Heritability Analysis of Spherical Equivalent, Axial Length, Corneal Curvature, and Anterior Chamber Depth in the Beaver Dam Eye Study

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Objective: To examine genetic influences for quantitative refraction. Spherical equivalent and its related binary traits of myopia and hyperopia are highly correlated within families. Many linkage regions have been reported for myopia, high myopia, and quantitative refraction. However, the measured phenotype of spherical equivalent is in large part dictated by the relationship between the underlying optical components of axial length, corneal curvature, and anterior chamber depth.

Methods: Using data from the fourth visit of the Beaver Dam Eye Study, we conducted familial correlation and heritability analysis of quantitative spherical equivalent, axial length, anterior chamber depth, and corneal curvature using data from 715 individuals in 189 pedigrees.

Results: Overall, every trait was highly heritable. Heritability estimates were 0.98 (SE 0.13) for spherical equivalent after adjustment for age, education, and nuclear sclerosis; 0.95 (SE 0.11) for corneal curvature after adjustment for age; 0.77 (SE 0.14) for corneal curvature after adjustment for height; 0.73 (SE 0.14) for anterior chamber depth after adjustment for age; and 0.78 (SE 0.14) for anterior chamber depth after adjustment for age, education, height, and nuclear sclerosis.

Conclusion: Refraction and the underlying traits of axial length, corneal curvature, and anterior chamber depth are highly heritable. Genetic analysis of these traits may provide greater insight into the development of refractive errors.


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these traits that may account for a substantial portion of the heritability of refraction. Several studies have indicated an inverse relationship between axial length and refraction (ie, longer axial length, more myopic). Additionally, these studies have shown that much of the variation in refractive error, especially in younger individuals, is due to variation in axial length.32-36 Heritability estimates for axial length range between 40% and 94%.11,30-34 Decreases in refraction have been correlated with increases in anterior chamber depth.33 Heritability estimates for anterior chamber depth range from 51% to 92%.11,30-32 In addition to increased axial length and deeper anterior chambers, individuals with more myopic refraction have steeper corneal curvatures.25,26 Because ocular refractive errors develop when there is not balance between axial length and corneal curvature, some investigators suggest that the simple ratio of axial length to corneal curvature may be a more appropriate measure. An inverse correlation between refraction and the ratio of axial length to corneal curvature has also been reported.25,28 However, these results were not consistent across studies.25,28,29 The heritability of corneal curvature has been estimated to be quite high, ranging from 60% to 92%.25,26,31,32 However, the Genes in Myopia study, a family study from Australia, recently reported a heritability of only 16% for corneal curvature. Modest evidence for linkage on 2p24, 3q, and 14q was reported for axial length; 2p25, 3p26, and 7q22 for corneal curvature; and 1p32 for anterior chamber depth.25,35

To our knowledge, the heritability of the biometric traits underlying refraction has not been examined in a US cohort. Therefore, to examine genetic influences for refractive error, we conducted familial correlation and heritability analysis of refraction (spherical equivalent), axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study, a large population-based sample of US European Americans in Wisconsin.

This study was reviewed and approved by the institutional review board of the University of Wisconsin School of Medicine and Public Health and informed consent was obtained from all study participants. Approval was obtained for data analyses from the institutional review boards of the Johns Hopkins School of Medicine and the National Human Genome Research Institute, National Institutes of Health. Tenets of the Declaration of Helsinki were followed.

STUDY POPULATION

Of the 5924 eligible individuals aged 43 to 86 years who resided in the town of Beaver Dam, Wisconsin, 4926 individuals participated in the baseline examination of the Beaver Dam Eye Study conducted between 1988 and 1990.34 Follow-up examinations have been conducted every 5 years. During the fourth examination period, May 2003 through May 2005, 2375 individuals were examined. Recruitment methods and study procedures have been described in detail elsewhere.36-40 Eye examinations were performed at each examination, including automated refractive error measurements as described later. Ocular biometry measurements were only available at the fourth visit.

In brief, during the fourth visit, ocular biometric measurements were obtained using partial coherence laser interferometry (IOLMaster, Carl Zeiss Meditec, Jena, Germany). Standardized noncycloplegic refraction measurements using an automated refractor (Humphrey, San Leandro, California) were also obtained. For individuals with a visual acuity of 20/40 or worse on Early Treatment Diabetic Retinopathy Study standards,41,42 a refraction was performed. Eyes without a lens, with an intraocular lens, or with best-corrected visual acuity of 20/200 or worse were excluded. Spherical equivalent (sphere power + [0.5 × cylinder power] measured in diopters) was calculated from the refraction measurements. Analysis was performed using both the right eye and left eye. Both eyes yielded very similar results and only the results of the right eye were presented. Age, height, and education were obtained at all visits. Nuclear lens opacity was determined by grading of slitlamp photographs using a standard protocol, resulting in a 5-level scale.43

Family relationships were collected during the baseline examination and verified at the first follow-up examination. Of the 5924 eligible individuals, 2783 had available information on familial relationships and could be classified into 1 of 602 pedigrees. Of the 2375 individuals who participated in the fourth examination, 1032 were members of families. Analysis was limited to families where biometry measures were available for at least 2 pedigree members, resulting in 715 individuals in 189 families. Because of software limitations, several of the more complex pedigrees were split.

STATISTICAL ANALYSIS

Familial correlation analysis was performed using FCOR, part of the S.A.G.E. version 4.5 statistical package.44 First, linear regression was used to determine whether measured covariates significantly predicted the quantitative phenotypes of the ocular biometric measures and spherical equivalent. For each of these quantitative phenotypes, familial correlations using phenotypic residuals after adjusting for statistically significant covariates (P < .05) were then calculated between relative pairs, with equal weight given to each relative pair.45 In all adjustments, age, height, education, and nuclear sclerosis were treated as continuous variables. The phenotypic residuals were calculated as the difference between an individual’s phenotypic measurement and the predicted phenotypic value after accounting for its covariates (the summation of the products of β coefficients for all covariates, plus the intercept). Heritability estimates (h²) for the quantitative phenotypes were obtained using SOLAR.46 Bivariate heritability analysis was also conducted to determine if there was evidence of shared genetic effects across traits. Overall phenotypic correlation was derived as

\[ r_p = \rho_e \sqrt{h_1^2 + h_2^2} \]

where ρ is the genetic correlation between 2 phenotypes, ρ is the environmental correlation between 2 phenotypes, and h and h denote the heritability of phenotypes, respectively.46 All significant covariates in our regression analysis were included in our variance component modeling using SOLAR, and adjusted heritability estimates were obtained under a variance component framework by conditioning the likelihood estimate on covariates.47

RESULTS

Of the 2375 participants in the fourth visit of the Beaver Dam Eye Study, 1827 had data available on spherical equivalent; 1962, on axial length and corneal curvature;
and 1675 had data available on anterior chamber depth. Of these, 715 participants could be classified into 189 pedigrees for familial correlation and heritability analysis. In this family subset, the mean spherical equivalent was 0.58 D; mean axial length, 23.56 mm; mean corneal curvature, 7.69 mm; and mean anterior chamber depth, 3.09 mm (Table 1). Overall, the family subset was similar to the rest of the cohort (Table 1) and those with biometry measurements were similar to those without.

We examined the intraindividual correlation between these measurements (Table 2). Spherical equivalent was strongly and inversely correlated with axial length (−0.45 [SE 0.04]) and positively correlated with corneal curvature (0.19 [SE 0.05]). There was an inverse correlation between spherical equivalent and anterior chamber depth (−0.10 [SE 0.05]). Corneal curvature was strongly positively correlated with axial length (0.34 [SE 0.04]), but there was no correlation between corneal curvature and anterior chamber depth. Axial length and anterior chamber depth were strongly correlated (0.35 [SE 0.04]). The ratio of axial length to corneal curvature was also strongly correlated with spherical equivalent (−0.60 [SE 0.03]) and anterior chamber depth (0.36 [SE 0.04]).

To examine the potential role of genetic factors in these traits, we calculated familial correlations using FCOR (Table 3). Overall, all traits demonstrated a high familial correlation, suggesting shared genetic and/or environmental components. For spherical equivalent, sibling correlation was high (0.33 [SE 0.08]) after adjustment for age, sex, and education and decreased to 0.12 (SE 0.01) among cousin pairs. Corneal curvature demonstrated the highest sibling correlation (0.44 [SE 0.07]) and remarkably high correlation between cousin pairs (0.23 [SE 0.07]). Axial length and anterior chamber depth were also strongly correlated between siblings (0.33 [SE 0.08] and 0.32 [SE 0.09], respectively) as was the ratio of axial length to corneal curvature (0.33 [SE 0.08]). Twice the sibling pair correlation provides an estimate of trait heritability. Little correlation was observed among more distant cousin pairs.

Among sibling pairs, we also examined intertrait correlation (Table 4). Spherical equivalent in one sibling was strongly inversely correlated with axial length (−0.25 [SE 0.07]) as well as the ratio of axial length to corneal curvature (−0.29 [SE 0.07]) in the second sibling. There was also modest correlation between axial length in one sibling and corneal curvature in the second sibling (0.15 [SE 0.07]). Additionally, we estimated heritability using the full-pedigree data with SOLAR (Table 3). These results are consistent with our correlation analysis. Overall, corneal curvature had the highest heritability (0.95 [SE 0.11]) after adjustment for height. Heritability for anterior chamber depth was 0.78 (SE 0.14) after adjustment for age, education, height, and nuclear sclerosis. The heritability of axial length was slightly lower, 0.67 (SE 0.14) af-

### Table 1. Overview of Study Population

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Family Data, Mean (SD)</th>
<th>Sample Size</th>
<th>Nonfamily Cohort, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>690</td>
<td>71.58 (8.17)</td>
<td>1430</td>
</tr>
<tr>
<td>Spherical equivalent, diopter</td>
<td>594</td>
<td>0.58 (2.25)</td>
<td>1233</td>
</tr>
<tr>
<td>Nuclear sclerosis, grade</td>
<td>553</td>
<td>2.92 (0.73)</td>
<td>1113</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>642</td>
<td>23.56 (1.14)</td>
<td>1325</td>
</tr>
<tr>
<td>Anterior chamber depth, mm</td>
<td>545</td>
<td>3.09 (0.37)</td>
<td>1321</td>
</tr>
<tr>
<td>Corneal curvature, mm</td>
<td>640</td>
<td>7.69 (0.28)</td>
<td>1322</td>
</tr>
<tr>
<td>AL:CC</td>
<td>640</td>
<td>3.07 (0.14)</td>
<td>1321</td>
</tr>
<tr>
<td>Education, y</td>
<td>687</td>
<td>11.95 (2.13)</td>
<td>1419</td>
</tr>
<tr>
<td>Female, %</td>
<td>690</td>
<td>54</td>
<td>1420</td>
</tr>
<tr>
<td>Height, in</td>
<td>688</td>
<td>65.70 (3.54)</td>
<td>1417</td>
</tr>
</tbody>
</table>

**Abbreviation:** AL:CC, axial length to corneal curvature ratio.

**a** At baseline examination.

### Table 2. Intraindividual Correlations

<table>
<thead>
<tr>
<th>Correlation (SE)</th>
<th>Spherical Equivalent a</th>
<th>Corneal Curvature b</th>
<th>Axial Length c</th>
<th>Anterior Chamber Depth d</th>
<th>AL:CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent a</td>
<td>1</td>
<td>0.191 (0.045)</td>
<td>−0.446 (0.040)</td>
<td>−0.996 (0.047)</td>
<td>−0.5999 (0.0331)</td>
</tr>
<tr>
<td>Corneal curvature b</td>
<td>1</td>
<td>0.344 (0.037)</td>
<td>−0.017 (0.047)</td>
<td>−0.3412 (0.0369)</td>
<td></td>
</tr>
<tr>
<td>Axial length c</td>
<td>1</td>
<td>0.348 (0.043)</td>
<td>0.7626 (0.0181)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior chamber depth d</td>
<td>1</td>
<td>0.3633 (0.0429)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** See Table 1.

a Adjusted for age, education, and nuclear sclerosis.

b Adjusted for height.

c Adjusted for education and height.

d Adjusted for age, education, height, and nuclear sclerosis.

e Adjusted for education (AL only).
ter adjustment for education and height. Consistent with our previous studies, as well as estimates from other populations, the unadjusted heritability for spherical equivalent was 0.62 (SE 0.13), slightly lower than the individual components.

To assess the evidence for shared genetic and/or environmental components between these traits, bivariate heritability analysis using SOLAR was also performed (Table 5). In these analyses, the observed phenotypic correlation was partitioned into the correlations because of genetic and environmental factors. Analysis was performed on the unadjusted phenotype values as well as for each phenotype adjusted for statistically significant covariates ($P < .05$). The overall estimates of phenotypic correlation were similar to those presented in Table 2 obtained using FCOR. The total phenotypic cor-

### Table 3. Family Pair Correlations of Refraction and Biometric Traits Using FCOR and Heritability Estimates Using SOLAR

<table>
<thead>
<tr>
<th>No. of Pairs</th>
<th>Adjusted Sibling Correlation</th>
<th>No. of Pairs</th>
<th>Adjusted Cousin Correlation</th>
<th>No. of Pedigrees</th>
<th>Adjusted Heritability</th>
<th>Unadjusted Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent</td>
<td>0.323 (0.083)</td>
<td>202</td>
<td>0.123 (0.008)</td>
<td>189</td>
<td>0.578 (0.127)</td>
<td>0.617 (0.127)</td>
</tr>
<tr>
<td>Corneal curvature</td>
<td>0.438 (0.072)</td>
<td>270</td>
<td>0.226 (0.075)</td>
<td>189</td>
<td>0.953 (0.108)</td>
<td>0.948 (0.104)</td>
</tr>
<tr>
<td>Axial length</td>
<td>0.335 (0.075)</td>
<td>273</td>
<td>-0.019 (0.068)</td>
<td>189</td>
<td>0.674 (0.136)</td>
<td>0.651 (0.137)</td>
</tr>
<tr>
<td>Anterior chamber depth</td>
<td>0.319 (0.094)</td>
<td>190</td>
<td>0.064 (0.088)</td>
<td>189</td>
<td>0.779 (0.142)</td>
<td>0.732 (0.154)</td>
</tr>
<tr>
<td>AL:CC</td>
<td>0.330 (0.075)</td>
<td>270</td>
<td>0.000 (0.068)</td>
<td>189</td>
<td>0.686 (0.126)</td>
<td>0.682 (0.127)</td>
</tr>
</tbody>
</table>

Abbreviation: See Table 1.

- Adjusted for age, education, and nuclear sclerosis.
- Adjusted for age, education, and nuclear sclerosis.
- Adjusted for age.
- Adjusted for age, education, height.

### Table 4. Sibling Pair Intertrait Correlations Using FCOR

<table>
<thead>
<tr>
<th>Trait 1</th>
<th>Trait 2</th>
<th>Correlation (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent</td>
<td>Corneal curvature</td>
<td>0.328 (0.083)</td>
</tr>
<tr>
<td>Corneal curvature</td>
<td>Axial length</td>
<td>0.438 (0.072)</td>
</tr>
<tr>
<td>Axial length</td>
<td>Anterior chamber depth</td>
<td>0.335 (0.075)</td>
</tr>
<tr>
<td>Anterior chamber depth</td>
<td>AL:CC</td>
<td>0.319 (0.094)</td>
</tr>
</tbody>
</table>

Abbreviation: See Table 1.

- Adjusted for age, education, and nuclear sclerosis.
- Adjusted for age, education, height.

### Table 5. Bivariate Heritability Analysis Using SOLAR

<table>
<thead>
<tr>
<th>Trait 1</th>
<th>Trait 2</th>
<th>Overall Phenotypic Correlation</th>
<th>Genetic Correlation</th>
<th>P Value vs Genetic Correlation Equal to 0</th>
<th>P Value vs Genetic Correlation Equal to 1</th>
<th>Environmental Correlation</th>
<th>P Value vs Environmental Correlation of 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent</td>
<td>Corneal curvature</td>
<td>0.19</td>
<td>0.25</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.94 (±0.32)</td>
<td>.009</td>
</tr>
<tr>
<td>Spherical equivalent</td>
<td>Axial length</td>
<td>-0.47</td>
<td>-0.30</td>
<td>.03</td>
<td>&lt;.001</td>
<td>0.26 (±0.60)</td>
<td>.72</td>
</tr>
<tr>
<td>Corneal curvature</td>
<td>Axial length</td>
<td>0.35</td>
<td>0.40</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>-1 (NA)</td>
<td>.003</td>
</tr>
<tr>
<td>Spherical equivalent</td>
<td>AL:CC</td>
<td>-0.62</td>
<td>-0.49</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.38 (±0.32)</td>
<td>.28</td>
</tr>
<tr>
<td>Anterior chamber depth</td>
<td>Axial length</td>
<td>0.37</td>
<td>0.36</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.39 (±0.32)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviation: AL:CC, axial length to corneal curvature ratio; NA, not applicable.

- Adjusted for age, education, and nuclear sclerosis.
- Adjusted for age, education, height.
relation between spherical equivalent and corneal curvature was 19%. This correlation was largely due to shared genetic effects, since the genetic correlation was estimated to be 0.25 ($P = .06$) and there was no evidence of shared environmental factors between spherical equivalent and corneal curvature, with an environmental correlation of $-0.01$ ($P = .98$). Overall, the inverse phenotypic correlation between spherical equivalent and axial length of $-0.47$ was attributed to both a strong inverse genetic correlation ($-0.30$ [$P = .031$]), as well as strong shared environmental effects, since the environmental correlation was $0.94$ ($P = .009$). While only some of the genetic influences on spherical equivalent act via axial length, most of the environmental factors that act on spherical equivalent influence axial length.

We also assessed the role of genetic and environmental factors in the observed correlation between axial length and corneal curvature, which demonstrated a phenotypic correlation of $0.35$. The phenotypic correlation was largely due to shared genetic factors ($0.40$ [$P < .001$]). However, there was some suggestion, although not statistically significantly, of shared environmental factors as well ($0.26$ [$P = .72$]), suggesting a role for genes that influence both axial length and corneal curvature but also genes that act independently on these traits. The strongest phenotypic correlation in all of our analyses was that of spherical equivalent and the ratio of axial length to corneal curvature, which demonstrated a $-0.62$ correlation. This correlation was due to strong genetic correlation ($-0.49$ [$P < .001$]) and strong environmental correlation ($-1$ [$P = .003$]) between these phenotypes. Thus, genes influencing the ratio of axial length to corneal curvature play an important role in determining spherical equivalent. There was also evidence of shared genetic effects between anterior chamber depth and axial length ($0.36$ [$P = .04$]) as well as between anterior chamber depth and the ratio of axial length and corneal curvature ($0.38$ [$P = .02$]). Overall, each phenotype was influenced by genetic factors and some genetic factors are shared among traits. Environmental factors seemed to play an important role in axial length and spherical equivalent, but less so for corneal curvature and anterior chamber depth.

Quantitative refraction and the related clinical phenotypes of myopia and hyperopia are under strong genetic control. However, the observed phenotype of quantitative refraction is influenced by the relationship of axial length to corneal curvature. Heritability estimates for axial length and corneal curvature were comparable or slightly higher than for quantitative refraction, suggesting that inherited genetic factors play an equally important role in the development of these components as compared with quantitative refraction (which is also influenced by phenotypic heterogeneity related to development of cataract and iatrogenic interventions, such as refractive procedures). These findings suggest that understanding the genetics of refraction should include the investigation of genetic determinants of these biometric traits.

Axial length reflects the total length of the lens, anterior chamber, and vitreous chamber. Linear regression analysis of the family data used in these analyses indicated no significant association between spherical equivalent and anterior chamber depth ($P = .61$) after adjustment for axial length. However, both anterior chamber depth and spherical equivalent are strongly associated with axial length ($P$ values $<.001$). This suggests that the heritability of axial length may in part be mediated by anterior chamber depth.

Our results were consistent with previous studies. However, unlike some previous studies, our study population was limited to older, white adults. The high heritabilities observed for these phenotypes in our study suggest that there is evidence of strong genetic effects on these traits in older adults, despite the variety of environmental exposures and other disease processes that may have occurred during these individuals' lifetimes. Because many ocular refractive errors, in particular myopia, first develop in childhood, many studies of refraction focus on young adults. However, our results indicate that genetic studies of refraction in older adults should have ample power to identify genetic loci. While more accurate measurement of early environmental factors, such as childhood nearwork, are possible on younger cohorts, extreme values of spherical equivalent, in particular myopia, can develop into the second and third decades of life (excluding later myopic shifts due to factors such as nuclear sclerosis). Therefore, misclassification because of changes of spherical equivalent in these early decades is less of a concern when studying adults. Our analysis suggests that environmental factors play a greater role in determining axial length than corneal curvature. The strong environmental correlation between spherical equivalent and axial length suggests that a large portion of the environmental influences on spherical equivalent are mediated through axial length. This is consistent with studies that demonstrated that nearwork is associated with increased axial length, leading to decreased spherical equivalent.

While we adjusted for years of education, our analysis still suggested a significant role of environmental factors in determining spherical equivalent and axial length. This could be due to years of education not being a sufficient surrogate for total nearwork, resulting in significant residual confounding. However, other unmeasured factors could also be involved. The heritability of corneal curvature was higher than either axial length or spherical equivalent. These results could be owing in part to a smaller role for environmental factors in determining corneal curvature because heritability is an estimate of the proportion of the total trait variation due to genetic factors.

Variance component models, including SOLAR, assume multivariate normality of the trait distribution. While the point estimates for heritability have been shown to be robust to nonnormality, type I error rates can be inflated. Despite slight nonnormality of some of these phenotypes, because of the observed consistency between our results using FCOR, which does not assume multivariate normality, and SOLAR, we chose not to transform our phenotypes in order to preserve the original distribution of these phenotypes.
Genetic heterogeneity, different genes that play a role in determining the same phenotype, not only makes it difficult to identify genes that underlie complex traits, such as spherical equivalent, but also has been demonstrated to be a substantial cause of the difficulty in replicating linkage findings. Given the biological complexity of spherical equivalent and the likely substantial genetic heterogeneity of this trait, it is not surprising there have been numerous reported linkages and differences in linkage peaks when comparing high myopia, myopia, severe hyperopia, and quantitative spherical equivalent. Additionally, the small to modest sample sizes of some studies may result in limited power to replicate linkage peaks.

Limitations of our study include the inability to examine the impact of nearwork, other than through the surrogate measure of years of education, on our various traits. Given the association between nearwork and myopia, this may cause a slight underestimation of our familial correlation. Also, because measurement of axial length, corneal curvature, and anterior chamber depth is only available for the fourth follow-up visit, our sample size reflects only a subset of the initial cohort and we cannot examine age-related changes in these traits.

The high heritability of these optical components of refraction suggests that using these traits in analysis aimed at understanding the genetic basis of ocular refraction errors may be useful. Our analysis builds on previous studies by suggesting there are genes that influence axial length, corneal curvature, and anterior chamber depth. However, our results also suggest that there are other genes that influence these traits independently. Since fewer genes are likely to impact axial length or corneal curvature as compared with the composite phenotype of quantitative refraction (less genetic heterogeneity), examining these traits independently is likely to result in greater power to detect genes. Linkage studies examining axial length, corneal curvature, and anterior chamber depth as well as spherical equivalent will provide further insight into the development of ocular refraction.

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REFERENCES

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