and 2 types of Reis-Bücklers dystrophy were diagnosed by the histochemical and ultrastructural characteristics of their abnormal aggregates. Dystrophic and normal corneas were compared for immunolocalization of βig-h3 protein.

Results: In normal corneas, immunoreactivity for βig-h3 protein was strongest in the Bowman layer, and next strong along stromal interlamellar junctions and attachment sites of collagen to the Descemet membrane. Antibody binding was intense on all dystrophic aggregates, mimicking somewhat the normal protein distribution. Mixed granular-lattice dystrophy had the most variation in βig-h3–immunopositive forms. The aggregates in both the “rod-shaped” Reis-Bücklers type and the “curly fiber” Thiel-Behnke type were strongly stained for βig-h3 protein, consistent with mutations on the βig-h3 gene.

Conclusions: The marked immunopositivity for βig-h3 protein in the abnormal deposits in these dystrophies indicates that βig-h3 protein is a major component. The variety and quantity of immunopositive forms suggests that they consist primarily of the mutant protein, self-polymerizing and/or incorrectly binding to other corneal components. Variability of forms may relate to both the specific mutation and regional interactions of this protein.
MATERIALS AND METHODS

MATERIALS

Corneal buttons were obtained after corneal transplantation from 2 corneas with LCD-I, 4 corneas with GCD, 2 corneas with ACD, 1 cornea with CDB-I, and 2 corneas with CDB-II. Corneas from normal donors of 20, 39, 45, 67, 69, and 73 years of age were obtained less than 16 hours postmortem from the Central New York Eye Bank, Syracuse, and processed similarly to the dystrophic corneas.

The βig-h3 antibody for immunostaining was made in rabbits to recombinant protein including the full-length complementary DNA sequence (210-683) of human βig-h3.19,22 This antibody reacts on Western blots with purified βig-h3 protein isolated from corneal extracts and identified in gel bands by amino–terminal sequence analysis.20 Secondary antibodies were biotinylated goat anti-rabbit used with a Vectastain Elite ABC kit (Vector Laboratories, Burlingame, Calif), or gold-labeled goat anti-rabbit antibody (E. Y. Laboratories Inc, San Mateo, Calif). Lowicryl K4M resin (Ted Pella Inc, Redding, Calif) and Embed-812 epoxy resin (Electron Microscopy Sciences, Fort Washington, Pa) were used for electron microscopic embedding.

METHODS

Immunohistochemistry and Histological Staining

Dystrophic and normal corneas were fixed in either freshly prepared 4% paraformaldehyde in 0.1-mol/L cacodylate buffer, pH 7.4, overnight at 4°C or in 10% neutral buffered formaldehyde at room temperature. Half of each cornea was dehydrated in ethanol and embedded in paraffin for light microscopy and the other half used for electron microscopy. For light microscopic immunostaining, 3-µm sections were deparaffinized, rehydrated in 0.01-mol/L phosphate-buffered saline (PBS), incubated in 3% hydrogen peroxide for 10 minutes at room temperature, and blocked for 1 hour with 3% nonfat milk in PBS and 2% bovine albumin. Slides were incubated for 1 hour at room temperature in βig-h3 antibody at 1:2000 dilution in PBS and 2% bovine albumin. Following rinses, biotinylated secondary antibody (1:200) was applied for 20 minutes, followed by ABC complex with diaminobenzidine as chromagen, and counterstaining with hematoxylin. Substitution of normal rabbit serum and omission of primary antibody were used as controls.

Paraffin sections of dystrophic and normal corneas were all stained routinely with Masson trichrome, Congo red, and periodic acid–Schiff stains for histopathological diagnoses.

Immunoelectron Microscopy

The dystrophic and normal corneal buttons for electron microscopy were sampled in both peripheral and central regions, including superficial, middle, and deep stromal Descemet membrane areas. The specimens were primarily fixed in 4% paraformaldehyde in 0.1-mol/L cacodylate buffer. They were dehydrated in methanol to 90% and embedded in resin at temperatures decreasing to −25°C, and polymerized under UV light as directed. Ultrathin sections were placed on uncoated nickel grids, and blocked in 3% nonfat dry milk with PBS and 2% bovine albumin. Following rinses, biotinylated secondary antibody (1:20) was applied for 30 minutes at room temperature. Sections were postfixed in 2% osmium tetroxide for 10 minutes, counterstained with uranyl acetate–lead citrate, and examined with a transmission electron microscope. Controls were the same as used for immunohistochemistry. For nonimmunostaining electron microscopy, specimens were fixed in 2.5% glutaraldehyde or transferred to it secondarily, and processed routinely in epoxy resin.

RESULTS

NORMAL CORNEAS

The normal corneal epithelium did not stain with βig-h3 antibody. The Bowman layer had the most concentrated diffuse stain by light microscopy (Figure 1, A). Stromal staining was moderate, outlining the pale horizontal and oblique collagen lamellae by gold labeling along their interfaces. Labeling was less intense but diffuse on the Descemet membrane. No staining of cells or changes with aging were seen.

Ultrasstructurally, occasional gold-labeled antibody was seen in the epithelial basement membrane, and on some anchoring fibrils as they passed into the Bowman layer (Figure 2, A). There was diffuse scattered gold label as single particles and clumps among the collagen fibers of the Bowman layer. A few unlabeled 3- to 5-nm thin wavy fibrils suggestive of collagen VI coursing among the collagen fibers. In the stroma, βig-h3 label was primarily along the junctions of large lamellar layers and scanty within lamellae (Figure 2, B), as clearly visible at interfaces between obliquely oriented lamellar bundles (Figure 2, C). Label was also denser on the 20- to 25-nm stromal fibers as they fanned out to attach on the Descemet membrane (Figure 2, D). The Descemet membrane had moderate clumped label in its outer fetal banded and nonbanded portions, decreasing to none close to the endothelial level (Figure 2, E).

LATTICE CORNEAL DYSTROPHY TYPE 1

In LCD-I, typical fusiform deposits of different sizes occurred in all levels of the stroma, but mostly in the inner two thirds (Figure 1, B). They were Congophilic and showed apple-green birefringence on polarization, which is diagnostic of amyloid (Figure 1, C). Ultrastructurally, the abnormal deposits were strongly labeled for βig-h3 protein (Figure 3, A), in much higher concentration and quantity than in any normal corneal region, as was also true for the βig-h3–positive deposits in the other dystrophies. The characteristic tapering ends of the aggre-
gates were seen to lie between collagen lamellae (Figure 3, A), where a thin layer of \(\beta\)-h3 epitopes is found normally. At high magnification the 8- to 10-nm amyloid fibrils showed a typical matted pattern (Figure 3, B). Labeling for \(\beta\)-h3 protein in the rest of the cornea appeared mildly reduced.

GRANULAR CORNEAL DYSTROPHY

By light microscopic histochemical analysis, the angular dense deposits of GCD in the superficial and mid-stroma showed a typical bright red positivity with the Masson trichrome stain (Figure 1, D). These crystallloid deposits were very electron dense ultrastructurally, with only a few small fenestrations, and labeled intensely for the \(\beta\)-h3 protein (Figure 4, A). Under high magnification they showed a structure of fine fibrils, 2 to 3 nm in diameter, and were more electron dense peripherally. The collagen fibers of the Bowman layer were unlabeled (Figure 4, B). Labeling for \(\beta\)-h3 protein in the surrounding stroma was mildly reduced, but appeared normal in the Descemet membrane and the deep attaching collagen fibers.

SUPERFICIAL GRANULAR DYSTROPHY WITH ROD-SHAPED DEPOSITS (CDB-I)

A superficial corneal dystrophy diagnosed clinically as Reis-Bücklers dystrophy showed by light microscopy alternating horizontal layers of collagen and confluent deposits of small Masson trichrome red rods, replacing the Bowman layer (Figure 1, E). By electron microscopy the deposits consisted of a plethora of 0.58- to 1.87-µm rod-like bodies, often 0.3 µm in thickness and tending to stack together in layers, producing some thicker and longer forms (Figure 5, A). They appeared homogenous and...
Figure 2. Normal cornea. Ultrastructural localization of βig-h3 protein by immunogold labeling. A, Basement membrane of corneal epithelium (BM) and anchoring fibrils have occasional gold labeling. More diffuse labeling among collagen in the Bowman layer. Scattered wavy thin fibrils (arrowheads) are usually negative (original magnification × 67770). B, Linear clumped label along the interface (arrows) between stromal lamellae coursing in different directions. Scanty label within the lamellae (original magnification × 25448). C, Labeling of curved interface (arrows) between obliquely oriented lamellar bundles. A few thin fibrils (arrowhead) run across collagen fibers (original magnification × 25448). D, Tangential section through top of the Descemet membrane (DM) shows label associated with splayed-out attachments (arrows) of collagen bundles (C) (original magnification × 16943). E, The Descemet membrane (DM) has moderate clumped labeling, decreasing to nothing near the endothelial level (bottom). Brackets indicate cropping of photomicrograph (original magnification × 25448).
intensely immunoreactive for βig-h3 protein (Figure 5, B). At high magnification a faint stippled-fibrillar structure was seen (Figure 5, B, inset), much finer than in the usual GCD (Figure 4, B). In the central cornea, small deposits of a similar nature were present in the deeper stroma.

MIXED GRANULAR-LATTICE DYSTROPHY

The corneas with ACD had areas of confluent and isolated Masson trichrome red deposits superficially, tending to elevate the epithelium, associated with irregular loss of the Bowman layer (Figure 1, F). The stromal amyloid deposits (Figure 1, G) resembled those in LCD-I but small patches were also seen in the region of the Bowman layer. Ultrastructurally the superficial aggregates were very electron dense but not as heavily labeled for βig-h3 protein as in the usual GCD. They contained numerous lucent spaces (Figure 6, A) surrounded by well-labeled amorphous material. At high magnification the dense deposits were featureless, merging with the adjacent fine fibrillogranular material (Figure 6, B). The deeper stromal amyloid deposits were strongly labeled, infiltrating between the collagen bundles similar to those in LCD-I, although their 6- to 8-nm fibrils were thinner (Figure 6, C). The intervening stroma showed some reduction in βig-h3 binding, but the Descemet membrane had normal staining. Linear fibrils in the superficial region were less densely labeled than the stromal amyloid, and were mixed with fine βig-h3–labeled material (Figure 6, D). Under degenerating epithelial cells, there were labeled aggregates of GCD-like but looser fibrillar material (Figure 6, D, inset).

THIEL-BEHNKE DYSTROPHY

In 2 patients with CDB-II dystrophy, saw-toothing of the epithelium over undulating subepithelial mounds and loss of the Bowman layer were noted by light microscopy (Figure 1, H). The βig-h3 antibody binding in the subepithelial region showed a diffuse pattern with intensely positive short strands and small clumps (Figure 1, I).
Ultrastructurally, the characteristic 12- to 16-nm curly fibers were very electron dense and most distinct after routine epoxy resin embedding, where the collagen in the Bowman layer and superficial stroma stained only faintly with the uranyl acetate–lead citrate counterstain [(Figure 7), A]. The curly fibers were often in packets of 2 to 3 curved short fibers stacked together, sometimes attaching to fragments of interrupted epithelial basement membrane. In immunostained Lowicryl sections, the curly fibers were strongly reactive for βig-h3 protein [(Figure 7), B]. There was no gold label on the intervening collagen fibers, which were now more visible with the counterstain. Aggregates of curly fibers formed broad βig-h3–labeled networks extending into the superficial stroma. These tracked along the interlamellar junctions, clearly visible in oblique sections [(Figure 7), C] and reminiscent of the normal concentration of βig-h3 epitopes at lamellar interfaces. Degenerate keratocytes and cell debris were more common than in most of the other dystrophies. The Descemet membrane had normal staining for βig-h3 protein.

**COMMENT**

The diffuse immunopositivity for βig-h3 in lesions of LCD-I, GCD, ACD, and both rod-shaped and curly fiber types of Reis-Bücklers dystrophy is consistent with reports of their association with missense mutations in the βig-h3 gene.1-3 The marked affinity of the βig-h3 antibody for the diagnostic deposits at high dilution and in greater concentration than in any area of the normal cornea indicates that this protein is a major component of the deposits, if not the main one. Supporting this hypothesis is evidence that βig-h3 protein is extractable in excess amounts from corneas with granular corneal dystrophy.20 Whether the deposits in these autosomal dominant dystrophies are composed solely of the mutant form of βig-h3 protein or contain a mixture of mutant and normal protein is currently unknown.

In 2 of our corneas diagnosed clinically as having Reis-Bücklers dystrophy, the presence of curly fibers ultrastructurally identified them as the Thiel-Behnke or CDB-II type.12,16,17 A third cornea, with the same clinical diagnosis, had the confluent form of superficial GCD, with a plethora of Masson trichrome red rodlike deposits,7-15 called the CDB-I type of Reis-Bücklers by Küchle et al.12 The specific although quite different deposits in CDB-I and CDB-II were strongly βig-h3–positive, supporting an origin for both Thiel-Behnke curly fiber and superficial granular rod-shaped dystrophies from mutations in the βig-h3 gene. It has not been shown whether both variants result from the same missense mutation in codon 555 (R555Q) of the βig-h3 gene found by Munier et al1 in an unspecified case of Reis-Bücklers dystrophy. Alternatively, the CDB-I type might share the GCD mutation (R555W) in the same codon or involve a mutation elsewhere in the gene. The ultrastructural and molecular genetic spectrum of Reis-Bücklers–like clinical entities may not yet be fully known, as another dystrophy reported to be a Thiel-Behnke type has recently been mapped to the long arm of chromosome 10 (10q23-q24).25

The βig-h3 protein appears to be an important structural component in collagenous connective tissues. It is widely distributed and can be produced by both mesenchymal and epithelial cells, as shown in the earliest reports,19,22,23 so the term “kerato-epithelin,” used for βig-
h3 protein in the corneal dystrophies,1-3 may be too restrictive for general usage. It seems to have an adhesive function and a role in regulation of growth and differentiation.19,24 In the normal adult cornea, the distribution of \( \beta \text{ig-h3} \) protein was similar to that in previous studies,26 which suggested an anchoring function between the corneal stroma and the adjacent Descemet membrane and subepithelial tissues. In the present study, postembedding staining showed the major stromal binding of \( \beta \text{ig-h3} \) antibody was at interfaces between collagen lamellae and at junctions of collagen bundles attaching to disparate types of collagen such as in the Descemet membrane, and diffusely in the Bowman layer. A similar distribution in the bovine cornea and other collagenous tissues has been suggested to represent a “bridging” function for \( \beta \text{ig-h3} \) protein.24 There is increasing evidence that \( \beta \text{ig-h3} \) protein colocalizes with type VI collagen in many tissues.24,26,27 The fine, wavy 3- to 4-nm fibrils we noted in the normal Bowman layer and at interlamellar junctions appeared to be collagen VI morphologically, but identification must be confirmed by specific immunostaining.

The similarity in distribution of dystrophic aggregates and the normal pattern of \( \beta \text{ig-h3} \) protein is noteworthy, with heaviest concentration in the Bowman region in the superficial dystrophies, and infiltration between lamellar tissue planes in dystrophies extending into the stroma. The continued expression of \( \beta \text{ig-h3} \) in fetal and adult corneal epithelium27,28 might lead to earlier and greater accumulation of mutant protein in the superficial dystrophies. Slower and later deposition in the stroma could be due to the low level of \( \beta \text{ig-h3} \) gene expression.

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**Figure 6.** Mixed granular-lattice dystrophy (“Avellino”). Specimen has been immunogold-labeled for \( \beta \text{ig-h3} \). A, Moderately labeled dense deposits show marked fenestration and irregular edges. Strong labeling of amorphous surrounding material (original magnification × 25 448). B, High magnification reveals little detail in dense deposits but positivity on surrounding fine fibrillogranular material (original magnification × 110 970). C, Heavy label on lattice amyloid fibrils among unstained collagen (C) (original magnification × 67 770). D, Variation in superficial deposits including dense fenestrated material, fine granular and fibrillar material, and some linear amyloid-like deposits (arrow) (original magnification × 67 770). Inset, Heavy labeling on fibrillogranular deposits under degenerating epithelial cell (E) (original magnification × 85 147).
in stromal cells beyond fetal life, except in healing or disease processes. The frequency of degenerate epithelial and stromal cells in the dystrophies suggests that the protein over time is damaging to cells, whose death could add proteolytic factors, further potentiating abnormal |beta|ig-h3 protein polymerization.

How the |beta|ig-h3 gene mutations result in the structural changes seen in the dystrophic aggregates is a more complex problem. Munier et al suggest that the mutation in codon 555 in both GCD and Reis-Bücklers dystrophy could interrupt a predicted coiled-coil domain, allowing precipitation of proteins and formation of dimers and rod forms. The substitutions in codon 124 resulting in lattice lesions in LCD-I and ACD were suggested to be amyloidogenic, possibly from abolishing a phosphorylation site. Further explanation is required, however, for the associated granular changes in ACD.

The variety of structural forms resulting from accumulation of |beta|ig-h3 proteins in the dystrophic aggregates is considerable, raising the question of whether other corneal components contribute to the aggregates. Substances reported to date include lectin-positive carbohydrate in LCD-I, GCD, and ACD, amyloid P protein in LCD-I, and phospholipids in GCD. Mutant |beta|ig-h3 protein may bind these lipid and carbohydrate moieties aberrantly so they become incorporated in the deposits. Thus the aggregate structure could be related to both the specific mutation and availability of other components in the matrix. The proportion of mutated protein and genetic differences in other matrix components may also affect the resultant forms, as suggested by the wide variation in clinical phenotype in some families with ACD.

Further study of |beta|ig-h3 mutations is expected to give valuable insights into the role of |beta|ig-h3 protein in normal corneal structure and function, and potentially lead to innovations in treatment of these dystrophies.

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ARCHIVES OF NEUROLOGY
Sensory Modulation of the Blink Reflex in Patients With Blepharospasm
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Objective: To measure the effects of a blink reflex responses elicited by an electrical stimulation of the supraorbital nerve in patients with blepharospasm with and without an effective sensory trick.

Design: Blink reflexes to supraorbital nerve stimulation were preceded in test trials by a prepulse electrical stimulus to the third finger at various leading intervals.

Setting: Ambulatory patients were treated regularly with botulinum toxin in the Neurology Department of the Hospital Clinic in Barcelona, Spain.

Subjects: Seventeen patients with dystonic blepharospasm and 11 age-matched control subjects. Eight of the patients with dystonic blepharospasm used a sensory trick to alleviate spasms and 9 did not.

Main Outcome Measures: We measured amplitude of R1 and area of R2 responses elicited by the supraorbital electrical stimulus and determined the percentage of facilitation or inhibition induced by the prepulse.

Results: Prepulse facilitation occurred in the R1 response at intervals of 60 to 100 milliseconds and was normal in all patients. Prepulse inhibition occurred in the R2 response at intervals between 50 and 200 milliseconds and was abnormally reduced in 11 patients (64.7%), including all 9 patients who did not use a sensory trick and 2 of the 8 patients who did use a sensory trick. There was a positive correlation between absence of sensory trick and abnormality of the prepulse effects ($\chi^2 = 23.8; P < .001$).

Conclusions: Prepulse inhibition of the trigemino-facial reflex is abnormal in a percentage of patients with blepharospasm, and this abnormality occurs more frequently in patients who do not use a sensory trick. This sensory derangement may contribute to the maintenance of the dystonic spasms by reducing the amount of physiological gating from peripheral nerve inputs on trigeminofacial reflexes. (1998;53:1233-1237)

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