Coordinated Genetic Scaling of the Human Eye: Shared Determination of Axial Eye Length and Corneal Curvature

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Purpose. To examine the extent to which the two major determinants of refractive error, corneal curvature and axial length, are scaled relative to one another by shared genetic variants, along with their relationship to the genetic scaling of height.

Methods. Corneal curvature, axial length, and height were measured in unrelated 14- to 17-year-old white European participants of the Avon Longitudinal Study of Parents and Children (ALSPAC; $n = 1915$) and in unrelated 40- to 80-year-old participants of the Singapore Chinese Eye Study (SCES; $n = 1642$). Univariate and bivariate heritability analyses were performed with methods that avoid confounding by common family environment, using information solely from genome-wide high-density genotypes.

Results. In ALSPAC subjects, axial length, corneal curvature, and height had similar lower-bound heritability estimates: axial length, $h^2 = 0.46$ (SE = 0.16, $P = 0.002$); corneal curvature, $h^2 = 0.42$ (SE = 0.16, $P = 0.004$); height, $h^2 = 0.48$ (SE = 0.17, $P = 0.002$). The corresponding estimates in the SCES were 0.79 (SE = 0.18, $P < 0.001$), 0.35 (SE = 0.20, $P = 0.036$), and 0.31 (SE = 0.20, $P = 0.061$), respectively. The genetic correlation between corneal curvature and axial length was 0.69 (SE = 0.17, $P = 0.019$) for ALSPAC participants and 0.64 (SE = 0.22, $P = 0.003$) for SCES participants. In the subset of 1478 emmetropic ALSPAC individuals, the genetic correlation was 0.85 (SE = 0.12, $P = 0.008$).

Conclusions. These results imply that coordinated scaling of ocular component dimensions is largely achieved by hundreds to thousands of common genetic variants, each with a small pleiotropic effect. Furthermore, genome-wide association studies (GWAS) for either axial length or corneal curvature are likely to identify variants controlling overall eye size when using discovery cohorts dominated by emmetropes, but trait-specific variants in discovery cohorts dominated by ametropes. (*Invest Ophthalmol Vis Sci.* 2013;54:1715–1721) DOI: 10.1167/iovs.12-10560

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Refractive errors, the most common form of eye disorder, arise because of an imbalance between the focusing power of the eye and the position of the retina. The former is governed primarily by the curvature of the cornea, as this provides two-thirds of the eye's refracting power. The plane of the retina relative to the cornea is determined by the axial eye length. Eyes with myopia and hyperopia are characterized by axial lengths that are excessively long and short, respectively. In eyes free from refractive error (emmetropia), axial length is carefully scaled with respect to the curvature of the cornea, and such eyes show a high phenotypic correlation between axial length and corneal curvature.[1,2] Animal studies suggest that this optimal relative scaling is achieved by the action of shared genetic variants, as gauged by genetic correlations ≥ 0.95 for these traits in populations of emmetropic chickens and mice.[3,4] Data for emmetropic human subjects have not been reported, but Klein et al.[5] estimated a genetic correlation of 0.40 between corneal curvature and axial length in an essentially population-based collection of families of western European descent. In contrast, randomized controlled clinical trials and experiments in animals models have documented convincing evidence for myopia-inducing axial elongation of the eye in response to cues from the visual environment—that is, with minimal accompanying changes to corneal curva-

ture.[6–10] Such visually induced responses would be expected to lower the genetic correlation between corneal curvature and axial length. As well as its association with corneal curvature, axial length is also associated with height. In a recent twin study, the bivariate heritability (the proportion of the phenotypic correlation that is mediated by a correlation at the genetic level[11]) for axial length and height was calculated to be 89% by Cholesky modeling.[12] In emmetropic chickens,[3] the phenotypic and genetic correlations between body size and axial length were both ~0.5.

Past studies into the role of genetic and nongenetic influences on ocular component dimensions have relied on studies of related individuals. This complicates the interpretation of the resulting observations because relatives typically have common environmental exposures as well as shared genetic variants in these study designs (an important exception is the classical twin study; however, this design invokes the assumption that monozygotic and dizygotic twins are exposed to "equal environments," which may not always be justified[13]). Recently, in addressing the "missing heritability" question,[14] Yang and coworkers have pioneered a novel statistical approach that has the additional benefit of circumventing the potential confounding between shared genes and shared environment.[15,16] Their method, which can be applied using the genome-wide complex trait analysis (GCTA) software package, relies in essence on quantifying the proportion of the phenotypic variance of a trait that can be explained by the (causal) genetic variants shared between pairs of unrelated subjects.[17] A linear mixed effects model is fitted to the trait data, and restricted maximum likelihood (REML) is used to estimate the proportion of the variation in the trait that is explained by the genetic variants present on the genotyping chip (by comparing the phenotypic similarity between pairs of individuals with a summary of their pairwise identity-by-state sharing across the genome). As current genotyping platforms capture information only on *commonly occurring* ("common") sequence variants, the approach is unable to explain much of the variation due to rare causal variants, since these are at best weakly tagged by common SNPs (single nucleotide polymorphisms). Thus it has been argued that the GCTA approach provides a lower-bound estimate of the additive genetic variance of a trait, that is, the lower bound of the trait's heritability in the narrow sense.[16] Deary et al.[18] have extended the GCTA approach by investigating, in unrelated subjects, how much of the correlation between traits is explained by shared additive genetic variation (for genetic variants tagged by the SNP chip used). Here, our aim was to estimate a lower bound on the genetic correlation between axial length and corneal curvature in a sample of unrelated subjects to explore the extent to which the relative scaling of these eye traits is due to common SNPs.

Methods

Avon Longitudinal Study of Parents and Children (ALSPAC) Sample

ALSPAC is an ongoing longitudinal birth cohort study designed to investigate the determinants of development, health, and disease during childhood and beyond.[19] Pregnant women with an expected date of delivery between April 1, 1991, and December 31, 1992, resident in the former Avon health authority area in Southwest England, were eligible to participate in the study. A cohort of 14,541 pregnant women was established, resulting in 13,988 children who were alive at 12 months of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases that had failed to join the study originally, resulting in an additional 548 children. Data collection has been by various methods including self-completion questionnaires sent to the mother, to her partner, and after age 5 to the child; direct assessments and interviews in research clinics held when the participants reached particular ages; and biological samples and linkage to school and hospital records. The study adhered to the Tenets of the Declaration of Helsinki. Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and the three local research-ethics committees.

Subjects were invited to a research clinic when they were approximately 15 years of age. Height was measured to the last complete millimeter using a Harpenden stadiometer (Holtain Ltd., Crosswell, UK). Refractive error was assessed by noncycloplegic autorefraction (Canon R50 instrument; Canon USA, Inc., Lake Success, NY). Midway through the period when the 15-year clinic was running, equipment was obtained to assess axial length and corneal curvature (Zeiss IOLmaster; Carl Zeiss Meditec, Welwyn Garden City, UK). Biometry measurements beyond 4 SD (standard deviations) from the mean were identified separately for boys and girls and excluded. Autorefraction readings were filtered to exclude outliers as described previously.[20] Trait values for corneal curvature, axial length, corneal astigmatism, and refractive error were averaged between fellow eyes in order to maximize statistical power.[21] Subjects were classified as myopic if their noncycloplegic autorefraction spherical equivalent averaged between the two eyes was ≤ -1.00 diopter (D) and as hyperopic if it was >1.00 D. A validation study[20,22] suggested that these criteria had a sensitivity of 0.90 (0.94) and a specificity of 0.94 (0.98) for detecting myopia (hyperopia) defined as a subjective refractive error <-0.75 D ($>+1.50$). DNA samples[19] were genotyped using Illumina HumanHap 550 bead arrays (Illumina, Inc., San Diego, CA) and subjected to quality control filters as previously described.[23] Briefly, individuals were excluded using the thresholds >3% missing genotypes, >10% identity-by-descent, abnormal heterozygosity, or sex discrepancy. Multidimensional scaling analysis was used to compare ALSPAC individuals with HapMap II, release 22, reference individuals of European, Han Chinese, Japanese, and Yoruba descent (http://hapmap.ncbi.nlm.nih.gov/). Subjects with non-European ancestry were removed. SNPs were excluded using the filter thresholds <95% call rate, <1% minor allele frequency (MAF), and Hardy Weinberg equilibrium P value $<5 \times 10^{-7}$. After these steps, genotypes for 464,311 autosomal SNPs were available for 8365 individuals. Genotypes were imputed at a total of 2,543,887 sites using MACH, with a reference panel of CEU (Utah residents with Northern and Western European ancestry from the Centre d'Etude du Polymorphisme Humain collection) subjects (HapMap release 22, Phase II NCBI B36, dbSNP 126).

There were 1968 subjects with complete data for height, axial length, corneal curvature, and genotypes. GCTA[17] was used to compute a pairwise genetic relationship matrix using all markers with an imputation quality Rsqr >0.3 and a MAF >1% from the set of 2,543,887 SNPs. Following the approach of Yang et al.,[15,16] one of each of 53 pairs of individuals with an estimated genetic relationship >0.025 (the degree of sharing expected, on average, for third or fourth cousins) was excluded, leaving 1915 subjects. Traits were transformed to normal deviates using Blom's method[24] prior to analysis, and estimates of the lower-bound heritability and phenotypic, genetic, and environmental correlations were calculated using GCTA and sequential oligogenic linkage analysis routines.[3,17] These analyses were repeated for the $n = 1478$ emmetropes in the sample, that is, after excluding individuals classified as myopic ($n = 309$), hyperopic ($n = 85$), or with missing refraction data ($n = 43$). In interpreting our results, we made the simplifying assumption that all genetic variants contributing to trait variation were unlinked.[25]

Replication Analysis in Subjects of Chinese Ancestry (SCES)

The Singapore Chinese Eye Study (SCES) is a population-based cross-sectional survey of eye diseases in Chinese adults aged 40 to 80 years

Table 1. Univariate Genetic Analysis for the ALSPAC Cohort

	All Subjects ($n = 1915$)		Emmetropes ($n = 1478$)	
Trait	**Lower Bound of Heritability**	**Variance due to Sex**	**Lower Bound of Heritability**	**Variance due to Sex**
Corneal curvature	0.422, SE = 0.159 ($P = 0.004$)	0.05 ($P < 0.001$)	0.480, SE = 0.193 ($P = 0.006$)	0.04 ($P < 0.001$)
Axial length	0.457, SE = 0.162 ($P = 0.002$)	0.10 ($P < 0.001$)	0.576, SE = 0.193 ($P = 0.001$)	0.13 ($P < 0.001$)
Height	0.475, SE = 0.165 ($P = 0.002$)	0.34 ($P < 0.001$)	0.491, SE = 0.201 ($P = 0.007$)	0.34 ($P < 0.001$)

residing in the southwestern part of Singapore.[26–28] The study adhered to the Tenets of the Declaration of Helsinki. A total of 2226 subjects underwent a comprehensive ophthalmologic examination that included ocular biometry (Zeiss IOLmaster). Genome-wide genotyping was performed in 1952 individuals using Illumina Human 610-Quad BeadChips. Data for 492,108 SNPs in 1860 individuals passed quality control filters.[29] Genetic relationships were computed using GCTA for subjects who had data available for genotypes, axial length, corneal curvature, and height. As above, one subject from each pair of individuals with an estimated genetic relationship >0.025 was excluded, leaving 1642 subjects in the final analysis. Estimates of the lower-bound heritability and genetic correlations were calculated using GCTA.[17]

Results

In the sample of 1915 unrelated white European teenagers (mean age 15.5 years), corneal curvature, axial length, and height all had lower-bound heritability estimates of 0.42 to 0.48 (Table 1). In the subset of 1478 emmetropes, the corresponding lower-bound heritability estimates were 0.48 to 0.58 (Table 1). For all three traits, the difference in the magnitude of the heritability point-estimates was higher in the full sample than in the emmetropes-only sample, with the ocular traits showing the greatest difference: axial length (0.58 vs. 0.46), corneal curvature (0.48 vs. 0.42), height (0.49 vs. 0.48). While this was suggestive of a greater role for additive polygenic inheritance in shaping eye size in emmetropes than in the full sample, none of these differences exceeded the level expected by chance (SE > 0.15 for all traits). Sex exerted a major influence on height, explaining approximately one-third of the intersubject variation, an effect that was independent of the variation explained by the common *autosomal* SNPs included in our analysis. Sex was responsible for much less of the intersubject variation in the two eye size traits than was the case for height, explaining 5% to 13% of the variation independent of common autosomal SNPs.

As reported previously,[1,2] corneal curvature and axial length were correlated (Fig. A; phenotypic correlations in Table 2). The phenotypic correlation in the full sample was considerably lower than that in the emmetropic subset ($\rho_p = 0.54$ vs. 0.73, respectively; $P < 0.001$), consistent with the concept that ametropia weakens the coordinated scaling of eye size components. Weaker phenotypic correlations were apparent between height and each of the two ocular traits (Figs. B, C) with the values being almost indistinguishable in the full sample compared to the emmetropic subset (height : axial length, $\rho_p = 0.204$ vs. 0.200; height : corneal curvature, $\rho_p = 0.216$ vs. 0.215; Table 2) suggesting that ametropia has no discernible effect on the relationship between eye size and stature.

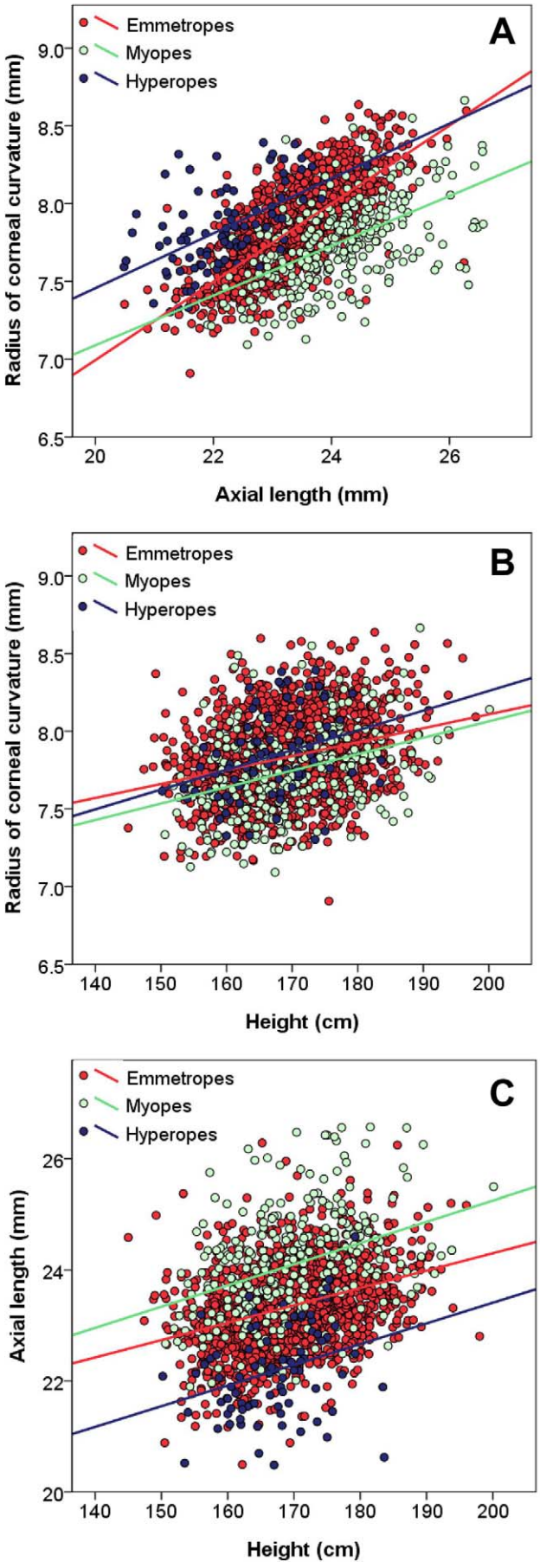
For the full white European teenage cohort, the phenotypic correlation between corneal curvature and axial length could be partitioned into a genetic correlation $\rho_g = 0.69$ (SE = 0.17, $P = 0.019$) and an environmental correlation $\rho_e = 0.43$ (SE = 0.16, $P = 0.056$). In the emmetropic subset the corresponding values were $\rho_g = 0.85$ (SE = 12, $P = 0.008$) and $\rho_e = 0.61$ (SE = 0.17, $P = 0.079$) (Table 2). The imprecision of these estimates meant that it was not possible to differentiate between the higher values in the emmetropic subset having arisen by chance or because of greater genetic covariation. In any case, these lower-bound genetic correlation estimates imply that commonly occurring, additively acting genetic variants are primarily responsible for the coordinated scaling of eye size in humans.

To explore the likely generality of these findings, analyses were also carried out in a sample of mature adults of non-European ethnicity: specifically, subjects of Chinese ancestry aged 40 to 80 years recruited from Singapore (SCES cohort; $n = 1642$). Because of the relatively higher proportion of ametropes in SCES compared to ALSPAC, analyses could be carried out only for the full sample: GCTA analysis of the emmetropes-only SCES sample ($n \sim 700$) failed due to insufficient statistical power. The lower-bound heritability estimates for corneal curvature, axial length, and height were more varied in the SCES cohort than in the white European sample (Table 3). Indeed, the estimate of 0.31 (SE = 0.20, $P = 0.06$) for height was lower than the range of 0.45 to 0.50 observed in previous studies using this methodology in subjects of European

Table 2. Bivariate Genetic Analysis in the ALSPAC Cohort

	All Subjects ($n = 1915$)			Emmetropes ($n = 1478$)		
	Correlation			Correlation		
Traits	**Phenotypic**	**Genetic**	**Environmental**	**Phenotypic**	**Genetic**	**Environmental**
Corneal curvature and axial length	0.543	0.686, SE = 0.174 ($P = 0.019$)	0.432, SE = 0.157 ($P = 0.056$)	0.73	0.853, SE = 0.115 ($P = 0.008$)	0.611, SE = 0.165 ($P = 0.079$)
Corneal curvature and height	0.216	0.095, SE = 0.253 ($P = 0.716$)	0.317, SE = 0.197 ($P = 0.134$)	0.215	0.267, SE = 0.286 ($P = 0.369$)	0.167, SE = 0.263 ($P = 0.541$)
Axial length and height	0.204	0.104, SE = 0.246 ($P = 0.680$)	0.292, SE = 0.207 ($P = 0.185$)	0.200	0.418, SE = 0.269 ($P = 0.129$)	−0.037, SE = 0.299 ($P = 0.901$)

Genetic correlation P values were calculated[39] for the null hypothesis of no difference from zero.



ancestry.[15,16,30] By contrast, the estimated lower-bound heritability for axial length of 0.79 (SE = 0.18, $P < 0.001$) in the SCES sample is to our knowledge the highest such value reported for any complex trait. Sex accounted for a significant proportion (~15%) of the variation in height between individuals in the adult Chinese SCES cohort (Table 3). However, this effect was only half as great as that observed in the white European teenage ALSPAC cohort. Likewise, sex was responsible for very little (<1%) of the variation in axial length and corneal curvature in SECS participants compared to ALSPAC children (5%–13%).

In view of the limited statistical support for a polygenic component of height in SCES subjects, a genetic correlation was calculated only for the combination of axial length and corneal curvature (Table 3). The result was similar to that observed in the younger white European sample ($\rho_g = 0.64$ vs. 0.69, respectively).

Discussion

These results provide the first heritability estimates for corneal curvature and axial length in unrelated subjects, and thus provide further evidence that ocular component dimensions are determined largely by genetic variants rather than appearing as familial traits simply due to shared environmental exposures.[31] Sanfilippo et al.[32] have reviewed heritability estimates for ocular traits from twin and family studies: The heritability in the narrow sense (derived from the family studies) for corneal curvature ranged from 0.16 to 0.95 and for axial length from 0.31 to 0.73, with the majority of studies reporting values toward the higher end of these ranges. Thus, the lower-bound ocular trait heritability estimates of 0.35 to 0.79 observed here are consistent with true heritabilities >0.8 (such as that for height) after taking account of our method's limited ability to capture the influence of rare variants. The lower-bound heritability for height of 0.48 (SE = 0.17) estimated here for white European teenagers is in the middle of the range reported previously for subjects of similar ancestry,[15,16,30] while that of 0.31 (SE = 0.20) for subjects of Chinese ethnicity is lower. Unfortunately, because of the imprecision with which such figures can be calculated, the surprisingly low heritability estimate in the SCES cohort could equally well have resulted from a greater than previously encountered impact of environmental influences on height or be a chance finding.

Corneal curvature attains almost its full adult dimensions by age 3 to 4 years, while axial length generally plateaus in the late teens (although not in subjects with progressive myopia[33]). At the age at which the ALSPAC participants were examined (~15 years; range 14.5–17.0), both traits would have been close to their adult size and therefore we expected that our heritability estimates would be representative of those for adult cohorts. The results for the adult SCES participants supported this conclusion, although the notably higher estimate of 0.79 for axial length suggests the intriguing possibility that common genetic variants continue to influence eye size beyond school age and well into adulthood.

The lower bound of the genetic correlation between corneal curvature and axial length estimated here for young,

Figure. Relationship between corneal curvature, axial length, and height in ALSPAC participants. Scatter plots for axial length versus corneal curvature (**A**), axial length versus height (**B**), and corneal curvature versus height (**C**). *Lines* show least-squares best linear fit for each refractive group.

Table 3. Replication Analysis in SCES Subjects of Chinese Ethnicity ($n = 1642$)

Trait	Lower Bound of Heritability	Variance due to Sex
Corneal curvature	0.354, SE = 0.197 ($P = 0.036$)	0.006 ($P < 0.001$)
Axial length	0.789, SE = 0.184 ($P < 0.001$)	0.003 ($P < 0.001$)
Height	0.309, SE = 0.200 ($P = 0.061$)	0.152 ($P < 0.001$)
Traits	**Genetic correlation***	
Corneal curvature and axial length	0.643, SE = 0.221 ($P = 0.003$)	

* The genetic correlation P value was calculated[40] for the null hypothesis of no difference from zero.

white European emmetropes ($\rho_g = 0.85$) implies that a large number of shared genetic variants, each of small effect, contribute to the coordinated growth and scaling of eye size during childhood. The corresponding genetic correlation in the full ALSPAC cohort and the full SCES cohort ($\rho_g = 0.64$ vs. 0.69, respectively) suggests that this polygenically determined scaling of eye size is probably a general phenomenon. The former result confirms findings obtained in emmetropic animal models,[3,4] where extraordinarily high genetic correlations have been observed ($\rho_g \geq 0.95$). The lower phenotypic correlation between corneal curvature and axial length in the full sample of subjects compared to the emmetropic subset ($\rho_p = 0.54$ vs. 0.73) demonstrates that in myopes and/or hyperopes, environmental exposures have acted to alter the growth of one ocular component to a different extent than the other. The genetic corollary of this is interesting in the context of the hypothesis that gene variants controlling axial length also confer susceptibility to refractive error[34,35]: Presumably, if the same set of eye size–determining variants were also refractive error susceptibility variants, there would be no decrease in the genetic correlation in the full sample compared to the emmetropic subset. The lack of precision in our estimates ($\rho_g = 0.69$ vs. 0.85, respectively) meant that we were unable to distinguish between these options. The literature offers evidence against this hypothesis, from a study in an animal model of myopia,[3] but also in support for the hypothesis, with the recent discovery of a human sequence variant associated with both axial length and high myopia.[29] Genome-wide association studies (GWAS) of ocular biometric traits and refractive error utilizing large numbers of subjects should soon settle this question.

We found limited evidence that the genetic variants that determine height also control eye size. The phenotypic correlations between height and corneal curvature ($\rho_p = 0.22$; $P < 0.001$) and between height and axial length ($\rho_p = 0.20$; $P < 0.001$) were less than half those between the two ocular traits themselves, and the corresponding lower-bound genetic correlation estimates were also approximately 50% lower ($\rho_g < 0.42$, SE = 0.20–0.25, $P > 0.1$). The bivariate heritability of 89% for axial length and height, reported in a recent analysis in young Chinese twins by Zhang et al.,[12] suggests a strong genetic involvement in the coregulation of these traits. However, from the Cholesky path model factor loadings presented by Zhang et al., we calculated a genetic correlation between axial length and height $\rho_g = 0.19$ for their twin sample (using the formula $\rho_g = a_{21}/\sqrt{h_2}$; $= 0.18/\sqrt{0.92}$; where a_{21} is the loading of common additive genetic effects on axial length and height, and h_2 is the heritability of height). The lower-bound estimate of the genetic correlation between axial length and height found here ($\rho_g = 0.10$–0.42) is in general agreement with that of Zhang et al.[12] Thus, while "generalized growth gene variants" do appear to be responsible for the approximate scaling of eye size and body size, eye-specific and stature-specific variants seem to be much more widespread and exert greater influence. Notably, we recently found that an allelic score for the set of 180 genetic variants so far identified as associated with adult height showed at most a weak association with corneal curvature, axial length, and refractive error in ALSPAC subjects.[22]

Sexual dimorphism was much greater for height than for ocular component dimensions, perhaps representing a difference in selective pressure. However, there were marked differences between the two study cohorts. Sex accounted for approximately 30% of the interindividual variation in height for the white European teenagers, yet for only approximately 15% of the variation for Chinese adults. Both age and ethnicity-related factors could have contributed to this disparity, acting either through direct, X-linked genetic variation or indirect, autosomal genetic variation.[23,36] The correspondingly lower sexual dimorphism for ocular component dimensions in the Chinese adults versus the white European children was even more pronounced—and surprising, given that the ALSPAC subjects' eyes would have reached nearly their adult size. It would seem plausible for specific sex-by-genotype interactions to have given rise to these differences between the cohorts, for instance if the variants concerned differed in allele frequency between Asians and Europeans. However, for the eye size effects, another cause of the differential influence of sex between the cohorts might have been the level of ametropia: More of the variance in axial length and corneal curvature may have arisen from "outside sources" in the highly ametropic SCES subjects compared to the largely emmetropic ALSPAC subjects, thereby reducing the variance explained by sex as a proportion of the total.

Our bivariate analyses have implications for future GWAS of corneal curvature and axial length that examine cohorts in which the majority of subjects are emmetropes: Namely, our results suggest that most SNPs identified in such a GWAS are likely to be eye size variants, rather than trait-specific variants or refractive error–associated variants. Consistent with this inference, a GWAS for corneal curvature in the ALSPAC cohort[38] identified a PDGFRA variant—independently discovered in a corneal curvature GWAS by Han et al.[37]—that influenced both corneal curvature and axial length, but that was not associated with refractive error (because of the relative-scaling between ocular component dimensions).

In summary, we found that common SNPs were able to explain 35% to 80% of the variation in axial length and corneal curvature in two samples of unrelated subjects, confirming that the high heritability reported for these traits is not due to "common family environment" effects. Bivariate analyses provided evidence that a set of shared genetic variants is largely responsible for the relative scaling of corneal curvature and axial length, and that the genetic contribution to this scaling is greater than previously thought, especially in emmetropic individuals. This latter result suggests that GWAS investigations of corneal curvature and axial length in cohorts dominated by emmetropes will tend to identify genetic variants associated with eye size. In contrast, GWAS investi-

gations of these traits in cohorts dominated by ametropes are more likely to identify variants that are also associated with refractive error.

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