

Micrometric Control of the Optics of the Human Eye: Environment or Genes?

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PURPOSE. The human eye has typically more optical aberrations than conventional artificial optical systems. While the lower order modes (defocus and astigmatism) are well studied, our purpose is to explore the influence of genes versus the environment on the higher order aberrations of the optical components of the eye.

METHODS. We have performed a classical twin study in a sample from the Region of Murcia (Spain). Optical aberrations using a Hartmann-Shack sensor (AOnEye Voptica SL, Murcia, Spain) and corneal aberrations (using corneal topography data) were measured in 138 eyes corresponding to 69 twins; 36 monozygotic (MZ) and 33 dizygotic (DZ) pairs (age 55 years, SD 7 years). Intraclass correlation coefficients (ICCs) were used to estimate how strongly aberrations of twins resemble each other, and genetic models were fitted to quantify heritability in the selected phenotypes.

RESULTS. Genes had a significant influence in the variance of most of the higher order aberration terms (heritability from 40% to 70%). This genetic influence was observed similarly in both cornea and complete eye aberrations. Additionally, the compensation factor of spherical aberration in the eye (i.e., how much corneal spherical aberration was compensated by internal spherical aberration) was found under genetic influence (heritability of 68%).

CONCLUSIONS. There is a significant genetic contribution to the variance of aberrations of the eye, not only at macroscopic levels, as in myopia or astigmatism, but also at microscopic levels, where a few micrometers changes in surface topography can produce a large difference in the value of the optical aberrations.

Keywords: optics of the eye, optical aberrations, heritability

The human eye is apparently a much simpler optical device than almost any other artificial optical system. The number of lenses required by the eye (cornea and crystalline lens) is very modest compared to artificial objectives that are, on the contrary, often composed by dozens of lenses used to optimize the optical quality and to precisely reduce the amount of optical aberrations affecting the image.

However, a more detailed inspection to the optics of the eye reveals that while clearly simpler than artificial systems, the eye also tends to balance some of the aberrations of the isolated ocular components (cornea and lens). When the optical quality of each component is analyzed individually, more aberrations are induced than in the coupled system of the total eye.^{1–5} Aberrations of the cornea are partially balanced by internal aberrations (mostly the lens), and typical defects such as spherical aberration (SA) and coma tend to be compensated between each element.⁶ This strategy greatly resembles an aplanatic optical system in which SA and coma are corrected.⁷ Additionally, the balance of horizontal/vertical astigmatism between cornea and internal components has been often reported.^{2,8}

Still, the mechanism is not 100% accurate, and the amount of compensation varies across subjects and aberrations types. Therefore, it would be interesting to establish if those defects that remain in the eye (i.e., the aberrations that are not fully compensated) are mostly a random or environmentally induced microscopic defect or if they have a genetic origin. The latter would mean that some eyes are genetically oriented toward more aberrations than other eyes. The ideal methodological approach to study this problem is a classical twin study to quantify the relative genetic and environmental influences in a phenotype^{9,10} (optical aberrations). The genetic background of some refractive phenotypes, like myopia or astigmatism, was previously studied using this methodology—briefly, approximately 80% of the variance of myopia^{11,12} and 50% of the variance of astigmatism¹² can be explained by genetic differences. However, the visual effects of myopia and astigmatism are very large compared to the effects of aberrations (typically, measured ocular wavefront errors are in the order of tenths of microns).^{13–15} For this reason, the “microscopic” phenotype of aberrations requires a more



precise characterization than a measurement of refractive errors in the eye.

To assess the extent to which aberrations are caused by environmental or genetic influences, an adequate optical sensing technology is also required. While it is true that commercial aberrometers are becoming common in eye clinics, for research purposes it is necessary to maintain homogeneity of measurements (for example, to keep the same pupil size to analyze aberrations, to avoid pupil extrapolations, to keep the same polynomial order in the analysis, to avoid confounding factors to aberrations like refractive surgery, contact lens wearers, subtle principle of cataracts). Using methods and instruments custom designed and tested in our laboratory,^{16,17} we present here a classical twins study to estimate the heritability, that is, the proportion of variance due to genetic factors, of the optical aberrations and of the cornea-internal aberration compensation in the human eye.

METHODS

Subjects

Participants were monozygotic (MZ) or identical and dizygotic (DZ) or nonidentical twins from same-sex twin pairs that are part of the Murcia Twin Registry.¹⁸ The Murcia Twin Registry is a population-based twin registry of adult multiples born between 1940 and 1966 in the region of Murcia, Spain. After being informed of the nature of the study and possible consequences, all subjects enrolled provided an informed consent, according to the tenets of the Declaration of Helsinki. Every prospective subject underwent a complete ophthalmological examination. Subjects were excluded if they had any history of ocular surgery (cataract, refractive, ocular trauma) and any other pathology that might increase ocular aberrations. Additionally, only subjects with low refractive errors ($|\text{Sphere}| < 1.5 \text{ D}$; $\text{Cylinder} < 1.5 \text{ D}$), assessed objectively as part of the research protocol with a Hartmann-Shack wavefront sensor (AOneEye, Voptica SL, Murcia, Spain) were included. Twin zygosity was ascertained by DNA analysis. In total, 36 MZ and 33 DZ twin pairs were selected for this study from the database of the Murcia Twin Registry. Both the MZ and the DZ groups had similar age (range: 47–70 years; mean age MZ = 55 ± 7 years; mean age DZ = 56 ± 7 years; $P = 0.61$).

Measurements

Corneal aberrations were estimated from corneal topography data (Atlas 9000, Carl Zeiss Meditec AG, Oberkochen, Germany). The elevation data were fitted to a Zernike polynomial expansion using programmed routines with Mathematica (Wolfram Research). A Cartesian grid of data obtained from that surface was then exported to an exact Ray-Tracing software (Zemax, Kirkland, WA, USA) that was used to calculate optical aberrations expressed also as a Zernike polynomial expansion. Initially, before the fitting procedure, the corneal elevation data were centered on the first Purkinje image (corneal reflection) at the origin of coordinates, but was then shifted to the center of the pupil as estimated from the image processing software of the corneal topographer.

Ocular aberration measurements were taken with a Hartmann-Shack wavefront sensor (VAO, Voptica SL). The VAO is an adaptive optics visual simulator that combines ocular aberration measurement by means of a Hartmann-Shack wavefront sensor and a Liquid Crystal On Silicon (LCOS) spatial light modulator to perform real-time aberration correction. The Hartmann-Shack technique has been described elsewhere.¹⁶ The instrument projects a very thin laser beam

toward the retina of the subjects. Light is reflected back from the retina that acts like a point source, emitting light that exits the eye and passes through a matrix of micro-lenses (optically conjugated to the eye's pupil plane). A pattern of spots generated by the micro lenses is recorded with a camera sensor. The position of the centroid of each spot with respect to the corresponding nonaberrated reference beam is proportional to the local derivative of the wavefront. The wavefront aberration functions (expressed as sum of Zernike coefficients) can be mathematically reconstructed from the position of each of the spots in that pattern. In particular, this instrument used light with a wavelength of 780 nm, the micro lens array had a pitch of 388 μm in pupil plane and an effective focal length of 3.17 mm. Analysis was run up to the eighth order of Zernike polynomials. Corneal topography and Hartmann-Shack measurements were recorded a minimum of three consecutive times in each eye. The mean value was used for the calculations. Previous studies have shown that this particular wavefront sensor provides consistent and repeatable aberrometric data.^{19,20}

All wavefront aberration measurements (corneal and ocular) were taken at least 20 minutes after instilling two drops of tropicamide 1% in each subject (pupil was pharmacology dilated and any remaining fluctuation of accommodation was paralyzed).

Data Analysis

Descriptive analysis was performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA), and to a significance level of $P = 0.05$. Normal distribution was checked by means of the Kolmogorov-Smirnov test. One of the variables (the SA compensation factor [CF], described later in this paragraph section) required renormalization prior to genetic analysis (to reduce the influence of some outliers in the normalization value, we used ranks and nonparametric methods in that calculation). Means, variances, and twin correlations were estimated in a saturated model and twin model assumptions were checked (see Ref. 21). The Intraclass correlation coefficient (ICC) was used to avoid problems with twin data dependence when making comparisons between siblings. In order to estimate the phenotypical influences of additive genetics (A), nonadditive (dominance) genetics (D), shared environment (C), or unique environment (E, which includes measurement error) on aberrations of the eye, the data were analyzed using Structural Equation Modeling (SEM) with the Open Mx package in R. We corrected for mean effects of age and sex, including them as covariates in the analyses. One of the limitations of the standard twin design is that it cannot model the effects of both nonadditive genetic (D—dominance) and shared environmental (C—common) influences simultaneously. For this reason, twin studies often test the “ACE” and “ADE” models separately. C is estimated when DZ correlation is higher than half the MZ correlation, while D is estimated when DZ correlation is less than half that of MZ twins.

To enable the analysis of all the data from complete and incomplete pairs, Full Information Maximum Likelihood estimation (FIML) with raw data was used. In this method, twice the negative log-likelihood ($-2LL$) of the data for each family is calculated, and parameters are estimated so that the likelihood of the raw data is maximized. Nested models (AE, CE, E) were compared to a full model (ACE/ADE) with likelihood ratio tests (LRTs) that were obtained by subtracting $-2LL$ for a restricted nested model from that for a less restricted model ($\chi^2 = (-2LL0) - (-2LL1)$). The resulting test statistic had a χ^2 distribution with degrees of freedom (df) equal to the difference in df between the two models. When the fit of a more restrictive (nested) model differs significantly from that

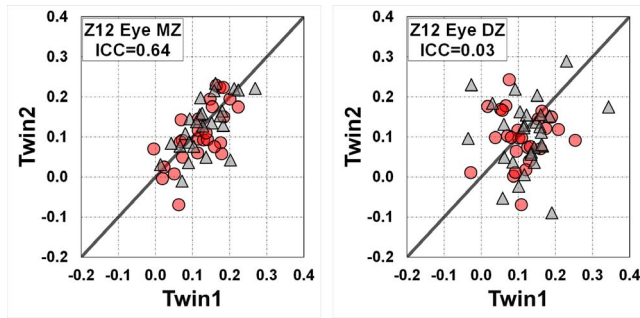


FIGURE 1. Correlation of ocular SA between twin pairs. Ocular SA (microns; 5-mm pupil diameter) for twins 1# plotted against twins 2# for MZ (left graph) and DZ (right graph) twin pairs. Circles and triangles represent right and left eyes. The solid line represents the Y = X identity. ICCs are shown in each graph.

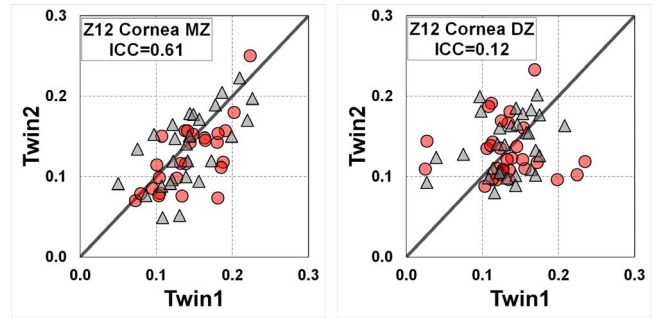


FIGURE 2. Correlation of corneal SA between twin pairs. Corneal SA (microns; 5-mm pupil diameter) for twins 1# plotted against twins 2# for MZ (left graph) and DZ (right graph) twin pairs. Circles and triangles represent right and left eyes. The solid line represents the Y = X identity. ICCs are shown in each graph.

of the less restrictive, it implies that the restriction imposed in the nested model does not hold for the available data. The best-fitting model was chosen in each case by deducting the residual deviance of the compared models and by comparing Akaike's Information Criterion (AIC).

The degree of compensation of aberrations between cornea and internal values was calculated as the ratio of internal aberration compared to the corneal aberration. In particular, the CF of SA was defined as the (negative) ratio between lens and corneal SA:

$$CF[Z12] = 1 - \frac{Z12[eye]}{Z12[cornea]} = - \frac{Z12[internal]}{Z12[cornea]}$$

Since the corneal values were always positive, the CF might take the following range of values and interpretations:

If CF[Z12]	{	≤ 0	No compensation
		0 < CF[Z12] < 1	Undercompensation
		1	Perfect compensation
		1 < CF[Z12] < 2	Overcompensation
		≥ 2	No compensation

RESULTS

Correlations of Optical Aberrations Between MZ and DZ Twins

All aberration data presented in this section corresponded to a pupil diameter of 5 mm, Zernike aberrations modes were named using the OSA single index scheme, and the degree of correlation between siblings was quantified using ICCs (calculated independently from left and right eyes, averaging both). Although this work was mostly focused at investigating higher order aberration terms, we also tested the lower order modes (defocus and astigmatism). In particular, defocus (Z4) of the eye was highly correlated in MZ twins (ICC = 0.79) compared to DZ (ICC = 0.27), which suggested a large contribution of genetic factors in the phenotype. Regarding astigmatism, we calculated the J0 and J45 components (using the Z3 and Z5 Zernike coefficients) from both corneal and total eye measurements. Correlations (ICCs) were systematically larger in MZ twins than in DZ twins, especially for the J0 component (0.46 vs. 0.14 in the cornea; 0.31 vs. 0.05 in the eye). The corneal oblique component (J45) showed also larger values in the MZ twins (0.39) compared to DZ (0.13). However, J45 in the eye showed much less difference between MZ and DZ twins (0.26 vs. 0.19), which suggested that the

crystalline lens contributed with a less genetic influence to this phenotype.

Regarding higher order aberrations, Figure 1 represents the correlation of SA (Z12) for the total eye between MZ twins (left panel) and between DZ twins (right panel). Figure 2 represents Z12 for the anterior corneal surface alone. The values of ICCs are also plotted in Figures 1 and 2. The ICCs were higher in MZ twins than in DZ twins. DZ twins' correlations were less than half of the MZ twins' correlation, suggesting the presence of dominant genetic factors in the phenotype (SA). Cornea SA and the total eye SA had similar ICCs. The correlation coefficients were also obtained for higher order aberration terms, like coma (vertical and horizontal components; Z7 and Z8) and trefoil (Z6 and Z9). Figure 3 shows the correlations between MZ and DZ twins for these phenotypes. The ICCs for the MZ twins were systematically larger than for DZ twins, which suggested the presence of genetic effects. Furthermore, the ICCs for corneal and total eye SA were very similar.

Heritability of the Higher Order Aberration Terms

Heritability is defined as a ratio of variances, specifically it is the proportion of total variance in a population for a particular measurement, taken at a particular time that is attributable to variation in total genetic factors (broad-sense heritability). A standard twin study design was used (see Methods for details) to partition the variance of each phenotype into additive genetic (A-additive), nonadditive genetic (D-dominance), and unshared or unique environmental influences on each individual, including measurement error (E). Only in two

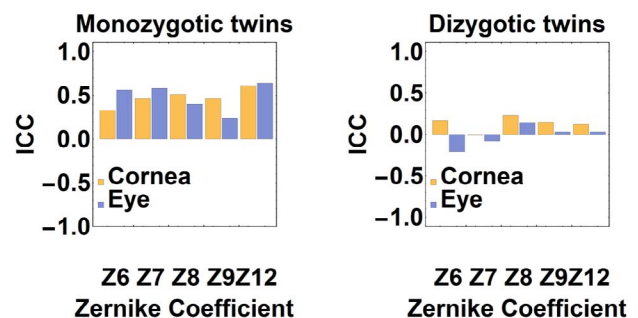


FIGURE 3. ICCs for the phenotypes (aberrations) measured in this study. ICCs from the correlations of different Zernike aberrations coefficients (Z6 and Z9 are trefoils, Z7 and Z8 are comas, and Z12 is SA) between twin pairs (MZ, left graph; DZ, right graph). Yellow and blue bars represent correlation coefficients for the cornea and the total eye, respectively.

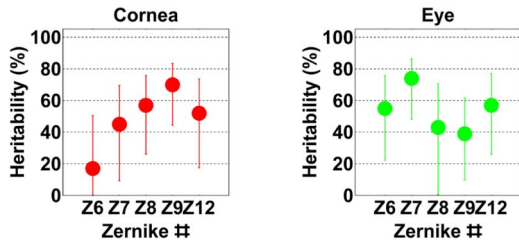


FIGURE 4. Heritability of optical aberrations. Heritability of several aberration coefficients (Z6 and Z9 are trefoils, Z7 and Z8 are comas, and Z12 is SA) of the cornea (left graph) and the total eye (right graph). Error bars represent the 95% confidence intervals for the estimation of heritability.

cases, the correlation structure oriented to an ACE model, where shared environmental factors (C) instead of dominant genetic factors (D) were modeled (Z6 and Z8 for cornea). The model fitting procedure showed that most of the aberrations terms were best fitted with a nested AE model (where A would include both dominance and additive genetic influence). In a few cases, genetic factors could be dropped without a significant worsening of fit (Z8 for eye and cornea; and Z6 for cornea). Details of the model fitting parameters are provided in the Supplementary Tables S1 to S3. Figure 4 shows the results of the heritability estimation (taken from the AE models) for each aberration term in the cornea (left panel) and the whole eye (right panel). These calculations were performed in the right eyes of subjects. The error bars represents the 95% confidence intervals for the estimation of heritability. Heritability estimates were moderate to large for all Zernike aberration terms (approximately 40% to 70%) except for one of the components of trefoil (Z6) at the cornea, where most of the variance could be explained as unique environment factors and measurement errors. Heritability of corneal and total eye SA (Z12) had very similar values (57% and 52%). As for the rest of the Zernike aberration terms, we did not find any systematic trend toward larger or smaller values of heritability for corneal aberrations than the total eye.

Heritability of the Compensation of SA

Typically, the components of the eye (cornea and internal optics) tend to balance ocular SA. In particular, the cornea has positive SA (peripheral rays focusing in front of central rays), while the internal optics tends to have negative values (peripheral rays focusing behind central rays).¹⁻⁸ This tendency was well reproduced in our data. Figure 5 shows SA for the

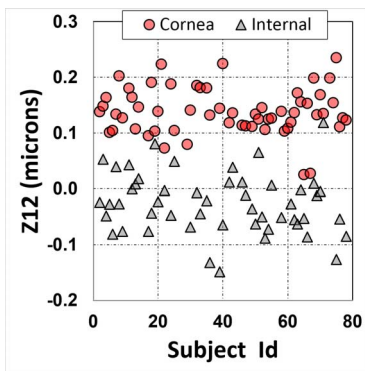


FIGURE 5. Corneal and internal SAs. Corneal (circles) and internal (triangles) SA (5-mm pupil diameter) for all twins set in the group 1# (MZ and DZ).

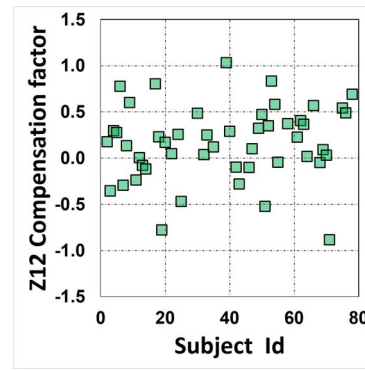


FIGURE 6. Z12 CF SA CF for all twins set in the group 1# (MZ and DZ).

cornea (circles) and for the internal optics (triangles) for half of the subjects participating in the study (in order to avoid familial aggregation confounding, one subject per twin couple was chosen). Internal SA was calculated as the direct subtraction of the corneal values to the total eye values. While, on average, internal SA was negative, some values were still clearly positive, which meant that no compensation or balance was present at all.

The CF[Z12] values, calculated for the same subjects of Figure 5, are plotted in Figure 6. On average, corneal SA was undercompensated by the internal values (mean CF 0.14; SD 0.41), but as shown in Figure 6, still a significant number of subjects had a negative CF (no compensation at all). The ICCs for the phenotype (CF) were estimated similarly to the isolated aberrations terms. Correlation plots are shown in Figure 7. ICC for MZ twins was more than twice than that of the DZ twins (ICC = 0.72; left plot versus ICC = 0.13; right plot). Once again, these ICCs values suggested the presence of genetic nonadditive (dominant) factors. In order to calculate heritability of the CF, the variance and covariance of the data were also fitted to an ADE model (and subsequently, to all nested models). The fitting procedure (details of the parameters are also included as Supplementary Table S3) showed that an AE model was, again, the best fitting one, with a heritability of 68% (95% confidence intervals ranging from 43% to 83%) for the CF[Z12].

DISCUSSION

Optical aberrations are apparently subtle errors typically presented in the eye, but because they are on average under a

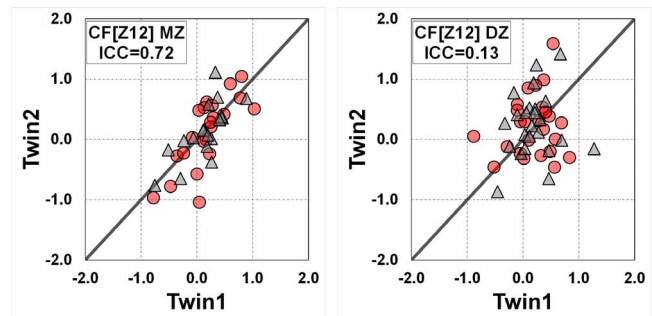


FIGURE 7. Correlation of the Z12 CF between twin pairs. SA CF for twins 1# plotted against twins 2# for MZ (left graph) and DZ (right graph) twin pairs. Circles and triangles represent right and left eyes. The solid line represents the Y = X identity. ICCs are shown in each graph.

quarter of Diopter and cannot be easily corrected, they are often present throughout our lives and most of the times go unnoticed. If aberrations are nonessential (in any optical sense) and serve no functional purpose, they might be considered, “a priori,” randomly generated optical irregularities somehow tolerated in the process of “building” (development of) the eye. However, our data revealed that there were genetic factors influencing most of the aberrations of each of the optical elements of the eye (cornea and lens) and the way that lens and corneal aberrations were combined in the eye together.

The combination of corneal and internal SA in the eye tends to be balanced between ocular components although some variability has been observed (some subjects compensate well while others poorly compensated). With this twin study, we have shown that a very large part of compensation variability (variance) is due to genetic factors. That is, a different genetic susceptibility may be associated to more or less SA compensation.

Still, the most striking feature of this situation is the tiny magnitude of the geometrical changes that would be required in the eye to physically modify these phenotypes (aberrations and SA CF). For instance, corneal SA ranged mostly from approximately 0.1 to 0.2 μm meaning that these micrometer differences in the surface profile between two corneas were at least partially controlled by genetic differences between individuals. To further illustrate this finding, a ray-tracing simulation through two corneas with difference levels of SA was performed. An anterior surface cornea model (7.8 mm of radius of curvature; the average value in a population; refractive index = 1.3375) was used as the base-model with the addition of SA using an aspheric conic constant term to the surface profile. Two corneal surface models were finally produced, one with 0.1 μm of SA and a second cornea with 0.2 μm . Surfaces were overlapped with the optical axis as the origin of the differences. Differences in the surface sag between both models were plotted as a function of surface height of up to 2.5 mm (a 5-mm pupil diameter). Results are presented in Figure 8 (black solid line). As expected, only small differences in the peripheral areas of the surface (under 5 μm differences) were required to generate the SA shift. Additionally, the surface sag difference between two corneas with two Diopters of dioptric power difference (radius of curvature 7.8 mm and 7.455 mm) is shown in the figure (red solid line). While this difference of two Diopters could still be considered as low myopia/hyperopia, it would require an existing geometric difference of more than five times the difference obtained with the SA case. This situation reflects that very small changes in the geometry of the ocular surfaces (just a few microns) would be enough to generate significant changes in the phenotypes of this study (aberrations) and how critical the choice of precise methodology was in reporting the aberrations, especially when compared to other refractive errors, as myopia or astigmatism.

In a recent report,²² the heritability of corneal SA was estimated for a Korean population to be 20%, a smaller value than the one obtained in our study (52%). Besides population and sample differences (the Korean study added data from other family members as well), the low heritability value (and low MZ correlation) might be the consequence of an ill-determined reference axis (not detailed). A change in the origin of coordinates over the corneal surface always implies a translation of values of aberrations from higher modes to lower modes^{23,24} (for instance, a shift in pupil position over the cornea generates more coma and less SA measured). Another difference regarding that study was the age distribution of the subjects as it was much wider than in our sample and included young, presbyopic, and older subjects. While calculations

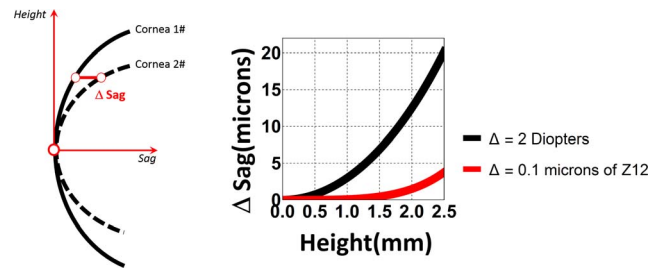


FIGURE 8. Topographical differences between two different cornea models. The difference of sag values (Δ sag, in micrometers) between two cornea models are plotted as a function of the height coordinate up to 2.5 mm (5-mm pupil diameter). The red solid line represents the difference between two corneas that only differ in 0.1 μm of SA. The black solid line represents the difference between two corneas that differ in 2 Diopters of optical power. The scheme on the left illustrates the calculation in the graphs.

could be corrected by age factors, ocular SA could have been dramatically altered by fluctuations of accommodation in young subjects.^{25,26} If measurements were taken under natural conditions without paralyzing accommodation (as it was the case), results could be influenced by a random source of error. In our case, accommodation was paralyzed in all subjects, even if the age was advanced enough to only allow very modest accommodation amplitude. The estimation of heritability of ocular SA in the Korean-population study (71%) was above our value (57%), which might reflect population differences, sample differences, and methodological differences. In a previous study, Dirani et al.²⁷ found an estimated value of heritability of ocular SA of only 8%, much lower than our values, which might be the consequence of a smaller sample (46 twin pairs) where correlations did not reach statistical significance.

Concerning other Zernike terms, as coma or trefoil, we were able to detect significant values of heritability, although in some cases, the best-fitted model (AE, explaining the observed variance by means of additive genetic and unique experiences plus measurement error) was not statistically different from the E model, which does not include any genetic component. This could be due to the limited statistical power of our study and, again, to the fact that we were measuring microscopic variables in the physical border of detection. However, the interpretation of these Zernike aberrations terms (Z8 for cornea and eye, Z6 for cornea) as phenotypes not caused by genetic factors might still be physically possible. It is plausible that these particular Zernike modes are just random inaccuracies generated in the development of the eye. The physical origin of both coma and trefoil is asymmetric in the shapes or in the position of the optical surfaces, which differs dramatically from the rotationally symmetrical shapes that generate SA. Perhaps, such asymmetries might happen as random events in the eye formation, while specific rotationally symmetric shapes are more influenced by genetics.

The fact that a genetic control of aberrations was present in the human eye prompted a discussion regarding the positive, negative, or neutral role of optical aberrations. Some works²⁸⁻³⁰ have suggested that having a normal level of aberrations, in general, might not even be harmful, as aberrations might increase depth of focus of the eye (i.e., the eye would be more tolerant to small amounts of defocus with aberrations than without aberrations). They might be also regarded as a defense against chromatic blur³¹ (eyes free of monochromatic aberrations might tolerate worse the chromatic differences in colors than eyes with a normal level of

aberrations). But more particularly, they might be specifically adapted for each individual, as the aberrations of each subject produced a better image quality than the same set of own aberrations randomly sorted in different modes.³² In this line of customized benefit, Artal et al.³³ also found that a modification in the subject's own aberrations (in the experiment, the subject's own pattern of aberrations was rotated in the eye using adaptive optics) generated a worst visual experience than with the original aberrations.³³ These results and similar ones^{34,35} have suggested that adaptation to a particular customized set of aberrations exists in each eye and we can now confirm that a certain genetic susceptibility existed in each individual, pointing to that particular set.

On the other hand, unusual high levels of optical aberrations are only associated to some refractive diseases such as keratoconus, where a significant influence of genetics has been found,^{36,37} or in traumatic injuries and refractive surgeries, both of which are environmental events. Additionally, intraocular scatter, which also has a clear influence in vision, has been recently investigated using a similar twin-study, showing less genetic effects and more environmental influence in the variance of the phenotype.³⁸ Those results complement our study, which offers novel information about the normal (nonpathological) level of aberrations.

While the genetic component was clearly present in the phenotypes of the aberrations studied here, the genes involved in them are still unknown. A large Genome-Wide Association Study (GWAS) would help to identify specific genetic variants. Perhaps, those variants involved in aberrations are similar to the candidate genes proposed for refractive diseases as myopia and astigmatism,^{39,40} where a previous genetic component had been identified. Our results for the lower order modes of aberrations (Z4, J0, and J45) showed similar correlations to previous works.^{11,12}

In conclusion, this study presents new evidences of a moderate to large genetic contribution to the optical aberrations of the eye. Our results suggest that genes partially control a coupling between corneal and internal SA, where a shift of few microns on the surface profile could have a dramatic influence on the assessment of the phenotype. Optical aberrations are an example of a tiny microscopic phenotype that could be genetically molded.

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