Disparity of Central-Peripheral Refraction Inheritance in Twins

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Abstract

The large incidence of myopia during the last decades is becoming a worldwide public health problem. Increasing myopia during childhood has been related to changing lifestyle and linked to larger eye growth, although the mechanism to explain how visual exposures affect ocular development is still unclear. The gene-environment interaction in myopia was investigated in a sample of 100 pairs of young twins with large prevalence of myopia. A classical twin's study model was performed on objective refraction measured with an open-view peripheral wave-front sensor across a wide range of horizontal retinal eccentricities. In this sample, variance of refractive errors at the area surrounding the line of sight was mainly related to variance in shared-environmental exposures. From there, while moving towards the retinal periphery, the environmental influence over peripheral refractive error variance decreased gradually towards a genetically-driven model. In conclusion, environmental exposures, responsible of the increase in myopia incidence, seems to be affecting mainly the central area of the retinal in young myopes.

Introduction

There is an increment in myopia incidence and progression at an alarming rate, especially in developed countries.[1–10] Although multiple research approaches have been conducted to breakdown and understand the possible origins and impact of myopia, there are still many unsolved questions. Over the last years, the influence of peripheral refraction (PR) in myopia development has taken the spotlight with increased research interest. However, the relationship between the visual feedback at the peripheral retina and axial elongation created a debate with opposite thoughts. The importance of peripheral optics in myopia began with the studies by Hoogerhide and Rempt et al. in 1971, where they measured peripheral refraction and predicted future myopia development in the presence of relative peripheral hyperopic defocus.[11,12] Some initial research on peripheral ocular optics supported the future myopia prediction by Hoogerhide and considered that PR with hyperopic shift could be a trigger for central myopia development.[13] However, several studies opposed to this theory and suggested the hyperopic relative PR is perhaps simply a consequence of central myopia.[14–17]

The role of genes and environmental exposures on myopia development is another area of interest. However, most previous heritability studies were restricted to estimate the variance for on-axis refraction, showing a general trend of high heritability estimated across different populations.[18–23] In contrast, a recent twin study with a young sample reported a considerably lower heritability estimate in comparison to a middle-aged twin population from the same twin registry.[24] To the best of our knowledge, there is only one published study estimating PR heritability, conducted in 120 Chinese children and adolescents, which reported a significant role of additive genetic factors to explain the variance of peripheral refraction,[25] thus supporting a relevant responsibility of genetic variation on myopia development. However, this study was limited in that they only studied peripheral refraction at a single peripheral angle (40° from the fovea), did not provide information about the refractive error at the line of sight (central measurements), and included a wide age span, ranging from children to young adults (8–20 years), with

very different levels of physical development and visual need or exposure. Hence, we found a gap in the literature regarding possible changes in heritability at different retinal locations in the periphery. Given the scarcity of data and the controversy regarding the role of PR on myopia development, we designed a twin study to extend our understanding of the genetic underpinnings of PR variance. Wave-front sensing technology allowed us to measure refraction at wide retinal eccentricities with high resolution (every 1-degree interval). The point-by-point refraction data gave us the power to pick up any fluctuation of heritability across the retinal eccentricities.

Results

This study included 200 participants (100 twin pairs) with an average age of 22.6 ± 4.0 (range: 19 to 30) years and 21.4 ± 2.4 (range: 19 to 36) years among MZ and DZ twin pairs, respectively. Average central objective refraction (spherical equivalent; SE) was − 2.08 ± 2.17 D (range: +3.8 to -7.0 D) in MZ twins, and − 2.28 ± 1.87 D (range: 0.0 to -9.8 D) in DZ twins. Participants showed a significantly higher female participation in both groups: 83 % in MZ and 69 % in DZ. However, the mean effects of age and sex were added to the model as covariates to control for their effect.[26] Study participants had a considerable high prevalence of myopia, where 78% showed myopia (SE<-0.50 D).

Twin correlations were always higher for MZ (range: 0.785–0.917) than for DZ (range: 0.355–0.695) across all retinal eccentricities, indicating a substantial role of genetic factors across all retinal eccentricities (Supplementary Table 1). Although for some of the data points, the correlation patterns (rMZ > 2rDZ) suggested the possibility of non-additive genetic effects, full ACE models were run for all retinal eccentricities in order to keep meaningful comparisons across all measures.

Figure 1 shows non-standardized estimates of corresponding genetic, environmental and total variances at 71 retinal eccentric points (± 35 degrees). The black line illustrates total phenotypic variance, while blue, red and green lines denote additive genetic, shared and non-shared environmental variances respectively. We found an average total variance of 3.64 ± 0.76 D with peak value at central retina (4.69 D at 11 degrees nasal retina) and gradual fall towards periphery. The individual average phenotypic components were 1.38 ± 0.66 D, 1.64 ± 0.81 D, and 0.62 ± 0.14 D for additive genetic, shared and non-shared environmental variances respectively. The additive genetic and shared environmental variances showed opposite trends across analysed retinal eccentricities (blue and red lines respectively). While additive genetic variance reached it minimum (0.46 D) at 7 degrees nasal, showing a gradual rise towards both sides, shared environmental variance showed an opposite trend, reaching it maximum (2.70 D) at 2 degrees nasal and decreasing thereafter. The non-shared environmental variance showed no significant fluctuation across the horizontal retinal eccentricity.

Standardized estimates were calculated as the proportion of phenotypic variance explained by additive genetic (A - heritability), shared (C) and non-shared (E) environmental variances respectively. Figure 2 represents the proportions of total phenotypic variance accounted for by additive genetics (A; Fig. 2, left)

shared environment (C Fig. 2, centre), and non-shared environment (E; Fig. 2; right) at each angle of horizontal eccentricity from 35 degrees nasal to 35 degrees temporal retinal eccentricity.

We found an average heritability of 39 ± 19 % having a large variability depending on horizontal retinal eccentricity (Fig. 2, left). Additive genetic variance accounted for a minimum of 12–15% and a maximum above 75% of the phenotypic variance which clearly indicates that the genetic and environmental influences are different depending on the retinal eccentricity point. The lowest values were around the fovea, while the highest were observed at a distal points of maximum eccentricity (temporal and nasal). In accordance to this ample variation, the data from the areas beyond 22 degrees in temporal retina and beyond 19 degrees in nasal eccentricity were best fitted with a constrained AE model (supplementary Table 2), where the shared environmental component could be dropped without deterioration of model fit. On the contrary, a CE model, where the genetic component could be dropped, showed the best fit in most of the central retinal zone (Supplementary Table 2).

Discussion

We performed a thorough point-by-point analysis to reveal any refraction heritability shift across a wide range of horizontal retinal scan. With the comprehensive SEM analyses, we found the highest total phenotypic variance (black line in Fig. 1) concentrated around the central retina, which gradually decreased towards periphery. When we looked at the contribution of individual phenotypic components of refraction variance, we found additive genetic influence was lowest at the foveal region, where the influence of shared environmental factors was highest. Interestingly, the decreasing total variance towards the peripheral retina, actually coincide with an increase of additive genetic influence (Fig. 2, left) accompanied by a gradual decrease in shared environmental impact (Fig. 2, centre).

The gradual increment of heritability towards the peripheral retina was distributed in such a manner that beyond specific thresholds (19 deg nasal and 22 deg temporal), it provoke a shift in the best fitting model from an environmental (CE) to a gene-environmental combined (AE) model. This deviation and the low heritability at the area surrounding the fovea suggest that variability at the central retina (around ± 20 degrees from the fovea) is greatly influenced by environmental factors than variability at the more eccentric areas of the retina. Moreover, the lower magnitude of unstandardized genetic variance around fovea would also indicate less dependence on genetic factors in this area and, hence, suggesting a higher sensitivity to the variation produced from environmental inputs. Consequently, our results would suggest that differences in myopia development are mostly explained by environmental effects that influence the eyeball at the central retinal zone. In contrast, eccentric zones of the eyeball would be less sensitive to environmental effects and dependent on genetic architecture. Concurrently, it is important to stress that the total variance and the raw shared environmental variance (Fig. 1) were both highest at central retina, suggesting greater visual exposure at central retinal region than at peripheral areas. Considering the above-discussed findings and the fact that the non-shared environmental variance remains stable across the analyzed retinal eccentricity, such environmental influences should be looked for within the shared visual exposures among siblings.

In agreement with our peripheral refraction heritability result, the study by Ding et al. in children and adolescents also reported a significant role of the additive genetic component to explain the variance of peripheral refraction.[25] However, they did not provide information about central and mid-peripheral refraction heritability. We couldn't find any other published literature on peripheral refraction inheritance. Whereas, all other studies on refraction heritability were restricted to foveal refraction only and generally suggesting a strong genetic influence on its variance.[18–23] On the contrary, the foveal and mid-peripheral refraction heritability in our study population showed a lower foveal refraction heritability with increased shared environmental impact.

The higher shared visual exposures at central retina and high myopia prevalence (78%) in our study population, may most likely include myopigenic factors: prolonged near visual tasks, time spent indoors, lighting conditions and reading text contrast or polarity etc. These factors are well connected to the modern lifestyle, massive urbanization, as suggested by recent myopia studies.[2,10,27–29] Our study population was also exposed to all these myopia causative factors as they are university students and belong to an urban area of a developed country. Myopia theories like 'accommodation lag theory' and 'mechanical tension theory' can further explain the mechanism of myopia development in a myopigenic environment prioritizing prolong near-work.[30–32] We could further connect these results with the neural and optical limitations of the retina resulting in poor sampling resolution at the periphery. The central retina is more sensitive to visual exposures (environmental influences) than the periphery mostly due to the high retinal resolution sensitivity threshold in the fovea, which rapidly decreases towards the peripheral retina.[33] Peripheral vision is compromised not only because of low cone density and limited ganglion cell density,[34] but also for increased optical aberrations at the peripheral retina.[17,35,36]

Development of myopic refractive error is mainly related to an increase in axial length (AL), following a rule-of-thumb that every 300 microns AL growth causes one diopter rise in myopia, considering no alteration of other ocular components.[37,38] However, the AL growth is unlikely to always confined at the macular area but extends to an unknown area at the posterior ocular wall. Based on biometrical and optical measures, Atchison et al.[39] proposed three possible scenarios to explain ocular growth linked to myopia: global expansion of the posterior chamber, extension of the posterior chamber induced by equatorial stretching of the eyeball, and posterior pole theory with an ocular growth confined to the area surrounding the macula. However, it has been complicated to validate these theories so far due to the limitations of the methods used for retinal off-axis measures. We used an alternate approach: instead of comparing measures performed within one single eye, we analyzed a wide range of off-axis refraction between eyes of twin siblings, who share genetic inheritance and environmental exposures. Thenceforth, we computed the relative influence of individual phenotypic components on its variance of refraction. These twins were born in a developed country at the end of the twentieth century, being most of them raised in myopigenic environment. As a result, we can predict that most of them have developed myopia related to an increase in eye size and less influenced by ocular optics. In that study, we found that variance of refractive error, induced by changes in eye size, was mainly influenced by variance in environmental exposures during ocular development.[24] An extensive SEM analysis of peripheral

refraction applied in this sample allowed us to differentiate to which point the variance of refractive error, measured from the LOS up to of up to ± 35 degrees retinal area, was influenced by variance in genes or childhood visual exposures. The central large environmental influence found in our study participants may predict a trend of ocular axial length growth limited mainly at the posterior pole of the eyeball, in an area from the optical disk to around 20 degrees temporal, supporting the 'posterior pole elongation' myopia theory.

Although myopia is not a disease itself, high myopia is a risk factor for severe ocular diseases and even blindness.[40–46] This study may contribute to facing this challenge, as it provides evidence and suggests mechanisms for environmentally driven myopia development. In summary, the refractive error variance showed a shift in the relative influence of genetic and environmental factors across horizontal retinal eccentricities. The total phenotypic variance showed its highest concentration at the macular region with gradual descent towards the periphery. Heritability showed an opposite pattern with its highest at the peripheral retina with gradual depletion towards fovea. We found the influence of shared-environmental factors to be the main source of individual differences explaining the central peak of total phenotypic variance.

Methods

Study Population

Peripheral refraction was measured in 100 twin pairs (54 MZ and 46 DZ), from the Murcia Twin Registry (MTR)[47,48]. All study subjects were either alumni or pursuing university students at Southeast Spain with age range of 18 to 30 years in MZ and 18 to 36 years in DZ twins. The study was designed considering the tenets of the Declaration of Helsinki[49] and informed consent was obtained from all study participants. The ethical approval was granted by the Research Ethics Committee of the University of Murcia (ID: 1108/2015). Subjects were recruited considering specific exclusion criteria, which includes active ocular pathology or allergy, previous ocular surgery, ocular trauma, amblyopia or a decimal corrected distance visual acuity below 0.9. The right eye measurements were considered in all cases as we found a very high correlation between both eyes. The present study sample was used previously to access heritability at fovea.[24]

Peripheral refraction

Peripheral wavefront aberrations were measured using an open-view Hartmann-Shack (HS) sensor (VPR, Voptica SL, Murcia, Spain). The VPR can scan a wide range of horizontal arc of 80 degrees (± 40 degrees) and provides 81 high-resolution HS images (measurements for each 1-degree interval) in 1.8 seconds. A complete measurement consists of four consecutive scans, resulting in 324 high-resolution HS images. Since often the data recorded in the extremes can be noisy, we decided to include only data for 71 degrees (± 35 degrees) scan arc. A near-infrared laser light source (780 nm) was used in the instrument considering ocular conform with a minimal pupillary light response. The intensity level (10μW) was kept

much lower than the permissible ocular safety limit standard for the selected wavelength. Further detail about the peripheral wavefront sensor can be found elsewhere.[50]

During measurement, subjects were asked to fixate at a laser fixation point at 3 meters distance while keeping a close eye on measurement fluctuations to avoid accommodation. The obtained HS images were then processed with a processing software (Voptica SL, Murcia, Spain) for 4 mm pupil and 5th order Zernike polynomials. Spherical equivalent (sphere + ½ cylinder) value was used as objective refraction at each retinal eccentric points.

Data analysis

Statistical analyses were performed using SPSS 24.0 (SPSS Inc. Chicago, IL) software and the OpenMx package in R.[51] Normal distribution was checked by means of the Kolmogorov-Smirnov test. Differences between variables were obtained by means of the Student t-test for normally distributed and the U Mann-Whitney test for non-normally distributed variables. The intraclass correlation coefficient (ICC) was used instead of the Pearson correlation coefficient to avoid problems with twin data dependence while performing the comparison between siblings. To estimate the components of phenotypical variance the data were analyzed using Structural Equation Modelling (SEM). SEM allows for a decomposition of phenotypic variance into additive genetic factors (A; the sum of allelic effects across all loci); non-additive genetic effects (D; the effects of genetic dominance and, possibly, epistasis); shared-environmental (C; environmental influences that make family members more alike) and non-shared or individual factors (E; idiosyncratic and random environmental influences that make family members less alike. It also includes measurement error). That is possible making use of the difference between MZ twins who share 100% of their DNA and DZ twins who share on average 50% of their segregating DNA. C and D cannot be estimated at the same time in a classical twin study using only data from twins reared together. Hence the selection of a model including ACE or ADE components, is based on the pattern of twin correlations. An ADE model is usually selected when the DZ correlation is lower than half of the MZ correlation. In contrast, an ACE model is selected if the DZ correlation is greater than half of the MZ twin correlation.[52] Mean effects of age and sex were added to the model as covariates to control their effect.[26]

Univariate analyses

One univariate ACE model was fitted to the data for each one of the 71 measured degrees. The ACE model was used for all the measured points in order to keep meaningful comparisons across all measures. The ACE model is also considered the standard approach to this kind of analysis. Assumptions of twin modelling were checked in the saturated models.

Heritability is defined as the proportion of the phenotypic variance explained by genetic factors (the same applies for common and non-shared environmental factors).[29] Unlike for other publications, where unstandardized variance components are not usually of interest, raw or unstandardized variance changes across each measured degree are reported. This allows us to compare the actual magnitude of the variance produced by genetic and environmental influences across all the retina points and not just their

relative proportions, which could yield similar estimates at every point if the magnitude of the different sources of variance grow or decrease parallely. Hence, both raw and standardized variance components are presented (Fig. 1, Fig. 2 and Supplementary Table 2).

Nested submodels (i.e. AE, CE and E) were also fitted to check if any of the components (A, C, or AC) could be dropped without a significant worsening of the model fit. The fit of each model was tested using the likelihood-ratio chi-square test and the Akaike's information criterion (AIC)[53] (supplementary Table 2).

Declarations

Authors' competing interests: The author(s) declare no competing interests.

Data and materials availability: Raw data, documentation, and code used in analysis (excluding any personal info) will be available upon request.

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Author contributions: DP, AB and PA conceptualized the original idea and constructed the methodology. DP and AB performed clinical examinations, data collection, and statistical analysis. JRO and JJM-V supervised twin subjects' recruitment and performed genetic analysis. DP wrote the original manuscript in consultation with AB. JRO and PA overall supervised the work, corrected, and edited the final version.

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Figures

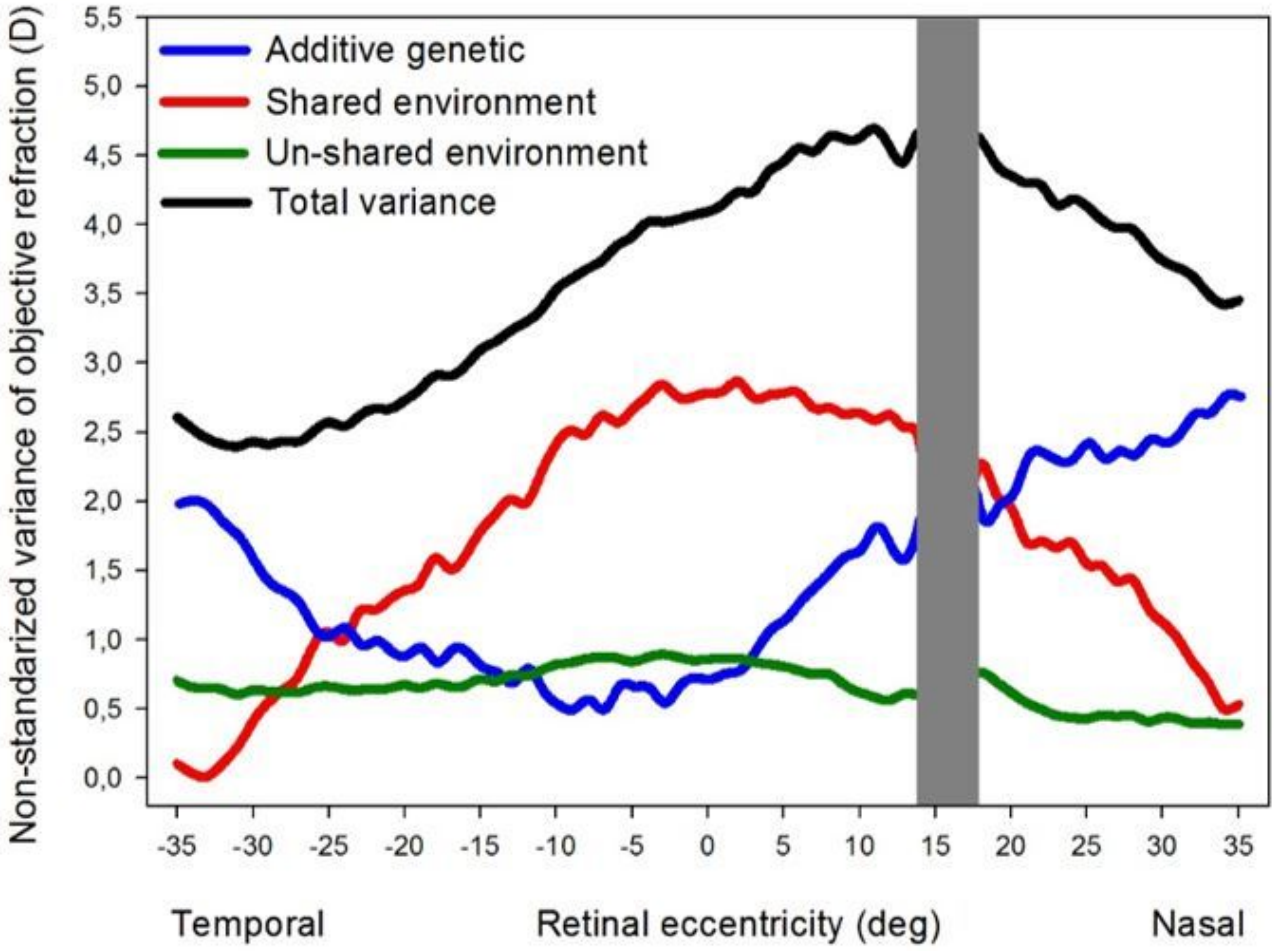

Figure 1

Variance components (ACE model) of objective refractive error, estimated by SEM analyses, across the horizontal retina. 0 degrees represent the position corresponding to the fovea; negative values indicate temporal retina, and positive values indicate nasal retina. Lines represent non-standardized estimates of additive genetic (blue), shared environmental (red), non-shared environmental (green), and total phenotypic (black) variance. The Grey area represents the area affected by the optic disk.

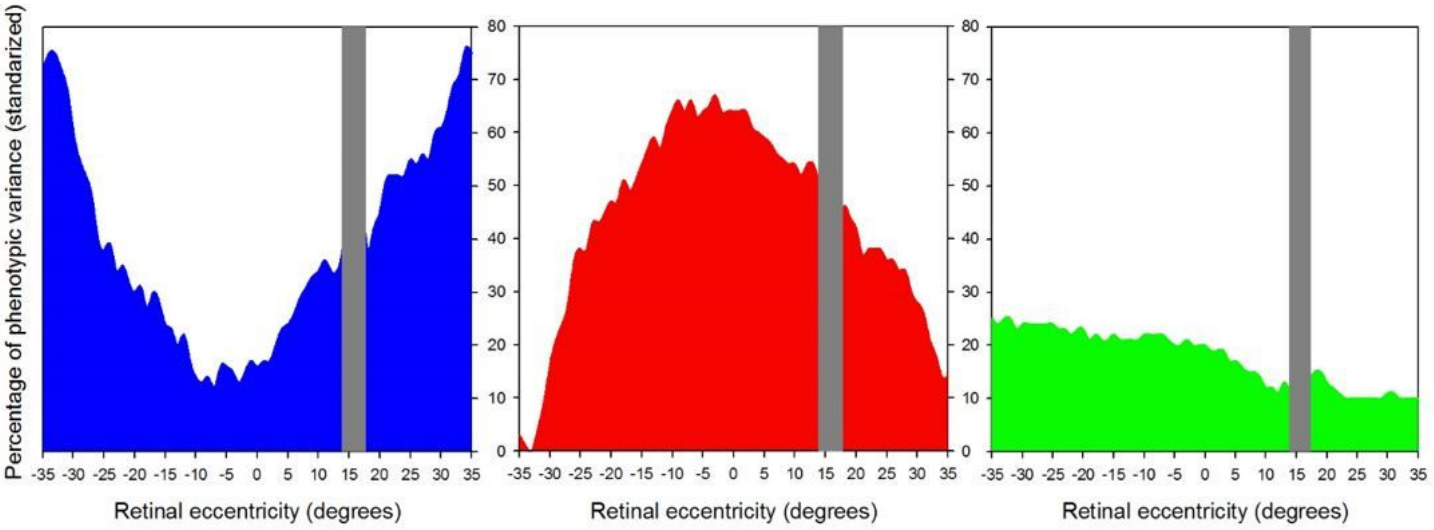

Figure 2

Percentage of phenotypical variance for variance components (ACE model) of objective refractive error, estimated by SEM analyses across the horizontal retina. 0 degrees represent the position of the fovea; negative values indicate temporal retina, and positive values indicate nasal retina. Left: heritability (blue).Center: shared environment (red). Right: non-shared environment (green). The Grey area represents the area affected by the optic disk.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.Twincorrelationsacrosshorizontalretinaleccentricities.xlsx
- SupplementaryTables2.SEMfittingsacrosshorizontalretinaleccentricities.xlsx