Mechanisms of Myopia in Cohen Syndrome Mapped to Chromosome 8q22

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PURPOSE. To analyze the mechanisms of myopia in Cohen syndrome (Mendelian Inheritance in Man [MIM] no. 216550).

METHODS. A cross-sectional study of 22 Finnish patients (age range, 2–57 years) with Cohen syndrome, which maps to chromosome 8q22, was undertaken to record cycloplegic refraction, keratometry (corneal power and radius of curvature), biometry (anterior chamber depth [ACD], lens thickness [LT], axial [AL] and vitreal length [VL]), and Hoffer Q-modeled lens power. These components of refraction were correlated to age and spherical equivalent (SE) at the corneal plane. Contribution to total myopia of refractive (corneal and lenticular) and axial components was modeled by multiple linear regression and by estimating the effect of deviation from population mean values.

RESULTS. The mean SE in patients with Cohen syndrome older than 10 years was -9.35 D; the mean cylinder power, +1.70 D; and the mean anisometria, 0.53 D. Relative to the emmetropic eye of a young adult, the AL and VL (mean, 23.9 and 16.6 mm, respectively) and lens power (mean, 30.30 D) were higher in 74% and 93% of patients, respectively, and the ACD (mean, 2.5 mm) was smaller and the LT (mean, 4.9 mm) and corneal power (mean, 45.63 D) higher than average in all patients. Corneal power (r = 0.513, P = 0.021) increased with age, but AL and VL (P = 0.46 and 0.54, respectively) and lens power (P = 0.89) did not correlate with age. The lens power decreased with AL (r = -0.564, P = 0.029) and tended to increase with corneal power (r = 0.475, P = 0.074). Multiple linear regression identified AL and corneal power as independent predictors of SE. Based on deviation from population means, the lens power explained 55%, corneal power 23%, and AL 22% of total myopia. ACD decreased and LT increased markedly with age, rendering angle-closure glaucoma a possibility.

CONCLUSIONS. Myopia in Cohen syndrome is mainly refractive in type and is due to high corneal and lenticular power, which is otherwise rare in young patients. It may be superimposed on axial myopia, probably related to polygenic factors that determine myopia in the general population. The refractive myopia in Cohen syndrome may result from dysgenesis and atrophy of the cornea, ciliary body, and iris, which in turn cause iridal and zonular laxity and spherophakia. (Invest Ophtalmol Vis Sci. 2002;43:1686–1693)

The Cohen syndrome (Mendelian Inheritance in Man [MIM] No. 216550) described by Cohen et al. in 1973,1 is an autosomal recessive disease that maps to chromosome 8q22.2,3 It is characterized by nonprogressive mental and motor retardation; a sociable and cheerful disposition; microcephaly;4 hypotony; dysmorphic features, including wave-shaped, often down-slanting, lid openings; thick eyebrows and eyelashes; a short philtrum with an inability to cover the upper teeth5; granulocytopenia6,7; and retinocochrional dystrophy.5,6,8–11

Myopia is another frequent hallmark of Cohen syndrome, and it is variously considered to be either a major or a minor diagnostic criterion (for a review, see Refs. 11,12). Of 22 Finnish patients with Cohen syndrome, all but one 5-year-old girl had myopia at the median age of 33 years. The myopia was often of high grade with a median spherical equivalent of -11 D.12 In other reports, myopia has mostly been moderate, but in four it was of high grade.5,9,10,13 The myopia in Finnish patients was progressive, with a median increase of -6.5 D during an average follow-up of 15 years.12

Myopia in general can be predominantly corneal, lenticular, or axial, or it may represent a more complex imbalance between the total refractive power and the axial length of the eye.14 Preliminary observations suggest that myopia in some patients with Cohen syndrome may be predominantly corneal and lenticular, rather than axial.12 Because this would be a relatively unusual combination in young-adult-onset myopia, we analyzed in detail the components of refraction with keratometry and biometry in patients of various ages with Cohen syndrome and searched for secondary changes related to axial myopia to better understand the mechanisms of myopia in Cohen syndrome.

PATIENTS AND METHODS

Inclusion Criteria

A nationwide survey of Cohen syndrome in Finland, organized between 1994 and 1996 by the Department of Pediatrics, Helsinki University Central Hospital, ascertained from hospitals, pediatricians, and clinical geneticists 29 patients who fulfilled the diagnostic criteria.5,15 Patients in this population-based cohort were eligible for participation in the present study. Informed consent was obtained from the guardians of 22 patients (inclusion ratio, 76%). The median age of the 10 enrolled male and 12 female patients was 31 years (range, 2–57). The Cohen syndrome gene (COH1) had been localized by linkage disequilibrium and haplotype analysis to chromosome 8q22 in all the patients except one, who did not undergo genetic analysis.5 The study followed the tenets of the Helsinki Declaration and was approved by the institutional review board.

Ophthalmologic Examination

The patients underwent manual refraction with streak retinoscopy while under cycloplegia induced by 0.5% cyclopentolate drops. Media opacities precluded adequate refraction in three patients (ages, 34, 50, and 57 years), including the two oldest ones. The corneal radius of

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The relative lens (center) position was calculated as the sum of the anterior chamber depth and half of lens thickness, and the vitreous length as the difference between the axial length and the sum of anterior chamber depth and lens thickness. The ratio of axial length to corneal radius of curvature was calculated. Lens power was modeled by calculating the predicted power of an intraocular lens that would produce the observed spherical equivalent of refraction by the Hoffer Q theoretical formula. 17

The contribution to total myopia of refractive and axial components was analyzed by two methods. The spherical equivalent was predicted by multiple linear regression based on keratometry and biometry readings. 19 The predicted change in spherical equivalent caused by deviation of the corneal power and axial length from the population means of 42.8 D and 23.5 mm, respectively, was calculated (assuming that 0.45 mm corresponds to 1.0 D of axial myopia). 13 Any deviation of predicted from observed spherical equivalent was attributed to lens power.

Results

Cycloplegic Refraction

Of 19 patients who underwent refraction, 18 had myopia and 14 had at least 1 D of astigmatism (the latest known refraction of the three patients with media opacities ranged from −8.5 to −13 D). The mean spherical equivalent at the corneal plane was −9.35 ± 3.35 D; Table 1, and the mean cylinder power and axes of the right and left eyes were +1.71 D × 107° and +1.70 D × 81°, respectively, vertexed to the corneal plane (Fig. 1). The median anisometropia was 0.53 ± 0.57 D; Table 1.

The spherical equivalent tended to decrease (myopia tended to increase) with age (Fig. 2A; r = −0.443, P = 0.057 Pearson product moment correlation), whereas the cylinder power did not correlate with age (r = −0.250, P = 0.30).

Biometry and Keratometry Related to Age

The axial and vitreous lengths (Table 1) were longer than the mean for the emmetropic eye of a young adult (23.5 and 16.2 mm, respectively) in 14 of the 19 patients (74%; 95% confidence interval [CI], 49–91) who underwent biometry and were older than 10 years. The axial length (Fig. 2B; r = 0.176, P = 0.46) and vitreous length (r = 0.151, P = 0.54) did not
correlate with age. The anterior chamber depth was less and the lens thickness more than the mean for the young adult eye (3.6 and 3.6 mm, respectively)\(^2\) in all 19 patients (95% CI, 82–100). The anterior chamber depth decreased (Fig. 2C; \(r = -0.727, P < 0.001\)) and the lens thickness increased (Fig. 2D; \(r = 0.789, P < 0.001\)) significantly with age. The relative lens position (Table 1) did not correlate with age (\(r = -0.236, P = 0.33\)).

The mean corneal power was higher and the radius of curvature smaller (Table 1) than the average for the emmetropic eye of a young adult (42.8 D and 7.79 mm, respectively)\(^2\) in all 18 patients who underwent keratometry and were older than 10 years (100%; 95% CI, 81–100). The corneal power increased (radius decreased) with age (Fig. 2E; \(r = 0.513, P = 0.021\)). The ratio of axial length to corneal radius was higher than 3.0 in all but one of 17 patients in whom it could be calculated, and all but one of 20 patients who underwent keratometry had more than 1.0 D of corneal cylinder (Table 1), the mean power and axis of which were +2.57 D \(\times\) 93° and +3.09 D \(\times\) 92° in the right and left eyes, respectively (Fig. 1). The corneal cylinder power did not correlate with age (\(r = 0.030, P = 0.90\)).

The lens power modeled by the Hoffer Q formula ranged from 22.75 to 37.0 D (Table 1). It was higher than the mean power for the emmetropic young adult lens (23.1 D)\(^2\) in all but one of the 14 patients in whom it could be calculated and who were older than 10 years (93%; 95% CI, 66–100). Lens power was unrelated to age (Fig. 2F; \(r = 0.038, P = 0.89\)).

**FIGURE 1.** A double-angle, plus-cylinder plot of total (A, B) and corneal (C, D) astigmatism in the right (A, C) and left (B, D) eyes of 19 Finnish patients with Cohen syndrome mapped to chromosome 8q22. The open circle (centroid) shows the mean cylinder power and axis.

**FIGURE 2.** Correlation between age and (A) vertexed spherical equivalent, (B) axial length, (C) anterior chamber depth, (D) lens thickness, (E) average corneal power, and (F) modeled lens power in 22 Finnish patients with Cohen syndrome mapped to chromosome 8q22 (two-sided Pearson product moment correlation). Lines are linear regressions with 95% CIs. Age correlated inversely with anterior chamber depth and correlated directly with lens thickness and corneal power.
Correlation between Spherical Equivalent and Refractive Components

The spherical equivalent decreased (myopia increased) with increasing axial length (Fig. 3A; $r = -0.513$, $P = 0.035$), vitreous length ($r = -0.592$, $P = 0.016$), and corneal power (Fig. 3B; $r = -0.508$, $P = 0.037$). It did not correlate with corneal cylinder power ($r = 0.042$, $P = 0.86$), anisometropia ($r = -0.207$, $P = 0.42$), anterior chamber depth ($r = 0.273$, $P = 0.29$), lens thickness ($r = -0.252$, $P = 0.39$), relative lens position ($r = 0.158$, $P = 0.56$), and modeled lens power ($r = -0.329$, $P = 0.25$).

Correlation between Refractive Components

The axial length did not correlate with corneal power (Fig. 3C; $r = -0.104$, $P = 0.68$), whereas the modeled lens power decreased with increasing axial length (Fig. 3D; $r = -0.564$, $P = 0.029$). The anterior chamber depth ($r = 0.155$, $P = 0.51$) and the lens thickness ($r = 0.266$, $P = 0.27$) were also unrelated to the axial length. The anterior chamber depth decreased with increasing lens thickness (Fig. 3E; $r = -0.746$, $P < 0.001$) and with decreasing corneal radius of curvature (Fig. 3F; $r = 0.694$, $P = 0.001$), but it did not correlate with the other variables studied. The lens thickness correlated inversely with the corneal radius of curvature (Fig. 3G; $r = -0.542$, $P = 0.025$) and the modeled lens power increased with decreasing relative lens position (anterior shift of the lens center; $r = -0.621$, $P = 0.018$), and it also tended to increase with corneal power (Fig. 3H, $r = 0.475$, $P = 0.074$). It did not correlate with lens thickness ($r = -0.224$, $P = 0.44$).

A graph of the contribution of anterior chamber depth, lens thickness, and vitreous-to-axial length in patients of increasing...
Increased axial length accounted for a major proportion (>40%) of total myopia in four eyes (Fig. 6).

**Family History of Early-Onset Myopia**

Presence or absence of juvenile and young-adult–onset myopia was known in parents of 15 patients (59%) from 10 families. The mother in one family and both parents in two families had had myopia of −2.0 to −6.0 D since the ages of 18 to 20 years. Of their offspring, one was estimated to have 46% axial myopia (Fig. 6; patient 3), one had a negligible axial component (patient 4), and the axial length of the third patient could not be reliably measured (patient 1).

**Retinal Changes Related to Axial Myopia**

None of the patients had any central (myopic crescent, lacquer cracks, Fuchs spots, posterior staphyoma) or peripheral retinal disease (lattice degeneration, white without pressure, retinal breaks, retinal dialysis) associated with myopia. One patient had a blind eye due to long-standing retinal detachment, attributed to injury.

**Discussion**

Finnish patients with Cohen syndrome mapped to chromosome 8q22, who had had moderate to high myopia from childhood, had eyes that showed a higher corneal and lenticular power, a shallower anterior chamber, and a thicker lens than the average eye of a young adult, but their axial length differed little from that of an emmetropic of similar age.14,23 Closer analysis indicated that three quarters of the myopia was refractive, especially lenticular. Correlation between refraction and age in cross-sectional analysis suggested that the myopia was progressive, which has been confirmed by longitudinal analysis.12 Progression was mainly due to age-related increase in corneal power. This is contrary to the rule that juvenile and early-onset adult myopia are axial in type.14,23 In juvenile myopia, the corneal power is greater than average, but axial length and anterior chamber depth should also be higher, and the lens power should not differ from that of emmetropes.25 In contrast, late-adult–onset myopia often is refractive.14 Cohen syndrome represents an unusual combination of refractive myopia and young age.

Frequent anterior segment abnormalities in patients with Cohen syndrome point to the possibility that, in them, myopia may result from dysgenesis or degeneration of the iris, ciliary body, zonules, and lens. Iridodonesis,24 together with increased thickness, apparent spherophakia, and anterior shift of the lens, suggests that zonular laxity and lens subluxation may act as mediators. This may be due to generalized atrophy of the uvea or a specific molecular defect of the zonules. In Marfan syndrome, zonular laxity is caused by abnormal fibrillin, a 350 kDa glycoprotein that is a major constituent of the lens capsule and zonules.24 This leads to stunted lens growth, spherophakia, iridodonesis, and cataracts,24,25 which seem to be part of Cohen syndrome as well. However, in Marfan syndrome the

<table>
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<tr>
<th>Coefficient</th>
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<tr>
<td>Constant</td>
<td>107.81 (21.75)</td>
<td>60.42 to 155.20</td>
<td>4.96</td>
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<tr>
<td>Axial length</td>
<td>−1.54 (0.37)</td>
<td>−2.36 to −0.72</td>
<td>−4.10</td>
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<tr>
<td>Mean corneal power</td>
<td>−1.77 (0.42)</td>
<td>−2.68 to −0.87</td>
<td>−4.27</td>
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$R^2 = 0.724$. 

The quantitative contribution to total myopia of corneal and lens power and axial length was modeled by calculating the predicted change in refraction caused by deviation from mean values for the young adult human eye (Fig. 6). In this analysis, the mean proportion of total myopia explained by disproportionately high lens power was 55% (95% CI, 44–65), whereas disproportionately high corneal power and axial length explained 23% (95% CI, 16–30) and 22% (95% CI, 11–34) of total myopia, respectively. Thus, a mean of 78% (95% CI, 66–89) of total myopia was refractive. Whereas lens and corneal power always contributed to myopia, a short axial length decreased it in three patients and the contribution of axial length to total myopia was negligible (<10%) in three other patients (Fig. 6).
cornea flattens rather than steepens, and frank luxation of the lens is typical, unlike in Cohen syndrome.\textsuperscript{12,25}

Iris atrophy, which had been observed in eight of our patients,\textsuperscript{5,12} possibly contributes to the increased lens thickness and the anterior shift of the lens diaphragm. Experiments with surgically aniridic rhesus monkeys show that the nonaccommodated lens becomes thicker and is shifted anteriorly if the iris is removed and no longer in contact with the lens.\textsuperscript{26} The investigators speculated that an intact iris diaphragm is necessary to keep the lens in position and to flatten it.

The corneal radius of curvature, which was always smaller than average, decreased with age, and the anterior chamber paradoxically became progressively shallower with decreasing corneal radius. The anterior chamber depth should correlate with the axial length,\textsuperscript{14} but this was not true in Cohen syndrome. Perhaps a concomitant decrease in relative diameter of the ciliary ring took place, which may have added to zonular laxity and anterior shift of the lens.\textsuperscript{27} A notable age-related change was an increase in lens thickness, which added to decreasing anterior chamber depth. In myopia, the anterior chamber is usually deep,\textsuperscript{14} but Cohen syndrome has the potential to cause primary angle-closure glaucoma in high myopia, as happened in both eyes of one of our patients, a 42-year-old woman with myopia of \(-12.0\) D.\textsuperscript{12}

Cohen syndrome shares these features with retinopathy of prematurity (ROP), another condition characterized by frequent myopia. Several studies agree that an anterior chamber that is more shallow and a lens that is thicker than average characterize ROP, especially if it has advanced to stage 3.\textsuperscript{28,29} Presumably, scarring related in part to treatment causes anterior shift of the lens diaphragm and relaxation of the zonules.\textsuperscript{29,30} However, in contrast to Cohen syndrome, no consistent abnormality of corneal power has been documented,\textsuperscript{29} and progression of myopia usually ends before 3 years of age.\textsuperscript{30,31}

\textbf{FIGURE 5.} Refractive and axial components of myopia in 15 Finnish patients with Cohen syndrome mapped to chromosome 8q22. (A) Observed spherical equivalent versus that predicted by multiple linear regression of average corneal power and axial length. (B) Axial length and average corneal power. (C) Axial length and modeled lens power (D), and average corneal power and modeled lens power relative to mean values in a young-adult emmetropic eye, divided by grade of myopia. Corneal and lens power were always higher than average, whereas axial length varied from short to long.

\textbf{FIGURE 6.} Estimated contribution of corneal power, lens power and axial length to the spherical equivalent in 14 Finnish patients with Cohen syndrome mapped to chromosome 8q22. Observed spherical equivalent is the arithmetic sum of the three elements; when all three components contribute to myopia, the observed spherical equivalent can be read directly.
Some patients with Cohen syndrome have had microcornea, suggesting corneal dysgenesis, and microphthalmia. In one patient described by Cohen himself, the microphthalmia was associated with a coloboma that involved the anterior and posterior uvea, and one patient in another series had bilateral colobomatous microphthalmia. None of the Finnish patients had either typical microphthalmia or a coloboma, even if they had small anterior segments. It is possible that different mutations of COH1 will be found to account for different phenotypes of Cohen syndrome, or that microphthalmia is a secondary defect in Cohen syndrome.

Modeled lens power tended to be lower when axial length was longer, suggesting some degree of emmetropization. Apparently, the lens also compensated for approximately one half of corneal astigmatism. Biomicroscopy and lens opacitometry showed frequent incidence of early nuclear sclerosis in our patients with Cohen syndrome. The lens thickness did not predict myopia by multiple linear regression, and lenticular myopia in Cohen syndrome probably is related more to an increase in the lens radius of curvature and the refractive index. Unexpectedly, lens power was unrelated to age in our series.

By comparing components of refraction to population averages, we could conclude that increased axial length was clinically significant in the myopia of Cohen syndrome in only 4 of 14 patients. When axial length was long, the myopia was always high. Notwithstanding the predominance of refractive myopia, axial length correlated with spherical equivalent, and the axial length in addition to the corneal power was a strong independent predictor of the spherical equivalent by multiple linear regression. Possibly as evidence of attempted emmetropization, shorter than average axial length compensated for increased corneal and lenticular power in three eyes. In most patients, the cornea was steep in relation to the axial length, however, and caused increased myopia.

Long axial lengths can be induced in animals subjected to visual deprivation. In Cohen syndrome, vision usually remains normal until the age of 10, and even when visual fields constrict and impair distance vision, reasonable reading vision is retained until the age of 30 to 40 years. Visual deprivation is not likely to explain the myopia of Cohen syndrome. Tectoretinal degeneration and chorioretinopathy associate with axial myopia in many syndromes, such as gyrate atrophy, progressive bifocal chorioretinal atrophy, long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, and several types of retinitis pigmentosa. The retinal pigment epithelial motiling, choroidal atrophy, narrow retinal arterioles, and an isoelectric electroretinogram in Cohen syndrome bear resemblance to symptoms in retinitis pigmentosa. However, none of our patients had retinal changes associated with axial myopia, thought to be the only reliable method of distinguishing eyes in which the posterior segment has expanded beyond that of normal growth.

The fairly normal range of axial lengths in our series suggests that elongation of the eye is probably independent of mutated COH1 and is determined by other factors. Similarly, it is postulated that axial myopia in premature infants withROP may be unrelated to retinopathy. Presumably, the refractive error of parents influences the axial component. This finds some support in the fact that many siblings with Cohen syndrome have similar refractions. In our series, the parents of two siblings who had myopia of −11 to −12 D had myopia of −2.0 to −6.0 D, and one of the siblings had notable axial myopia. The refraction of the parents of other children who had notable axial myopia remained unknown. A family has been reported in which the child had myopia of −14.0 D and the parents of −5.0 and −7.0 D. Intuitively, parental hyperopia may lead conversely to a shorter than average axial length and may counterbalance myopia in Cohen syndrome.

Hypermobility of joints, skeletal and postural anomalies such as long and slender hands and fingers, cubitus valgus, genu valgum, pes planovalgus, scoliosis, and kyphoscoliosis are common in Cohen syndrome, and mitral valve prolapse and decreased left ventricular function are occasionally observed. These features hint that there is a generalized disorder of connective tissue in Cohen syndrome. Myopia and cataract are common to several collagen mutations, such as Stickler syndrome, Wagner disease, and Kniest dysplasia. However, the myopia in these connective tissue syndromes is axial in type and is often associated with an increased risk of retinal detachment, which is not the case in Cohen syndrome.

All evidence taken together, the myopia in Finnish patients with Cohen syndrome mapped to chromosome 8q22 is predominantly refractive and due to a disproportionately high power of the cornea and the lens, but it may be modulated by an axial component that is independent of COH1, the Cohen syndrome gene. The refractive components in Cohen syndrome resemble those in late-adult-onset myopia, a fact that may be related to dysgenesis, degeneration, and premature aging of the anterior segment of the eye in this syndrome. Future identification of the COH1 gene is likely to reveal a specific molecular defect that can lead to nonaxial high myopia. Regardless of its exact pathogenesis, correction of myopia is indicated in Cohen syndrome. Our patients enjoyed wearing spectacles as a rule, and correction of myopia and astigmatism affected their development positively.

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**References**


