Review Article

An update of the Guangzhou Twin Eye Study

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Abstract: The Guangzhou Twin Eye Study (GTES) is a population-based study of young twins residing in Guangzhou City. The major aim of GTES is to explore the impact of genes, environmental factors and gene-environment interactions on common eye diseases. From 2006, for more than 1,300 twin pairs, age 7–26 years old, progressive ocular phenotypes, such as refraction, ocular biometrics, weight, and height were collected annually, while non-progressive phenotypes such as parental refraction, corneal thickness, retinal fundus, intraocular pressure and DNA only collected at baseline. In the current study, we summarize the major findings on the etiology of myopia in recent decades.

Keywords: Twin study; gene; environment; myopia; prediction

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The Guangzhou Twin Eye Study (GTES), begun in 2006, is a population-based twin registry study. It aims to explore the contribution of genetic and environmental factors to the major eye diseases, especially school-age myopia. As of 2018, we have enrolled more than 1,300 twin pairs, aged 7–26 years old, and carried out 11 years of follow-up visits. This paper aims to present a summary of the major recent findings.

Phenotypic heritability study

Twin studies offer a unique opportunity to estimate the relative contribution of genetic and environmental effects to the development of complex traits and diseases. The total phenotypic variance is decomposed into additive (A) or dominant (D) genetic variance and shared (C) or unique (E) environmental variance. The E variation also contains measurement error. If the pairwise correlation in DZ twins is less than half of that in MZ twins, it suggests a contribution of genetic dominance. In this case, the model is fitted with an ADE (A and D genetic variances, and unique E variance) model; otherwise, the model is fitted with an ACE (A genetic variances, C common and E unique variance) model. Our study has explored common ocular biometric heritability, which have been published in the past 10 years (1), including iridotrabecular angle width (2), axial length (AL), anterior chamber depth, and angle opening distance (3), optic disc parameters (4), anterior chamber depth (5), corneal thickness (6), lens thickness (7), peripheral refraction (8), peripheral eye length (9) and ocular domain (10).

It is assumed that both ACE and ADE models may overestimate the phenotypic heritability due to the fact that the effects C and D confound each other in the classical twin design (11). If we included parental phenotypic information in the model, using an extended twin family design study (12), we can distinguish the effects C and D from each other, and scholars have shown that the ACDE model is less biased in heritability estimation (13). However, if we use this ACDE model in myopic research, it may meet

some problems: because there is a tremendous difference in environment exposures between parent and children in the last three decades in China, so there is heterogeneity of the common environmental effects between generations. We built a statistical model to test if this heterogeneity (H) effect existed in our sample. We have called this the ACDE-H model (14).

Three myopia related biometrics: spherical equivalent (SE), AL and corneal curvature (CC) were evaluated by three models: ACE or ADE model based on classic twin study, traditional ACDE model based on extended twin study, and our ACDE-H model based on an extended twin study. We found that comparing to classic twin study (ACE or ADE model), extend twin study (ACDE) significantly decreases the phenotypic heritability of AL and SE, but not CC. Furthermore, environmental heterogeneity between parents and children was only significant for SE and AL, which explained about 10.0% for SE variation, and about 20.0% for AL variation (15). This heterogeneity effect of SE and AL also supported the idea that environment change contributed a great role to the myopia boom in recently decades (16).

Genetic study of GTES

If we want to understand the role of genetics in myopia, we must identify susceptibility genes. Genome-wide association studies (GWAS) is a most common used method to find susceptible genes, and it has revolutionised our understanding of complex disease genetics, over the course of the past decade. For myopia, genome-wide discovery efforts have identified more than 50 genetic loci associated with myopic and related traits (17), largely due to the efforts of the CREAM consortium (consortium for Refractive Error and Myopia) (18), which was established in 2012. We joined this consortium in 2013.

Despite the great success, the overall genetic risk explained by these loci remains very low, less than 5%. Only a small proportion of heritability has been accounted for, leading to the term "missing heritability". One of the explanations of this phenomenon is that current GWAS studies may be underpowered to detect genetic variants with moderate-to-small effect, since a stringent significance level is used to control the false discovery rate. To overcome some of these limitations, we assume that a testing on multiple correlated traits may be more powerful than testing a single trait at a time, especially for myopia which has two important parameters: SE and AL. Because this joint analysis on correlated traits may increase the power in detecting genetic variants with moderate effects across multiple traits by exploiting the correlation between traits.

Based on this hypothesis, our group developed a univariate decomposition analysis (UDA) framework for jointly considering two or more traits together (19), in GWAS analysis. We applied the proposed UDA approach to our GTES data, and then validated using Singapore data. Preliminary results are promising, but the full analysis of the CEAM data will not be completed for several months. Now we have collected more than 20,000 samples including Europe, the United States, Australia and Asia. All data were under clean, the final results will disclose later.

Prediction study

With the increasing demands of precision medicine, prediction models have been proposed for risk estimation of various diseases. Risk prediction is also critical for myopia control since the side effects of current available interventions may cause adverse events. Prediction of myopia development can identify high-risk individuals at early stage, and avoid unnecessary treating on children without progressive myopia. Thus risk prediction of myopia and high myopia has been explored using our longitudinal data.

Reference centile curves have been widely used to screen abnormalities of an individual relative to a reference population in clinical practice. Inspired by this, we published the first prediction paper on ophthalmology by using reference centile curves to predict high myopia based on our longitudinal data. We found that the 5th centile showed the most effective diagnostic value in predicting the development of high myopia before the age of 15 years, providing an age-specific estimation on a severity scale of refractive error in school-aged children (20).

In order to explore the pattern of myopia progression, analysis on annual changes in spherical equivalent refraction (SER) and AL was conducted, showing that the progression of changes accelerated before the year of onset and then slowed down after myopic refraction (using the criterion –0.5 D) was established (21). Cluster analysis and principal component analysis (PCA) were further applied. A total of 637 first-born twins in GTES with 6-year annual visits were clustered into 1 to 3, representing stable, slow and fast progressing groups of refraction respectively, and showed significantly difference in baseline age and refraction, paternal refraction, maternal refraction and proportion of two myopic parents. We have also found that myopia

progression can be extracted to three major components (average refraction, acceleration, myopia stabilization and late onset of refraction progress/myopic shift) using PCA. Younger children with severe myopia, more near work time, and severer parental myopia tended to have faster myopic progression. Female was associated with myopia "Stabilization", which implied that teenage girls is more likely to reach to a stable stage of refraction growth. Increased outdoor time was related to component "Late onset of refraction progress" (22), meaning that time outdoors was associated with a postponed onset of myopic shift.

Environmental risk factors of myopia based on MZ twin study

For analysis of environmental risk factors for myopia, previous studies were unable to adjust for genetic background, or just adjusted by including parental refraction in the regression model, which is a relatively crude and contestable method. Since MZ twin pairs have a very similar genetic background, so MZ twin pairs is a unique sample to explore the environmental factors of complex disease.

We enrolled 490 MZ twin pairs and explored the differences in variation of two myopia-related environmental factors (nearwork and time spent outdoors activity difference) on difference in discordance in refraction discordance. A standard questionnaire was used to estimate environmental factors, which the same as previous used (23). Mixed model analysis shows that nearwork was a risk factor for myopia for the whole sample, while outdoor activity was a protective factor only significant in the 13 years old and above. Furthermore, we explored the ability of variation of collected environmental variables to explain the variation in total phenotypic discordance. We found that both nearwork and outdoor activity difference explained less than 5% of total SE discordance variation among MZ twin.

Domestic and international collaborations

In 2013, since we first published a review of our twin study (1), we received an international collaborative invitation from the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) consortium. This consortium aims to explore the genetic and environmental influences of height, weight, body mass index, from birth to old age with a large sample size (24-28).

In addition, we have collaborated with psychologists. We measured risk-taking propensity using youth-oriented version of the Balloon Analogue Risk Task (BART) and intellectual ability using age-appropriate Wechsler Intelligence Scales (WISC-IV-Chinese version) to explore the factors that influence risk-taking propensity in twins. In the multivariable mixed models analyses of risk-raking propensity, old age significantly increased the propensity of risk taking. A significant relationship was also found between increased IQ and decreased ANP values. Female showed fewer propensities towards of risk taking behaviors than males, but the difference did not reach statistical significance.

Conformity, usually referred as changing one's behavior to be harmonious with others, is common and fundamental to human societies, with both positive and negative consequences. Conformity has been studied by psychologists for six decades followed by recent neuroimaging studies of the underlying brain regions, with few genetic studies. Individual differences exist in the tendency to conform, which is generally explained by environmental influences. Evidence for genetic contribution to conformity is lacking. Here we developed two behavioral assays, word memorization and price estimation, to examine conformity in twins. Results from two behavioral assays were highly consistent. We found that correlations of conformity in monozygotic twins were around 0.36, whereas those in dizygotic twins were 0.14–0.24. Taking advantage of the classic pathway analysis, conformity was indeed heritable with heritability estimations of 0.25 to 0.37. We conclude that there may be a genetic contribution to social conformity, providing a basis for further research on molecular mechanisms underlying conforming behavior in humans. Furthermore, we performed GWAS at multiple levels (single locus, haplotype, gene, and pathway) to find specific genetic elements associated with social conformity, and found several strongly associated genes, including *NAV3*, *PTPRD*, *ARL10* and *CTNND2*.

Further directions

Since MZ twins are better matched for age, sex, and high similarity of genetic background, and partly for early environmental influences, so it is the unique sample to explore the mechanism of DNA methylation on disease onset and development, which is our next major direction. The GTES data collection is still ongoing and growing, and we have an open policy with respect to any collaboration. Request for any collaborations can be addressed to Dr. Mingguang He (mingguang_he@yahoo.com).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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