PURPOSE. To quantify the prevalence and effect on visual acuity of macular cysts in a large cohort of patients with retinitis pigmentosa.

METHODS. In 316 patients with typical forms of retinitis pigmentosa, visual acuity was measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, macular cysts were detected with optical coherence tomography (OCT), and retinal thickness was quantified by OCT. The FREQ, LOGISTIC, and GENMOD procedures of SAS (SAS Institute, Cary, NC) were used to evaluate possible risk factors for cyst prevalence, and the MIXED procedure was used to quantify the relationships of visual acuity to retinal thickness measured at different locations within the macula.

RESULTS. Macular cysts were found in 28% of the patients, 40% of whom had cysts in only one eye. Macular cysts were seen most often in patients with dominant disease and not at all in patients with X-linked disease (P = 0.006). In eyes with macular cysts, multiple regression analysis revealed that visual acuity was inversely and independently related to retinal thickness at the foveal center (P = 0.038) and within a parafoveal ring spanning an eccentricity of 5° to 10° from the foveal center (P = 0.004).

CONCLUSIONS. Macular cysts are a common occurrence in retinitis pigmentosa, especially among patients with dominantly inherited disease. Visual acuity is influenced by edema in the parafovea, as well as in the fovea. (Invest Ophthalmol Vis Sci. 2008;49:4568 - 4572) DOI:10.1167/iovs.08-1992

In a previous study of 162 patients with retinitis pigmentosa, we used optical coherence tomography (OCT) to demonstrate that visual acuity was best related to central foveal retinal thickness by a second-order polynomial for eyes without macular cysts.1 By cross-sectional analysis, visual acuity declined both with decreasing retinal thickness due to photoreceptor loss and with increasing retinal thickness, presumably due to edema. Although the acuity loss due to retinal thinning was marked, we could not precisely relate the acuity loss due to macular edema, because the increases in retinal thickness were generally small.

For the present study, we enlarged our cohort of patients with retinitis pigmentosa evaluated by OCT and included in our analyses eyes with macular cysts. We first quantified the percentage of patients with macular cysts, which has ranged from 13% to 70% in reports based on smaller groups of patients,2-9 to estimate the midpoint and confidence limits for cyst prevalence in retinitis pigmentosa. We next determined whether the likelihood of cysts depended on genetic type—which was found in one report5—but not in another6—or on age, gender, or previous cataract surgery. Last, we investigated the extent to which central and off-center macular edema impacted visual acuity in patients with cysts, because in a prior study visual acuity was found to be more closely related to the width (transverse extent) of edema than to the central foveal thickness in patients with retinitis pigmentosa.5

METHODS

Patients

The protocol was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School and conformed to the tenets of the Declaration of Helsinki and HIPAA (Health Insurance Portability and Accountability Act) regulations. Informed consent was obtained from all patients. We examined 316 consecutive unrelated adults with typical forms of retinitis pigmentosa (57% male; ages, 18–68 years) who had best-corrected Snellen visual acuities of 20/20 to hand motions. There were 71 dominant cases (22.5%), 44 recessive cases (15.9%), 15 X-linked cases (4.7%), 167 simplex (i.e., isolate) cases (52.9%), and 19 cases of undetermined inheritance (6.0%).

Visual Acuity Measurements

We measured best corrected visual acuity with transilluminated Early Treatment Diabetic Retinopathy Study (ETDRS) charts.10 The ETDRS charts contain five letters of comparable difficulty on each line, and letters on each lower line decrease in size by 0.1 log10-unit (21%). ETDRS acuity was scored as the number of letters correctly read, each letter being valued at 0.02 log10-unit.

OCT Evaluations

We used a Stratus High-Resolution Optical Coherence Tomographer (Model 3000, Carl Zeiss Meditec, Dublin, CA) with software version 5 to assess retinal structure and measure retinal thickness after pupillary dilation. With this third-generation instrument (OCT3) we recorded from each eye six 6-mm line scans in a radial spoke pattern of 30° intervals intersecting at the foveal center.11 Each tomogram consisted of 512 A-scans, each A-scan comprising 1024 data points spanning a 2-mm depth, and location of the foveola in the scan was routinely monitored and centered by the examiner (MAS).1 However, in eyes with macular cysts, it was sometimes difficult to confirm that the foveola was precisely centered in the scan, and in such cases the examiner relied on the patient’s fixation.

Each radial scan group was analyzed as a retinal thickness map by the automated OCT software, which identified the vitreoretinal interface and retinal pigment epithelium (RPE)/choriocapillaris complex as regions of high reflectance. As illustrated in the schematic of Figure 1, we coded the retinal thickness at the foveal center, the mean retinal thickness for a central area of 1 mm diameter, the mean retinal thickness for an inner ring of 1-mm inner diameter (ID) and 3-mm outer diameter (OD), and the mean retinal thickness for an outer ring.
of 3-mm ID and 6-mm OD. In rare cases, we quantified the central foveal thickness of individual scans by manually positioning the software calipers. Recording and quantification of tomograms were performed with the examiner masked to the patients’ visual acuities.

**Statistical Analyses**

We used PROC FREQ of SAS (ver. 9.1; SAS Institute, Cary, NC) to assess the prevalence of macular cysts by genetic type or gender and PROC LOGISTIC to assess the prevalence of macular cysts by genetic type controlling for age. We used PROC GENMOD with a binary outcome distribution and repeated measures to determine whether macular cysts were significantly more common in pseudophakic eyes than in phakic eyes. We used PROC MIXED with repeated measures to regress ETDRS acuity on retinal thickness measured at different locations, singly or in combination, in eyes with macular cysts, taking into account the correlation between eyes of the same patient. Other analyses were performed with a second SAS package (JMP, ver. 6; SAS Institute).

**RESULTS**

**Representative Tomograms**

Figure 2 illustrates the variety of edematous changes that we observed in the tomograms, in order of increasing central foveal thickness. Some tomograms showed a rare vacuole of 50-μm diameter in the inner nuclear layer situated eccentric to the foveal center (Figs. 2A, 2D), some showed medium-sized cysts symmetrically located around the foveal center (Fig. 2C), and others had single or several large centralized cysts, distorting multiple layers (Figs. 2E, 2G, 2H). Rarely, pronounced foveal swelling was accompanied by small cysts (Figs. 2F). Some tomograms had thickening mostly confined to the fovea (Figs. 2E, 2G, 2H), whereas others showed diffuse swelling into the parafovea, either asymmetrically (Fig. 2B) or symmetrically (Figs. 2C, 2D, 2F). In our population, central foveal thickness averaged 256 μm in eyes with cysts versus 170 μm in eyes without cysts OD and 262 μm in eyes with cysts versus 167 μm in eyes without cysts OS (normal mean, 167 μm). Both of these increases in retinal thickness due to cysts were statistically significant (P < 0.001).

**Prevalence of Macular Cysts**

Eighty-nine (28%) of the patients had macular cysts by OCT. Thirty-seven (40%) of these patients with cysts had them in only one eye. The patients with bilateral cysts were not significantly different in average age from those with unilateral cysts (P = 0.30). However, the bilateral group had an average central foveal thickness based on both eyes (273 μm) that was significantly larger than the average central foveal thickness of the cystic eyes of the unilateral group (219 μm, P = 0.001).

We found macular cysts in 26% of the men and in 34% of the women after excluding patients with X-linked disease; this variation by gender was not statistically significant (exact test, P = 0.16). Two patients had diabetes mellitus but were negative for cysts. Twenty-seven patients were pseudophakic in both eyes: six had bilateral cysts, four had unilateral cysts, and 17 had no cysts. Ten patients were pseudophakic in one eye: two

---

**Figure 1.** Schematic of retinal locations evaluated in the present study. Retinal thicknesses were quantified for the foveal center, a central area of 1 mm (3.3°) diameter, an inner ring of 1 mm (3.3°) ID to 3 mm (10°) OD, and an outer ring of 3 mm (10°) ID to 6 mm (20°) OD.

**Figure 2.** Tomograms from eight patients with retinitis pigmentosa and macular cysts. The tomograms are from the right eye of a 33-year-old man with dominant disease (A), the left eye of a 41-year-old woman with simplex disease (B), the right eye of a 29-year-old man with simplex disease (C), the right eye of a 44-year-old woman with simplex disease (D), the left eye of a 35-year-old woman with simplex disease (E), the right eye of a 37-year-old man with simplex disease (F), and the left eye of a 47-year-old woman with dominant disease (H). Each tomogram subtends 6 mm horizontally.
had cysts and eight had no cysts in that eye. The probability of having a cyst in one or both eyes was not significantly related to being pseudophakic in those eyes ($P = 0.36$).

Figure 3 shows that the prevalence of macular cysts was highest (37%) in patients with dominant disease, less (23%) in patients with autosomal recessive disease, and lowest (0%) in patients with X-linked disease; this variation was statistically significant (generalized exact test, $P < 0.006$). Since patient age varied by genetic type ($P < 0.001$)—mean ages were 41 years in patients with dominant disease, 39 years in patients with autosomal recessive disease, and 30 years in patients with X-linked disease—we hypothesized that differences in age could underlie the differences in cyst prevalence by genetic type. However, by multiple logistic regression we found that cyst prevalence remained significantly related to genetic type, even when adjusting for differences in patient age ($P = 0.009$).

### Regression of Visual Acuity on Retinal Thickness by Location

Table 1 lists the slope and level of significance for the regression of ETDRS acuity on retinal thickness by location for eyes with macular cysts. Each of the four locations showed an inverse relationship between visual acuity and retinal thickness. However, the slopes were significantly different from 0 only for two retinal locations—the foveal center and the outer ring—and these two inverse relationships are illustrated in Figure 4. The variation in central foveal thickness explained 6% of the variation in visual acuity (i.e., $r^2 = 0.06$), whereas the variation in mean retinal thickness of the outer ring explained 12% of the variation in visual acuity (i.e., $r^2 = 0.12$). When these two measurements were included in a multiple regression model, both were independent predictors of visual acuity (Table 2) and their combination provided a better fit to the

![Figure 3](https://example.com/f3.png)

**Figure 3.** Number of patients with retinitis pigmentosa with and without macular cysts by genetic type.

![Figure 4](https://example.com/f4.png)

**Figure 4.** Regression of ETDRS visual acuity on central foveal thickness (top) and on the mean retinal thickness of the outer ring with a 3-mm inner diameter and a 6-mm outer diameter (bottom) based on data from cystic eyes of 89 patients with retinitis pigmentosa. The regression lines were estimated by PROC MIXED of SAS and are $y = 51.4 - 0.017x$ (top) and $y = 63.6 - 0.076x$ (bottom), where $y$ is ETDRS acuity in letters and $x$ is retinal thickness in micrometers. For reference, an ETDRS acuity of 61 letters corresponded to a Snellen acuity of 20/20 in eyes with cysts, and 95% confidence limits are 118–216 μm for central foveal thickness and 214–266 μm for the mean retinal thickness of the outer ring based on data from 22 normal volunteers evaluated in our test system.

### Table 1. Regression of ETDRS Visual Acuity on Retinal Thickness in Patients with Retinitis Pigmentosa and Macular Cyst

<table>
<thead>
<tr>
<th>Retinal Location</th>
<th>Cases/Eyes with Cysts*</th>
<th>Slope (Letters/100 μm)†</th>
<th>$P$‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal Center</td>
<td>89/141</td>
<td>$-1.7 \pm 0.8$</td>
<td>0.052</td>
</tr>
<tr>
<td>Central Area (1 mm diameter)</td>
<td>88/137</td>
<td>$-1.7 \pm 1.1$</td>
<td>0.105</td>
</tr>
<tr>
<td>Inner Ring (1 mm ID to 3 mm OD)</td>
<td>89/139</td>
<td>$-4.4 \pm 2.4$</td>
<td>0.067</td>
</tr>
<tr>
<td>Outer Ring (3 mm ID to 6 mm OD)</td>
<td>89/139</td>
<td>$-7.6 \pm 2.7$</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* The variation in the number of cases or eyes with cysts reflects instances where retinal thickness could not be correctly quantified by the software at a given location.

† Estimates of mean slope ± SE by PROC MIXED of SAS (SAS Institute, Cary, NC).

‡ The two-tailed significance level with respect to 0 slope.
patients tested with OCT in which all six radial scans were
higher prevalence estimate (49%) was recently reported for 39
confirmed that visual acuity is inversely related to central
only vertical and horizontal scans to detect macular cysts.7,8 A
combined total of 75 patients from two OCT studies that used
six radial lines at the highest resolution, and we observed many
edema, at risk of worsening and involving the second eye.
This suggests that those with unilateral cysts have earlier-stage
tended to be smaller than those in patients with bilateral cysts.
most likely is at least one third of cases. In our study, 40% of
lence of edema with or without cysts in retinitis pigmentosa
in no cases with X-linked disease. This variation confirms a
dominant disease, in 23% of cases with recessive disease, and
section to macular cysts, which were found in 37% of cases with
pigmentosa. However, we documented a genetic predisposi-
tion to macular cysts in our patients with retinitis
pigmentosa.12 We used a protocol of scanning each eye with
six radial lines at the highest resolution, and we observed many
patients who had a cyst in one or two tomograms and not in
the other four or five tomograms. Perhaps for this reason, a
lower prevalence estimate (21%) was obtained based on a
combined total of 75 patients from two OCT studies that used
only vertical and horizontal scans to detect macular cysts.7,8 A
higher prevalence estimate (49%) was recently reported for 39
patients tested with OCT in which all six radial scans were
used.9 If we combine their results with ours, we obtain a
prevalence of 30%. Since we have reported that some patients
had retinas that appeared swollen without cysts,4 the preva-
ience of edema with or without cysts in retinitis pigmentosa
most likely is at least one third of cases. In our study, 40% of
patients with cysts had them in only one eye, and the cysts
tended to be smaller than those in patients with bilateral cysts.
This suggests that those with unilateral cysts have earlier-stage
edema, at risk of worsening and involving the second eye.
We did not find age, sex, diabetes, or pseudophakia to affect
the risk of having macular cysts in our patients with retinitis
pigmentosa. However, we documented a genetic predisposi-
tion to macular cysts, which were found in 37% of cases with
dominant disease, in 23% of cases with recessive disease, and
in no cases with X-linked disease. This variation confirms a
previous report based on biomicroscopy of 94 eyes,5 which
found cysts in 69% of eyes of patients with dominant disease,
in 17% of eyes of patients with recessive disease, and in no eyes
of patients with X-linked disease. Despite the fact that neither
their study nor ours detected cysts in patients with X-linked
disease, there are reported instances of macular cysts in pa-
tients with this genetic type.6,7,13

Clinical Significance of Macular Cysts
in Retinitis Pigmentosa

Of three smaller studies that measured the association between
visual acuity and central foveal thickness in patients with ret-
initis pigmentosa and macular cysts, one found a significant
relationship6 and two did not.7,9 In the present study we
confirmed that visual acuity is inversely related to central
foveal thickness in eyes with macular cysts; ETDRS acuity
declined by an average of 1.7 letters for each 100-μm increase
in thickness. We previously reported an 11-letter average de-
cline in ETDRS acuity for each 100-μm decrease in central
foveal thickness due to cell loss in eyes of patients with retinitis
pigmentosa without macular cysts.1 By taking a ratio of these
two figures (i.e., 11 letters/1.7 letters), we find that for a given
change in central foveal thickness the impact of cell loss on
visual acuity appears to be 6.5 times the impact of edematous
swelling on acuity in this disease.

Remarkably, we found in our patients with macular cysts
that ETDRS acuity declined due to increases both in central
foveal thickness and in the mean retinal thickness within an
outer ring spanning an eccentricity of 5° to 10° from the foveal
center (see Fig 4, top and bottom). The retinal thicknesses in
the bottom graph likely underestimate the magnitude of edema
at that location, since patients with retinitis pigmentosa gen-
erally have marked parafoveal cell loss, as evidenced by the
tomograms of eyes without macular cysts.1 Thus, much of the
retinal thickness data in the bottom graph reflect the net result
of cell loss and swelling.

Although the dependence of visual acuity on edema at the
foveal center, where acuity is measured, is intuitive, the basis
of its dependence on edema in a parafoveal region is not
obvious, especially given that these two dependencies appear
to be independent according to our analysis. That is, our data
indicate that the loss of acuity due to edema represents the
sum of the effect of edema in the foveal center and the effect
of edema in the parafovea. It may be relevant to note that in
some patients with retinitis pigmentosa and cystoid macular
edema, marked reductions in retinal thickness within the fovea
after treatment with a topical carbonic anhydrase inhibitor14 or
an intravitreal steroid15 were not associated with commensu-
rate improvements in visual acuity. It is possible that these eyes
had reduced acuity due to foveal cell loss before the edema or
developed irreversible functional damage as a result of the
edema itself,8 and treatment benefit was therefore limited by a
ceiling effect. However, it is also possible that the treatments
did not effectively reduce parafoveal edema (as was evident in
one illustration15). Our results suggest that, in evaluating the
benefit of any treatment for macular edema in retinitis pigmen-
tosa, its effect on both the foveal and parafoveal retina should be
considered.

Acknowledgments

The authors thank Bernard Rosner, PhD (Professor of Medicine and
Biostatistics, Harvard Medical School) for guidance regarding the use of
SAS.

References

1. Sandberg MA, Brockhurst RJ, Gaudio AR, Berson EL. The association
between visual acuity and central retinal thickness in retinitis

<table>
<thead>
<tr>
<th>Retinal Location</th>
<th>Slope (Letters/100 μm)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal Center</td>
<td>−1.6 ± 0.8</td>
<td>0.038</td>
</tr>
<tr>
<td>Outer Ring (3 mm ID to 6 mm OD)</td>
<td>−7.7 ± 2.6</td>
<td>0.004</td>
</tr>
</tbody>
</table>

† The two-tailed significance level with respect to zero slope controlling for the relationship of visual acuity to retinal thickness at the other location. The regression line is \[ y = 67.9 - 0.016 x_1 - 0.077 x_2, \]
where \( y \) is ETDRS acuity (letters), \( x_1 \) is central foveal thickness (μm), and \( x_2 \) is mean outer ring retinal thickness (μm); the overall model has a \( P = 0.0004. \)


