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Outdoor time influences VIPR2 polymorphism rs2071623 to regulate axial length in Han Chinese children

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Clinical relevance: Identification of individuals with a higher risk of developing refractive error under specific gene and environmental backgrounds, especially myopia, could enable more personalized myopic control advice for patients.
Background: Refractive error is a common disease that affects visual quality and ocular health worldwide. Its mechanisms have not been elaborated, although both genes and the environment are known to contribute to the process. Interactions between genes and the environment have been shown to exert effects on the onset of refractive error, especially myopia. Axial length elongation is the main characteristic of myopia development and could indicate the severity of myopia. Thus, the purpose of the study was to investigate the interaction between environmental factors and genetic markers of VIPR2 and their impact on spherical equivalence and axial length in a population of Han Chinese children.
Methods: A total of 1825 children aged 13~15 years in the Anyang Childhood Eye Study (ACES) were measured for cycloplegic autorefraction, axial length, and height. Saliva DNA was extracted for genotyping three single-nucleotide polymorphisms (SNPs) in the candidate gene (VIPR2). The median outdoor time (2 h/day) was used to categorize children into high and low exposure groups, respectively. Genetic quality control and linear and logistic regressions were performed. Generalized multifactor dimensional reduction (GMDR) was used to investigate gene–environment interactions.
Results: There were 1391 children who passed genetic quality control. Rs2071623 of VIPR2 was associated with axial length (T allele, β=–0.11 se=0.04 p=0.006), while SNP nominally interacted with outdoor time (T allele, β=–0.17 se=0.08 p=0.029). Rs2071623 in children with high outdoor exposure had a significant interaction effect on axial length (p=0.0007, β=-0.19 se=0.056) compared to children with low outdoor exposure. GMDR further suggested the existence of an interaction effect between outdoor time and rs2071623.
Conclusions: Rs2071623 within VIPR2 could interact with outdoor time in Han Chinese children. More outdoor exposure could enhance the protective effect of the T allele on axial elongation.

Refractive error, particularly myopia, is one of the most pressing epidemiological challenges today. By 2050, it is predicted that nearly 50% of the world's population will be affected by myopia, with 10% experiencing high myopia [1]. School myopia, also known as common myopia, is caused primarily by axial elongation of the eyeball, which is accompanied by structural alterations in the choroid and sclera. High myopia can result in severe sight-threatening complications, such as myopic macular degeneration, retinal detachment, and glaucoma [2].

The etiology of myopia has not been well defined. Both genetic and environmental factors have been shown to contribute to the disease. However, none of these factors alone can explain the change in myopic refraction, especially for school myopia, which differs from some types of genetic myopia (e.g., early-onset high myopia, which is largely determined by genes). Many studies have focused on the relationship between genes and the environment in myopia, reporting that gene–environment interactions have an impact on myopia onset and development [3–7]. According to the classical definition of gene–environment interaction, the statistical effect of a genotype on a phenotype depends on the environment of the individuals under study and vice versa [8].

Previous studies have examined which gene sites might have a greater impact on refractive error under high near-working burdens (i.e., higher education degree in adults or more near working in children) [5–7,9]. However, one study that used a stratified analysis reported an opposite result, finding that people carrying certain single-nucleotide polymorphisms (SNPs) were prone to developing myopia in a less risky environment (lower education level) [10]. Apart from

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near-work burdens, there is no evidence indicating that other environmental factors interact with a specific gene.

Most myopia is caused by axial elongation rather than high corneal power [11]. Therefore, axial length has always been deemed an endophenotype in genetic studies and could be an indicator of spherical equivalent (SE). In a previous study, genetic markers within vasoactive intestinal peptide receptor 2 (VIPR2) were reported to increase susceptibility to high myopia in a Chinese population. Based on a three-stage meta-analysis, Shi and colleagues [12] found that rs2071623 within VIPR2 was the most significant variant associated with high myopia. Yiu et al. [13] also found that a haplotype consisting of four variants in VIPR2 could impact the risk of high myopia. Therefore, we selected rs2071623, rs2730220, and rs885863 as our candidate variants. The purpose of this study was to identify the interactions between these genetic markers and the environment related to refractive error, especially axial length.

METHODS

Population, phenotype, and environmental factor assessments: In the present study, the population was drawn from the Anyang Childhood Eye Study (ACES), whose methodology had been published elsewhere [14]. We recruited individuals with a visual acuity of 20/20 or better. The exclusion criteria were as follows: (1) The parents were unable to give informed consent or fully understand the study; (2) Saliva could not be obtained for genetic examinations; (3) Concomitant with amblyopia, strabismus, retinal diseases, and other illness affecting visual acuity and refraction; (4) Anisometropia more than 1.50 D; (5) Application of atropine or orthokeratology lens to control myopia; and (6) Not Chinese Han nationality.

Cycloplegic autorefraction (HRK7000 A, Huvitz, Gunpo, South Korea), axial length, and other ocular biometric parameters (LenStar, LS900, Haag-Streit, Koeniz, Switzerland) were measured three times for each eye, and the average value was calculated [14]. Spherical equivalent (SE) was calculated as spherical refraction plus half of the cylinder refraction. The definition of myopia was cycloplegic SEM less or equal to −0.5D. Height and weight were recorded using an automatic and professional integrated set. Saliva was collected using sterilized tubes and stored in a freezer at −80 °C immediately after collection. Genomic DNA was extracted using the Magnetic Beads DNA isolation kit (AU70011, BIOTEKE CORPORATION [WUXIN] CO. LTD) following the manufacturer's instructions.

Outdoor time was determined by interviewer-administered questionnaires, as described in previous reports [15–17]. The specific question was as follows: How much time per week did your child spend on outdoor activities (school time and vacations separately) in the past year?

Ethics: The study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of Beijing Tongren Hospital, Capital Medical University, approval number TRECKY2018–030. Written informed consent was obtained from the participants' parents/legal guardians/next of kin to participate in the study.

Marker selection and genotyping: Three SNPs of the VIPR2 gene with known relationships to myopia were selected (Table 1). DNA was quantified with a spectrophotometer (NanoDrop2000, Thermo). The polymerase chain reaction (PCR) and single-base extension were completed with primers designed using MassARRAY® Assay Design 3.1 Software (SEQUENOM, Inc., San Diego, CA). The endpoint PCR products of each sample were then desalted and transferred to a SpectroCHIP® array pad for genotyping (Agena Bioscience, San Diego, CA), following the manufacturer's instructions.

Quality control: Prior to the association test, several genetic quality control processes were performed [18]. The specific filtration rules were as follows: (1) genotyping rate of each SNP <98%; (2) genotype call rate of an individual <98%; (3) MAF<0.01; (4) Hardy–Weinberg p value<1×10^{4}; (5) heterozygosity was outside the ±3 SD range; and (5) proportion identity-by-descent (IBD) >0.2, proportion IBD=P(IBD=2) +0.5×P(IBD=1; SD=standard deviation; p=probability).

Statistical analyses: The analyses were conducted using the average axial length and SEM values of both eyes, and monocular data if only one eye was available. Based on the median outdoor time, the population was divided into a high exposure group (≥2 h/day) and a low exposure group (<2 h/

Table 1. Basic information of 3 genetic markers within VIPR2.

Marker		GF		AF(A1/A2)
rs885863	CC/TC/TT	0.68/0.30/0.020	T/C	0.17/0.83
rs2730220	CC/TC/TT	0.72/0.26/0.022	T/C	0.15/0.85
rs2071623	CC/TC/TT	0.36/0.48/0.16	T/C	0.39/0.61

GF=Genotype Frequency; AF=Allele Frequency; A1/A2=minor allele/major allele

day). Myopia, emmetropia, and hyperopia were defined as SEM ≤–0.5D, >–0.5D and ≤0.5D, >0.5D, respectively. The specific analyses were as follows:

(1) Association between three SNPs and myopic phenotypes (myopia, SE, axial length). Age, gender, and height were included as covariates. In addition, the interaction term between SNPs and outdoor time was included in the analysis.

(2) In each exposure group, linear regression was used to investigate the association between single SNP sites and axial length. Age, gender, and height were included as covariates.

PLINK v1.90 software was used for the analyses and genetic quality control, and the genetic model was set to the default additive model (genotypes with two minor alleles, one minor allele, and zero minor allele were coded as 2, 1, 0, respectively). R software (4.0.5) was used for interaction analyses. After Bonferroni adjustment, a p value of 0.016 (0.05/3) was considered significant for association testing.

(3) The gene–environment interaction was also evaluated using GMDR v1.0 software, which could analyze both quantitative and dichotomous traits in a non-parametric way. The best model was selected based a significant sign test with a p value <0.05, best cross-validation consistency (CVC), and best prediction accuracy [19].

(4) As gene–environment correlation (rGE) could confound the results [20], we further tested whether rGE existing. This means that genotypes might impact the environmental choices of the population.

RESULTS

Population characteristics: After data selection, 1391 of the 1825 middle school students were included in the analyses (Figure 1). To ensure the authenticity of the phenotypes and environments, missing data were excluded. Of the students, 47.1% were male, with a mean age of 13.3±0.5 years. The mean SEM and axial length were −1.63±1.98 D and 24.15±1.06 mm, respectively. Myopia, emmetropia, and hyperopia accounted for 68.4%, 18.4%, and 13.2%, respectively.

Association of SNPs with myopic phenotypes: Only rs2071623 was associated with axial length after adjusting for age, gender, and height (β=–0.11 se=0.04 p=0.006), which was still significant after multiple correction. However, none of the SNPs showed an association with SEM or myopia (Supplementary Table 1 and 2). Rs2071623 could interact with outdoor time and showed its protective effect in controlling the elongation of axial length, with a nominal p value (β=–0.17, SE=0.08, p=0.029). This means that the protective effect of an increased T allele dosage would only be useful for individuals with greater outdoor time exposure.

Stratified analyses of different outdoor time exposure: Figure 2 shows the axial lengths of children with different genotypes in different exposure groups. Rs2071623 had significant effect on axial length (β=–0.19, SE=0.056, p=0.0007) in children with high exposure, with each copy of a minor allele (T allele) associated with an additional 0.19-mm reduction in axial length.

GMDR to detect the interaction effect: Figure 3 presents the gene–environment interaction between outdoor time and minor allele dosage of SNPs analyzed using GMDR. The evaluation of the SNP–outdoor time combination on axial length revealed only one significant model for rs2071623 for all three SNPs, in which the p value of the sign test was 0.0107 (<0.05 was considered significant; Table 2). None of SNPs exhibted interaction effects with environmental factors on SEM or myopia.

DISCUSSION

Our study suggests that outdoor exposure may influence the effect of rs2071623 on axial length in Chinese children. Children whose daily outdoor time was at least two hours had lower axial lengths as the number of T alleles increased. Based on the linear regression results, which were consistent with the GMDR findings, outdoor time and rs2071623 interacted to control axial length. The adjusted R-square increased about 0.3% after adding an interaction term to the linear model (9.4% versus 9.7%). Additionally, SNPs were not correlated with the environment (not shown in the results), and thus potential confounding effects of rGE could be excluded.

Duncan [21] summarized several interaction models, noting that in qualitative interaction “the effect of genotype is present at only one level of environment,” and such interactions are independent of the choice of scale. Based on our findings, rs2071623 (VIPR2) impacted axial length only in the population with high outdoor exposure, which fit the abovementioned model. There were significant differences between the fitted linear models of the two exposure situations (Figure 2). Despite the existence of the interaction phenomenon, children of each genotype with less exposure had longer axial lengths, demonstrating that the environment might have a major influence on common myopia. In addition to the nominally significant interaction term, GMDR also confirmed the interaction between SNPs and outdoor time. Thus, the finding regarding the interaction effect of rs2071623 and outdoor time should be reliable.

Genetic and environmental factors have been widely studied in the process of myopia onset and development. Greater exposure to outdoor environments and less continuous reading/near-work activities have been reported as protective

factors against myopia progression in children [17,22,23]. Fan et al. [6,9] found that some SNPs are associated with educational levels in adults as well as with near-work time in children based on a large ethnically diverse population. They also conducted a stratified analysis and found that the myopic shift effects of SNPs of SHISA6-DNAH9, GJD2, and ZMAT4-SFRP were larger in the higher education group than in the lower education group [7]. Enthoven and colleagues [20] found that environment risk scores (ERS) based on various environmental factors interacted with genetic risk scores (GRS) which was based on 175 SNPs. Because this method is far more challenging than identifying genetic main effects, the majority of studies using the G×E interaction term for analyses require large samples to discover interactions.

In a Chinese Han population, Cheong et al. [24] found that rs885863 from VIPR2 and rs7829127 from ZMAT4 were significantly associated with high myopia (as spherical equivalent refraction ≤ −6.00DS) under the dominant and co-dominant models. Interestingly, Leung et al. [25] found that two different loci within VIPR2 had the opposite effect on myopia risk. VIPR2 encodes intestinal peptide receptor 2, which is mainly located in retinal bipolar cells, and VIPR2 knockout mice showed a significant myopic shift [26]. As the receptor of vasoactive intestinal polypeptide, VIPR2 plays an important role in the functioning of the dominant circadian pacemaker, and mice lacking this gene exhibit impaired synchronization to environmental light [27]. It is believed that the circadian rhythm has an impact on refractive development [28]. Thus, VIPR2 might interact with light conditions in myopia development, warranting further investigation.

GMDR is a versatile tool for investigating gene–gene and gene–environment interactions [29]. While no confirmed interaction effect was found using common linear regressions when adding an interaction term to the model, GMDR revealed that rs2071623 had an interaction effect with outdoor time. Using GMDR, Xiao et al. [30] also reported that rs11178469 (PTPRR) interaction with rs6554163 (PDGFRA) in myopia incidence. However, to the best of our knowledge,

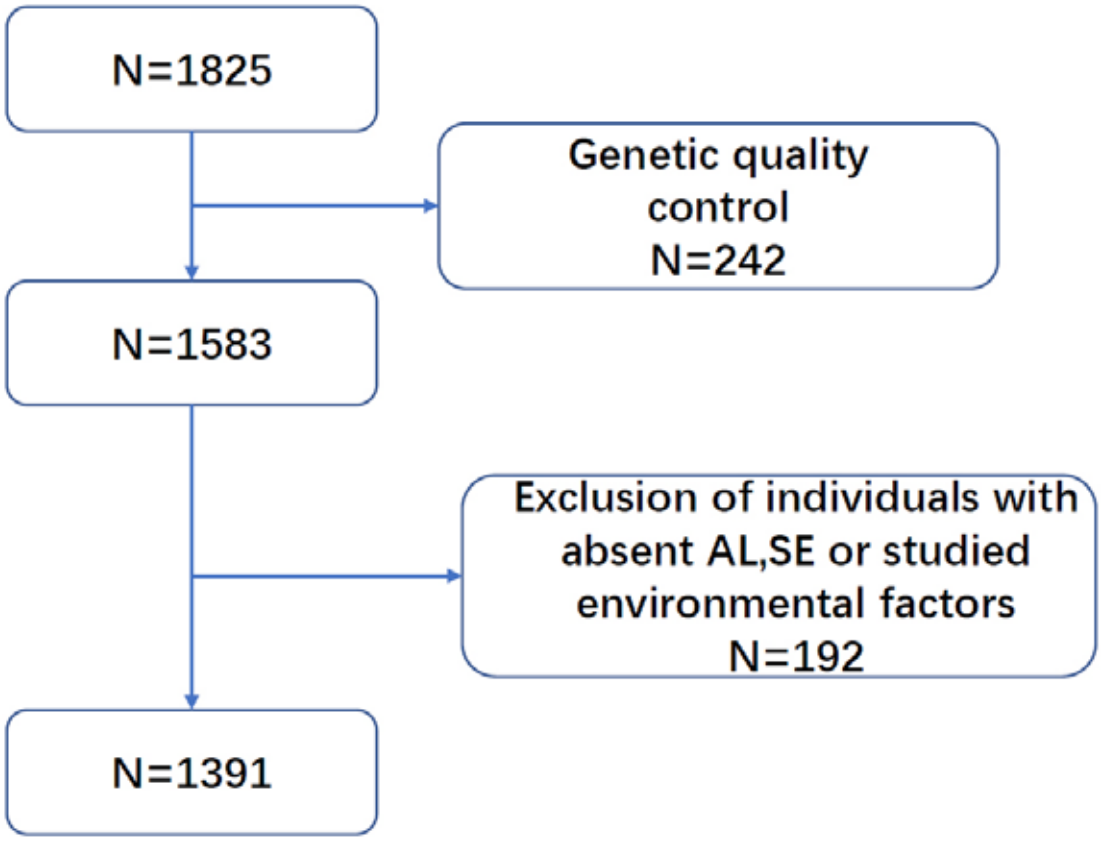

Figure 1. Flowchart of population selection.

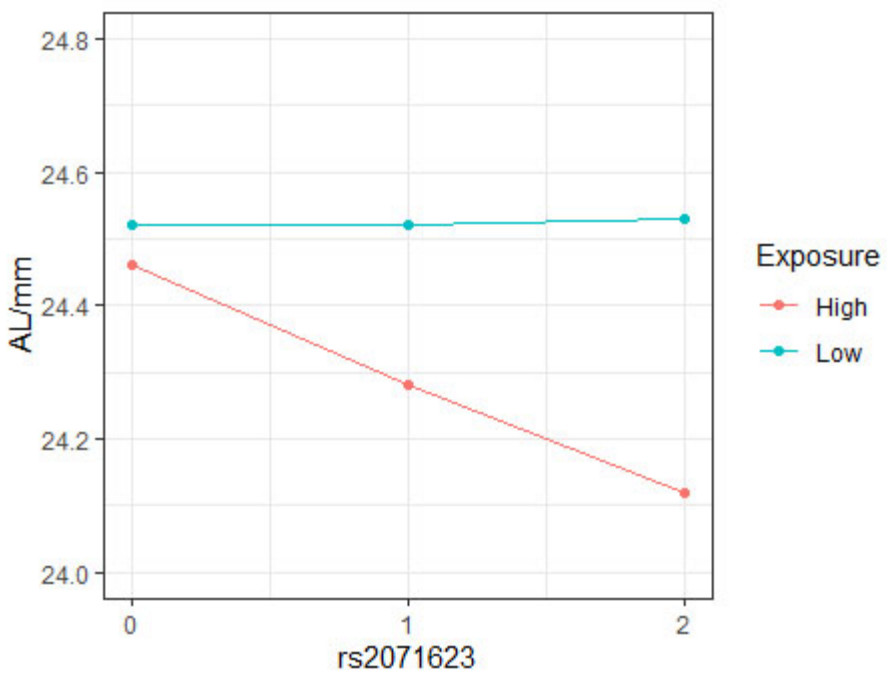

Figure 2. Fitted linear models between allelic dosage of rs2071623 and axial length under different levels of outdoor exposure. 0,1,2 represent the number of T alleles. The red line represents high outdoor exposure, while the green line represents low outdoor exposure. Axial length changes significantly with different genotypes under high exposure while remaining stable under low exposure. AL: axial length.

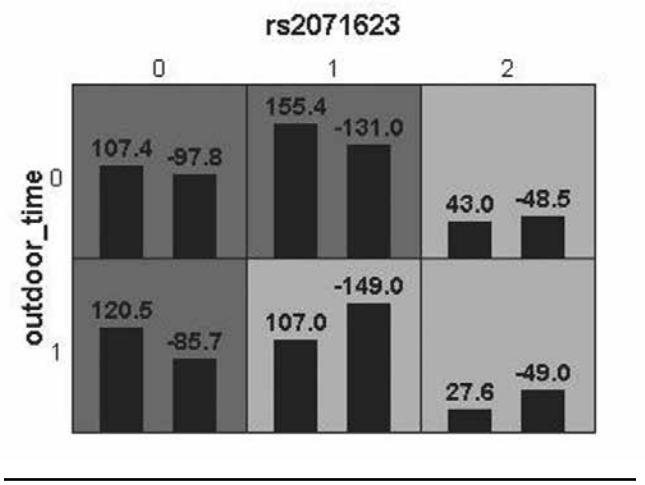

Figure 3. Gene–environment interaction between outdoor time and minor allele dosage of rs2071623. Outdoor time in vertical direction: 0=low exposure; 1=high exposure. 0,1,2 in horizonal direction represent minor allele dosage of the SNP. Light gray bars indicate low risk, and dark gray bars represent high risk. The left column in each bar represents positive scores, while the left column shows negative scores. If the negative column is higher than the positive column, the combination of the SNP and the environment was protective, and vice versa.

Table 2. Best GMDR model.

Model	Training balanced accuracy	Testing balanced accuracy	Sign test	CVC
Outdoor time rs2071623	0.5611	0.5493	9 (0.0107)	10/10

CVC: cross validation consistency

this study is the first to report the interaction effect between VIPR2 and outdoor time using a non-parametrical statistical method. Based on the results, interactions might not be detected using a linear model, and thus more sophisticated mathematical analyses might be useful for revealing interaction effects.

We found that individuals carrying rs2071623 (T allele) were more likely to have shorter axial lengths in lower-risk environments. However, no interact effect was found between SNPs and environmental factors for SEM or myopia onset. This discrepancy might be due to the complex regulatory process of refractive error, which is not only determined by axial length but also influenced by the refractive power of the cornea and crystalline lens. Further investigations are needed to examine the way in which genes and the environment regulate other ocular parameters and to identify a regulatory network among genes related to these components.

The strength of this study is that three methods were used to investigate the interaction between outdoor time and SNPs within VIPR2, adding to the reliability of the results. Further, it was the first study to successfully identify a gene–environment association in myopia using GMDR. The study also had some limitations. First, the results are based on a cross-sectional study, and a long-term follow-up study is required to determine the G×E interaction analysis. Second, the pathological mechanism of G×E interaction, namely, the function of VIPR2 under different light exposure conditions, should be further studied.

In conclusion, the results showed that the protective effect of the T allele of rs2071623 was more obvious in children who had higher levels of outdoor exposure. This result suggests that, although more work is needed, it may be possible to modify outdoor/near-work interventions for children with different genotypes to maximize the impact of interventions or provide more individualized strategies for myopia control. For instance, reminding parents to ensure their children engage in outdoor activities was shown to be a cost-effective way to reduce myopia incidence [15]. Therefore, it is likely that this method (increasing outdoor time) could be used to enhance the protective effect for those carrying specific genotypes (rs2071623).

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