

Ocular Amyloid Deposition in Familial Amyloidosis, Finnish: An Analysis of Native and Variant Gelsolin in Meretoja’s Syndrome

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Purpose. To analyze the deposition of amyloid and its precursors in eyes of patients with familial amyloidosis, Finnish (FAF; Meretoja’s syndrome), a hereditary systemic amyloidosis.

Methods. Autopsy eyes from three patients with FAF and ten control eyes were studied by Congo red staining and with antibodies to the nonmutated part of gelsolin (GS-2C4), the mutated gelsolin Asn-187 fragment (AGel), and amyloid-P component (AP).

Results. Congo red and antisera to AP and AGel bound to amyloid deposits in the cornea and conjunctiva, the sclera, the perineurium of ciliary nerves, the walls of ciliary vessels, the optic nerve sheaths, the stroma of the ciliary body, and along the choriocapillaris. mAb GS-2C4 bound weakly and focally to most deposits and strongly around the choriocapillaris. It labeled the corneal epithelium and endothelium, keratocytes, scleral fibroblasts, trabecular and lens epithelial cells, the ciliary muscle and epithelium, the iris sphincter and dilator, and stromal cells of the conjunctiva and uveal tract.

Conclusions. Local production, especially in the cornea, conjunctiva, sclera, and ciliary muscle, and systemic deposition, particularly in blood vessels and in the sclera, may contribute to amyloid deposits in FAF. To explain the complex pattern of deposition, microenvironmental factors such as lamellar architecture of the cornea and sclera, altered processing of gelsolin, or blood-tissue barriers must be invoked. In addition to corneal lattice dystrophy type II, the observed deposits help to explain glaucoma in patients with FAF. Invest Ophthalmol Vis Sci. 1994; 35:3759–3769.

Familial amyloidosis, Finnish (FAF),¹ also called Meretoja’s syndrome after the Finnish ophthalmologist who described it, is an autosomal dominant, systemic amyloidosis causing a slowly progressive cranial and peripheral neuropathy, dry and itchy skin, intermittent proteinuria, and cardiac abnormalities.²⁻⁸ The patients have a typical facies with droopy eyelids and protruding lips.²⁻⁶ Corneal lattice dystrophy, lace-like deposition of amyloid within its stroma, called type II in this context, is the earliest clinical finding and another hallmark of the syndrome.²⁻⁸ It is most common in southeastern Finland,⁴ but it is encountered elsewhere in Europe, the United States, and Japan.⁹⁻¹⁶

The amyloid fibrils correspond to a degradation product of gelsolin, a calcium-dependent regulatory cytoplasmic and plasma protein named after its role in reversible gelation and solation of tangled actin filaments.¹⁷⁻¹⁹ Gelsolin is implicated in severing, capping, and nucleating actin filaments as part of cell locomotion and actin scavenging.²⁰⁻²¹ The amyloid protein (AGel) spans from position 173 to 243 in the native protein, in which asparagine 187 has been substituted for aspartic acid in Finnish, Dutch, American, and Japanese families,¹⁶⁻²²⁻²⁸ and for tyrosine in Danish and Czech patients studied.²⁹ These variant proteins result from a transition of guanine to adenine or thymine, respectively, at position 654 of the gelsolin gene.¹⁶⁻³⁴ This abnormality in the gelsolin molecule eventually leads to release, polymerization, and deposition throughout the body of the highly amyloidogenic AGel subunit protein.³⁵⁻³⁶
The purpose of this study is to analyze in detail the deposition pattern of amyloid and its precursors in eyes of patients with FAF both by Congo red staining and with antibodies to the nonmutated part of gelsolin, the mutated gelsolin–Asn 187 fragment (AGel) and amyloid-P component (AP) to understand the mechanisms of amyloid deposition in FAF. The eye, which is a major site of amyloid deposition in this syndrome, lends itself particularly well to such an analysis. It contains diverse tissues that are functionally distinct, histogenetically different, and variably vascularized.

**MATERIALS AND METHODS**

**Histologic Specimens**

Four eyes from three Finnish patients (66, 72, and 78 years of age) with FAF were obtained during autopsies at the Department of Pathology, University of Helsinki. All had clinical findings consistent with the heterozygous phenotype of FAF, with a relatively late onset of lattice dystrophy, type II, and cranial neuropathy; nephrotic syndrome was absent. They had family histories of FAF and came from the Kymenlaakso region in southeastern Finland, which has a high prevalence of FAF. Two patients had also chronic open-angle glaucoma, which progressed at the Department of Pathology, University of Helsinki; nephrotic syndrome was absent. They had family histories of FAF and came from the Kymenlaakso region in southeastern Finland, which has a high prevalence of FAF.

**Antibodies**

A rabbit antiserum, raised against purified amyloid subunit fraction isolated from kidneys of a patient with FAF, was used to detect variant gelsolin. This fraction is homologous to human gelsolin, starting at position 173, except for substitution of asparagine for aspartic acid at position 187. In immunoblotting, it reacts with the AGel amyloid subunit and, weakly, with normal plasma gelsolin. It labels amyloid deposits in basement membranes of skin, sweat glands, renal glomeruli, perineurium, and blood vessels in patients with FAF, but not those in controls. Absorption with the amyloid subunit abolishes the reaction.

The optimal dilution was 1:800.

A murine monoclonal antibody to native human gelsolin (Clone GS-2C4, IgG, Lot 041H-4847; dilution 1:750) was obtained from Sigma Chemical (St. Louis, MO). It detects a carboxy-terminal epitope on a chymotryptic cleavage peptide corresponding to residues 407 to 755 of gelsolin. It does not react on immunoblots with AGel, derived from its amino-terminal end, but it detects a 65-kd, FAF-specific circulating proteolytic fragment of the variant gelsolin in patients with FAF. A rabbit antiserum to human amyloid-P component (A302, Lot 118; dilution 1:500) was purchased from Dakopatts (Glostrup, Denmark).

**Immunoperoxidase Staining**

The sections were deparaffinized in xylene and rehydrated in an ethanol series. Pretreatment with pepsin was not found to enhance the positive immunoreaction with the antibodies used. Endogenous peroxidase activity was destroyed with a 30-minute treatment in methanol containing 0.5% hydrogen peroxide. The sections were incubated with normal serum (goat for polyclonal and horse for monoclonal primary antibodies; Vectastain ABC Elite Kits; Rabbit and Mouse IgG; Vector Laboratories, Burlingame, CA; 1:50) in a moist chamber for 30 minutes at room temperature. The sections were washed for three 10-minute changes in phosphate-buffered saline (PBS; pH 7.4) between every step. Antisera were diluted in PBS containing 2% (wt/vol) bovine serum albumin (BSA).

Incubation with primary antisera was carried out in a moist chamber at 37°C for 60 minutes. The sections were then incubated with biotinylated secondary antisera (goat anti-rabbit IgG or horse anti-mouse IgG; Vectastain ABC Elite Kits; 1:200) and subsequently with the avidin-biotinylated peroxidase complex (Vectastain ABC Elite Kits, reagents A and B, both diluted 1:160 and mixed 30 minutes before use) in a moist chamber at 37°C for 30 minutes.

The color reaction was developed with 3-amino-9-ethylcarbazole (Sigma; 40 mg in 12 ml N,N-dimethylformamide and 200 ml acetate buffer, pH 5.0, containing 0.03% hydrogen peroxide) for 20 minutes at room temperature. To evaluate the positive label in pigmented cells, 3,3'-diaminobenzidine tetrahydrochloride (Sigma; 150 mg in 16 ml of dimethylsulfoxide and 200 ml PBS containing 0.03% hydrogen peroxide) for 10 minutes at room temperature was alternatively used. It yields a dark brown reaction product resistant to hydrogen peroxide. Melanin was then bleached in 3% (vol/vol) hydrogen peroxide and 1% (wt/vol) disodium hydrogen phosphate for 18 hours at room temperature. Residual melanin was easily differentiated from true positive immunoreaction by its yellowish color and coarse granularity. Finally, the
specimens were cautiously dried, and coverslips were mounted with Aquamount (BDH Chemicals, Poole, UK).

**Control Experiments**

Omission of the primary or secondary antibody or the ABC complex abolished the positive immunoreaction. Normal rabbit serum (Ortho Diagnostics, Stillwater, MN) and an unrelated murine IgG antibody (anti-synaptophysin; clone SY38, Lot 11618322-02; Boehringer Mannheim, Mannheim, Germany; 1:5) were also used as negative controls. Purified amyloid protein was no longer available for preabsorption.

**RESULTS**

All eyes with FAF were structurally normal under the light microscope, except for the presence of amyloid deposits, moderate loss of ganglion cells in the two eyes with glaucoma, and mild infiltration of the ciliary body and the iris by lymphocytes. No amyloid was seen in control eyes with Congo red. The immunohistochemical results are summarized in Table 1.

**Cornea**

Congo red (Fig. 1A) and antisera to AP (Fig. 1B) and to AGel (Fig. 1C) labeled subepithelial amyloid deposits along Bowman’s layer, the lattice lines, and strands of amyloid between stromal lamellae, as recently described in detail. In the limbal region of control eyes, the epithelial basement membrane, keratocytes, Bowman’s layer, and Descemet’s membrane reacted for AP. mAb GS-2C4 to gelsolin (Fig. 1D) focally labeled lattice lines, and sometimes the subepithelial deposits. The epithelium (Fig. 1D), scattered keratocytes, and single corneal endothelial cells also reacted for gelsolin in all specimens, including controls.

**Conjunctiva**

Congo red revealed focal deposits of amyloid at the level of the epithelial basement membrane, scattered within the stroma, and in walls of blood vessels. Antisera to AP (Fig. 1E) and to AGel (Fig. 1F) reacted more strongly and uniformly with them. mAb GS-2C4 (Fig. 1G) also labeled, weakly and variably, limbal epithelial cells. In controls, many stromal elements reacted for AP, and the epithelial basement membrane was labeled focally. mAb GS-2C4 bound variably to the epithelium, including some basal dendritic cells, and to the walls of several blood vessels.

**Anterior Chamber Angle**

With Congo red, amyloid was seen adjacent to intrasceral collector channels, but not within the trabecular meshwork or Schlemm’s canal (Fig. 2A). The immunoreaction pattern for AP (Fig. 2B) and AGel (Fig. 2C) paralleled that for Congo red. mAb GS-2C4 also bound to many trabecular and stromal cells in the adjacent sclera and ciliary body (Fig. 2D), as it did in controls. Especially in control eyes, stromal cells of the adjacent ciliary body even reacted for AP (Table 1).

**Sclera**

Congo red revealed widespread deposits of amyloid within the sclera (Figs. 3A, 3B). Smaller deposits were streak-like and sometimes pushed the keratocyte to one side. Larger ones resembled corneal lattice lines, but were more irregular (Fig. 3A). They were common in the anterior (Fig. 3A) and scarce in the posterior sclera (Fig. 3B), and they were mainly unassociated with vessels. The antiserum to AP delineated these deposits in the anterior (Fig. 3C) and equatorial sclera, and scleral lamellae in the equatorial and posterior sclera were weakly but diffusely labeled (Fig. 3D). The anti-AGel antiserum revealed lattice-like deposits in the anterior (Fig. 3E) and equatorial (Fig. 3F) sclera and scattered small deposits in the posterior sclera (Fig. 3G). mAb GS-2C4 focally labeled the anterior lattice-like deposits and gave a granular, fairly diffuse labeling of scleral lamellae, particularly in the equatorial sclera (Fig. 3H). In the posterior sclera, fibroblasts were often labeled (Fig. 3I). In controls, mAb GS-2C4 (Fig. 3J) labeled fibroblasts in all regions, and the antiserum to AP also yielded a granular labeling of scleral lamellae (Table 1).

**Lens**

No amyloid was seen with Congo red in the crystalline lens. The antiserum to AP (Fig. 4A) and to AGel (Fig. 4B) did not react with it or with the zonules. In contrast, mAb GS-2C4 labeled with variable intensity the lens epithelium, particularly its equatorial region (Fig. 4C), but not the lens capsule, fibers, or zonules. The reaction patterns in control eyes were identical.

**Iris**

No amyloid was seen in the iris with Congo red or with the antisera to AP (Fig. 4A) or to AGel (Fig. 4B). In controls, inconsistent labeling for AP was seen in blood vessels and the dilator (Table 1). mAb GS-2C4 focally labeled the sphincter muscle, scattered stromal cells, and the walls of larger blood vessels in some eyes. The reactivity was stronger and more uniform in controls (Fig. 4D), including faint labeling of the dilator in several eyes (Table 1).

**Ciliary Body**

Congo red revealed minute deposits of amyloid among ciliary muscle fibers, and more obvious ones in the walls of blood vessels and beneath the ciliary epithelium in the pars plana (Fig. 4E). Antisera to AP...
### TABLE I. Reactivity of Ocular Tissues in Control Eyes and in Eyes With Familial Amyloidosis, Finnish (FAF), With Congo Red and Antibodies to Amyloid-P Component (AP), the Variant Gelsolin Amyloid Protein (AGel), and Gelsolin (GS)

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<td>(+)+‡</td>
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BM = Basement membrane; ICTL = inner connective tissue layer; RPE = retinal pigment epithelium; ++ = strong; + = moderate; (+) = weak; ± = equivocal; − = no reaction.

* Area with smooth muscle actin-positive cells between the trabeculum and ciliary muscle.\(^5^{58}\)

† Reaction in the limbal region.

‡ Reaction variable in different areas.

§ Reaction also in a population of dendritic cells.

‖ Reaction mainly in the posterior part.

¶ Reaction mainly in the anterior part.

** Reaction in glia in the ora serrata region.

\(\text{BM} = \text{Basement membrane; ICTL} = \text{inner connective tissue layer; RPE} = \text{retinal pigment epithelium; ++} = \text{strong; +} = \text{moderate;}
(+) = \text{weak; ± = equivocal; − = no reaction.}

* Area with smooth muscle actin-positive cells between the trabeculum and ciliary muscle.\(^5^{58}\)

† Reaction in the limbal region.

‡ Reaction variable in different areas.

§ Reaction also in a population of dendritic cells.

‖ Reaction mainly in the posterior part.

¶ Reaction mainly in the anterior part.

** Reaction in glia in the ora serrata region.
FIGURE 1. Immunohistochemistry of cornea and conjunctiva in FAF. (A) Congo red. (B–G) Immunoperoxidase staining. Stromal lattice lines (arrowhead) and a layer of amyloid (arrow) under Bowman’s layer are stained with Congo red (A) and labeled with antibodies to AP (B) and to AGel (C), but the corneal epithelium remains negative. In contrast, mAb GS-2C4 to gelsolin (D) reacts strongly with the epithelium, faintly with lattice lines (arrowhead), and not at all with the subepithelial amyloid layer (arrow). Antibodies to AP (E), AGel (F), and gelsolin (G) all label the region of the epithelial basement membrane (arrow), the vascular endothelial (arrowhead), and focally the stroma of the conjunctiva. The conjunctival epithelium reacts weakly for gelsolin. ep = Epithelium; str = stroma. Magnifications: A, ×100; B–G, ×105.

FIGURE 2. Immunohistochemistry of anterior chamber angle and aqueous outflow system in FAF. (A) Congo red. (B–D) Immunoperoxidase staining. Congo red (A) reveals amyloid only close to the intrascleral collector channels (arrowheads), and no obvious deposits are visible in adjacent cornea, sclera, trabecular meshwork, or Schlemm’s canal. These deposits (arrowheads) are also immunoreactive for AP (B), AGel (C), and, albeit focally, with mAb GS-2C4 to gelsolin (D). The ciliary muscle reacts moderately for AGel and AP and strongly for gelsolin. Note the punctate staining pattern, seen only with mAb GS-2C4, that results from labeling of scleral fibroblasts (asterisk [*]) and cells lining the trabecular meshwork. cor = Cornea; scl = sclera; tm = trabecular meshwork; sc = Schlemm’s canal; cm = ciliary muscle. Magnifications: A–D, ×40.

and AGel (Fig. 4F) bound to them, the latter labeling the stroma of the ciliary muscle quite extensively, but little immunoreaction was observed in ciliary processes. mAb GS-2C4 also labeled the ciliary muscle and some stromal cells (Fig. 4G). In controls, the antiserum to AP mainly labeled stromal cells and basement membranes of the ciliary epithelium (Table 1). Blood vessels, the ciliary muscle, and the cytoplasm of the nonpigmented ciliary epithelium reacted with mAb GS-2C4 (Fig. 4H).

Choroid

Focal amyloid deposits around the choriocapillaris and within the stroma of the anterior choroid were seen with Congo red (Fig. 5A). Uneven, often extensive labeling around these vessels was seen with antisera to AP (Fig. 5B) and to AGel (Fig. 5C, 5D) and with mAb GS-2C4 (Fig. 5E), whereas Bruch’s membrane reacted for AP only (Fig. 5B). All antibodies bound to the walls of ciliary arteries and focally to stromal connective tissue (Figs. 5B, 5C), including those in controls. In the control eyes, labeling around Bruch’s membrane and choriocapillaris was seen for AP only (Table 1).

Retina

Although no amyloid was seen with Congo red, weak immunoreaction for AP (Fig. 6A) was present in walls
FIGURE 3. Immunohistochemistry of sclera in FAF. (A, B) Congo red. (C–J) Immunoperoxidase staining. Congo red stains many amyloid deposits (arrowheads) that resemble haphazard lattice lines in the anterior sclera (A), but only rare and small deposits (arrowheads) in its posterior parts (B). The anterior deposits (arrowheads) react with antiserum to AP (C), whereas in the equatorial (D) and posterior sclera a rather diffuse, granular labeling of scleral lamellae is seen. The antiserum to AGel labels the deposits (arrowheads) in the anterior sclera (E), gives a diffuse immunoreaction in the equatorial region (F), and labels the rare amyloid deposits (arrowheads) in the posterior sclera (G). In the anterior sclera, mAb GS-2C4 to gelsolin labels in a granular pattern many scleral lamellae (H). In the posterior region, such reaction is most prominent in the episclera, and several scleral fibroblasts (arrowheads) show labeling of their cytoplasm (I). In control eyes (J), the immunoreaction with mAb GS-2C4 is confined to scleral fibroblasts (arrowhead). es = Episclera; If = lamina fusca. Magnifications: A–B, ×130; C–J, ×105.

of larger retinal arteries, which were negative for AGel (Fig. 6B). mAb GS-2C4 reacted moderately with larger vessels (Fig. 6C). No labeling of the neuroretina (Figs. 6A, 6B, 6C) or the pigment epithelium (Figs. 5B, 5D, 5E) was observed with any antibody. Some radial glia bound mAb GS-2C4 close to the ora serrata in controls, which otherwise reacted identically.

Optic Nerve
Congo red revealed heavy deposits of amyloid in the peripapillary sclera (Fig. 6D), moderate deposits in optic nerve sheaths and in the walls of posterior ciliary arteries, and, in one eye with glaucoma, within the central retinal artery, all of which also reacted for AP and AGel (Figs. 6E, 6F). In some eyes, the septa of the optic nerve reacted for AGel. mAb GS-2C4 reacted identically to AGel (Fig. 6G), and weakly labeled the nerve fibers in some control eyes (Table 1).

Ciliary Vessels and Nerves
Congo red, antiserum to AP and AGel, and mAb GS-2C4 showed widespread reaction in the intima and media of ciliary arteries. In controls, some blood vessels also reacted for AP and mAb GS-2C4, albeit much less extensively. In FAF eyes, the perineurium of ciliary nerves was constantly labeled with all three antibodies (Table 1). In control eyes, it reacted for AP but did not generally bind mAb GS-2C4.

DISCUSSION
In FAF, amyloid was seen in the stroma and epithelial basement membranes of the cornea and conjunctiva,
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The deposits bound antibodies to AGel and AP, but only weakly and focally bound mAb GS-2C4 to a nonmutated part of gelsolin. In heterozygotes, the latter should detect normal and variant gelsolin before proteolysis, and it should detect their carboxy-terminal degradation products. The labeling might represent limited codeposition of any of these molecules, or their local processing to yield AGel.

Because gelsolin is a circulating plasma protein

the pars plana of the ciliary body, in the choriocapillaris, and in the sclera adjacent to the optic nerve.

FIGURE 4. Immunohistochemistry of lens, iris and ciliary body in FAF. (A–D, F–H) Immunoperoxidase staining. (E) Congo red. Antiserum to AP (A) is unreactive with iris stroma and lens fibers, epithelium (arrowhead), and capsule (arrow). The pigmented iris epithelium and the myoepithelial cells of the dilator muscle (asterisk [*]) are visible because of their melanin content. None of the above structures binds the AGel antiserum as seen after bleaching of melanin (B). mAb GS-2C4 (C) labels the lens epithelium (arrowhead) but not its capsule (arrow). In control eyes, it labels the sphincter muscle of the iris (D). In the ciliary body, Congo red (E) labels fibrillary deposits of amyloid (arrowhead) under the ciliary epithelium. This area (arrowhead) also reacts for AGel, whereas both the nonpigmented and pigmented ciliary epithelial remain negative, as seen after bleaching of melanin (F). mAb GS-2C4 (G) labels the subepithelial layer (arrowhead) and the basement membrane (arrow) of the pigmented ciliary epithelium, but the nonpigmented epithelium is unreactive. In control eyes (H), it labels the nonpigmented epithelium, some cells in subepithelial stroma, and the ciliary muscle (arrowhead). str = Stroma; le = lens fibers; pe = pigmented epithelium; ne = nonpigmented epithelium; sph = sphincter muscle; ce = ciliary epithelium. Magnifications: A–C, ×105; D, ×155; E, H, ×140; F–G, ×210.

FIGURE 5. Immunohistochemistry of choroid in FAF. (A) Congo red. (B–E) Immunoperoxidase staining. Only faint, thin deposits of amyloid (arrowhead) are seen with Congo red (A) around the choriocapillaris (asterisks [*]). The overlying retinal pigment epithelium (arrow) and melanocytes of the choroid are visible because of their melanin content. Antiserum to AP (B) reveals variably extensive immunoreaction (arrowhead) around the choriocapillaris (asterisks [*]) and ciliary arteries, and labels Bruch’s membrane (arrow). The antiserum to AGel (C) gives a similar reaction pattern around the choriocapillaris (arrowhead) and ciliary arteries. No amyloid deposits are seen on the choroidal side of lamina fusca, and the solitary deposit (asterisk [*]) in the sclera is not directly associated with either choroidal or scleral blood vessels. Despite immunoreaction for AGel (D) and with mAb GS-2C4 to gelsolin (E) around the choriocapillaris (asterisk [*]) and ciliary arteries, Bruch’s membrane (arrow), retinal pigment epithelium (arrowhead), and choroidal veins are not labeled. mAb GS-2C4 additionally binds to some stromal cells of the choroid. ch = Choroid; ca = ciliary arteries; If = lamina fusca; scl = sclera; cv = choroidal veins. Magnifications: A–B, D–E, ×210; C, ×105.
In eyes with FAF, labeling was often weaker than its, clinically seen as lattice lines, correspond to amyloid degeneration of corneal nerves, but electron microscopy has not confirmed this. The presence of such deposits within the avascular cornea (the epithelium, stromal cells, and endothelium of which reacted for gelsolin suggests that local production of amyloid contributes to lattice dystrophy type II. This theory is further supported by the existence of lattice dystrophy types I and III, both with corneal amyloid deposits unassociated with systemic amyloidosis, although the evidence for the lack of systemic involvement rests on biopsy studies of single patients and tissues. Genetic defects underlying lattice dystrophy types I and III remain unknown, but at least the former seems unrelated to gelsolin.

In FAF, amyloid is often deposited to skeletal, cardiac, and many smooth muscles, which secrete gelsolin. In spite of deposition in the mesodermal extracellular and in the mesneuroectodermal ciliary muscle in the present study, the neuroepithelial sphincter and dilator muscles of the iris lacked amyloid. They all reacted with mAb GS-2C4 to gelsolin in normal eyes, suggesting altered gelsolin processing, postranslational modification, or both in the iris muscles. The iris muscles also have unusual cytoskeletons, which may reflect their unique histogenesis.

An alternative mechanism for the nonrandom deposition of amyloid is leakage from blood vessels. Amyloid is prominent in the intima and media of arteries, in capillaries, and, rarely, in the veins of most studied tissues in FAF, including the central nervous system and central retinal artery before its entry into the eye. Meretoja attributed preferential deposition of amyloid in the anterior sclera to nearby ciliary arteries, and short posterior ciliary arteries might contribute to the peripapillary amyloid deposits. However, scleral fibroblasts immunoreactive for gelsolin may also produce the scleral deposits.

In contrast, vessels of the iris and retina were devoid of amyloid. Lack of amyloid from the avascular lens despite labeling of its epithelium for gelsolin is also noteworthy. Several other familial amyloidoses differ from FAF in frequently showing prominent deposits in retinal vessels, within the iris, and on the lens. Lack of both amyloid and an immunoreaction for Agel from these tissues not only argues against intraocular production of amyloid, but also suggests that the blood-retinal and blood-aqueous barriers effectively exclude amyloid precursors from them.

In the uveal tract, amyloid has been found in chorioidal arteries only, and the minute deposits around the choriocapillaris hitherto have escaped attention. Although the choriocapillaris is fenestrated to enable diffusion of nutrients, and although it was surrounded by a heavy immunoreaction with mAb GS-2C4 and antibodies to Agel and AP, no labeling with mAb GS-2C4 was seen in controls. The reaction in FAF eyes may represent leakage of abnormal circulating...
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are known. The presence of scarce Congo red-positive amyloid around the choriocapillaris, despite heavy labeling for AGel and AP, suggests either that the local environment does not facilitate amyloid deposition or that the abundant presence of mAb GS-2C4-positive polypeptides somehow interferes with it. In familial amyloidoses related to variant transthyretin, the choriocapillaris may be nearly filled with amyloid, and vitreous is a major site of deposition. The retinal pigment epithelium (RPE) synthesizes Gelsolin is not demonstrable in the RPE, and the vitreous body is devoid of amyloid in FAF. Low aqueous outflow facility and primary open-angle glaucoma are frequent in FAF. Although amyloid around intrascleral aqueous collectors might contribute to them, the trabecular meshwork was devoid of deposits, despite labeling of trabecular cells for gelsolin and their involvement in several other systemic amyloidoses with glaucoma. Because gelsolin is an actin-modulating protein, the possibility remains that its mutation nevertheless affects the function of trabecular cells, which contain both nonmuscle and smooth muscle actin. The heavy scleral and ciliary arterial deposition around the optic nerve head suggests that changes in its extracellular matrix and vascular insufficiency, probably germane to the pathogenesis of glaucomatous optic neuropathy in general, may contribute to disc damage.

Other factors contributing to nonrandom amyloid deposition in FAF must be investigated. Microenvironmental features such as the lamellar, highly ordered architecture of the cornea, and, to a lesser extent, that of the sclera might explain why the most prominent deposits are found in these two tissues. Biochemical differences, such as intercellular matrix composition, may be another contributing factor. Despite our knowledge of the gene defect in FAF, we do not yet understand well its pathophysiology at the tissue level.

Key Words
amyloid, choroid, corneal lattice dystrophy, familial polyneuropathy, gelsolin, glaucoma, lens, retina

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