Refractive Status and Biometric Characteristics of Children With Familial Exudative Vitreoretinopathy

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PURPOSE. To compare biometric characteristics between patients with early-stage familial exudative vitreoretinopathy (FEVR) and healthy controls.

METHODS. This case-control study included 50 FEVR eyes in stage 1-2 and 50 control eyes matched by age, gender and spherical equivalent (SE). Biometric parameters including axial length (AL), white-to-white diameter (WTW), central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), pupil diameter, vitreous chamber depth, anterior and posterior corneal surface curvature radius (ACR and PCR), anterior lens surface curvature radius (ALR) and posterior lens surface curvature radius were measured using IOLMaster 700 and compared between cases and controls using paired t-test. Correlations between SE and biometric measures were assessed using Pearson correlation coefficient (r) in cases and controls.

RESULTS. Both FEVR cases and matched controls had a mean age of 7.6 years, 48% female and mean SE of −5.3 D (80% myopia). Compared to controls, FEVR eyes had smaller AL ($P = 0.009$), WTW ($P = 0.001$), ACD ($P < 0.001$), and ALR ($P = 0.03$), but larger CCT ($P = 0.02$) and LT ($P = 0.01$). In FEVR eyes, SE was negatively correlated with AL ($r = -0.79, P < 0.001$), positively correlated with ACR ($r = 0.29, P = 0.04$) and PCR ($r = 0.33, P = 0.02$), whereas in controls, SE was negatively correlated with AL ($r = -0.82, P < 0.001$) and LT ($r = -0.34, P = 0.02$), positively correlated with ALR ($r = 0.29, P = 0.04$).

CONCLUSIONS. Patients at early stage of FEVR exhibited a unique eye morphology resembling ocular development arrest, which may help to develop screening and early detection tools for FEVR. In FEVR patients, myopia is very prevalent and significantly associated with corneal curvature increase.

Keywords: familial exudative vitreoretinopathy, ocular development, refractive error, axial length, corneal curvature

Familial exudative vitreoretinopathy (FEVR), first proposed by Criswick and Schepens in 1969,[1] is an inherited disease characterized by congenital retinal vascular dysplasia. FEVR patients can present with high heterogeneous phenotypes, but they share a common initial manifestation of peripheral retinal avascular zones. As the disease progresses, additional abnormalities of posterior segments including subretinal exudation, retinal neovascularization, macular or disc dragging, retinal folding, and even retinal detachment will be exhibited, leading to vitreous opacities, strabismus, hypopsia, nystagmus, and ultimately blindness.

Moreover, the prevalence of myopia and high myopia was reported to be substantially high in FEVR patients but is only sparsely studied in the past.[2–4] The increased risk of myopia and high myopia predisposes patients to the subsequent high incidence of pathological myopia, and the resulting increased risk of irreversible vision loss.[5–7] Therefore it is important to understand the pathophysiological mechanisms of myopia or high myopia in patients with FEVR. However, only a few researchers explored this topic. Qi et al.[3] conducted a cross-sectional study that found a significant association between the degree of myopia and changes in lens shape, rather than axial length. In contrast, a retrospective cohort by Chen et al.[8] reported that individuals with FEVR had higher degree of myopia and longer axial length than controls. These findings suggest that FEVR patients may undergo different morphological development of their eyes which may increase their susceptibility to myopia. However, these studies focused on only small number of ocular features and had small sample sizes. In this study, we aim to gain a more comprehensive understanding of the ocular morphological features that contribute to myopia development specifically in FEVR by analyzing a variety of ocular biometric parameters on a larger group of FEVR patients and their matched controls.

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METHODS

This study was designed as a matched case-control study in Shenzhen Eye Hospital, P. R. China. The study was approved by Shenzhen Eye Hospital Ethics Committee (2023KYPJ006) and followed the principles of Declaration of Helsinki.

The cases (50 eyes from 33 patients) included children aged three to 14 years and with a diagnosis of FEVR at Shenzhen Eye Hospital from 2021 to 2022. The controls (50 eyes from 46 children), recruited from patients who visited the Department of Myopia Prevention and Control in the Shenzhen Eye Hospital, were healthy children matched with FEVR cases with respect to gender, age, and refractive status.

FEVR

All FEVR patients in this study were diagnosed by certified and experienced ophthalmologists with more than 10 years of clinical experience, and patients whose FEVR could not be definitely diagnosed were excluded from this study. The diagnoses were independently reviewed and confirmed by two experienced ophthalmologists. The diagnosis of FEVR required that all of the following criteria were met:[9–11] (1) full-term births or late preterm births (34–36 weeks of gestational age)[12] without a history of retinopathy of prematurity (ROP); (2) a definite temporal peripheral retinal avascular zone in at least one eye; (3) vitreoretinal traction and retinal vascular abnormalities including vascular leakage, brush-like increase of vascular branching, vascular tortuosity, and capillary anomalies. All FEVR patients had undergone fundus fluorescein angiography (FFA) examination. The staging of FEVR was based on the clinical classification of FEVR published in 2014,[13] and the eyes included were all in stage 1-2 of FEVR. Patients who had received treatments (including laser photocoagulation, vitrectomy, intravitreal injection of anti-VEGF drugs, cryotherapy, scleral buckling surgery, or any other surgeries) or had comorbidity (other systemic or ocular diseases) were excluded. To ensure
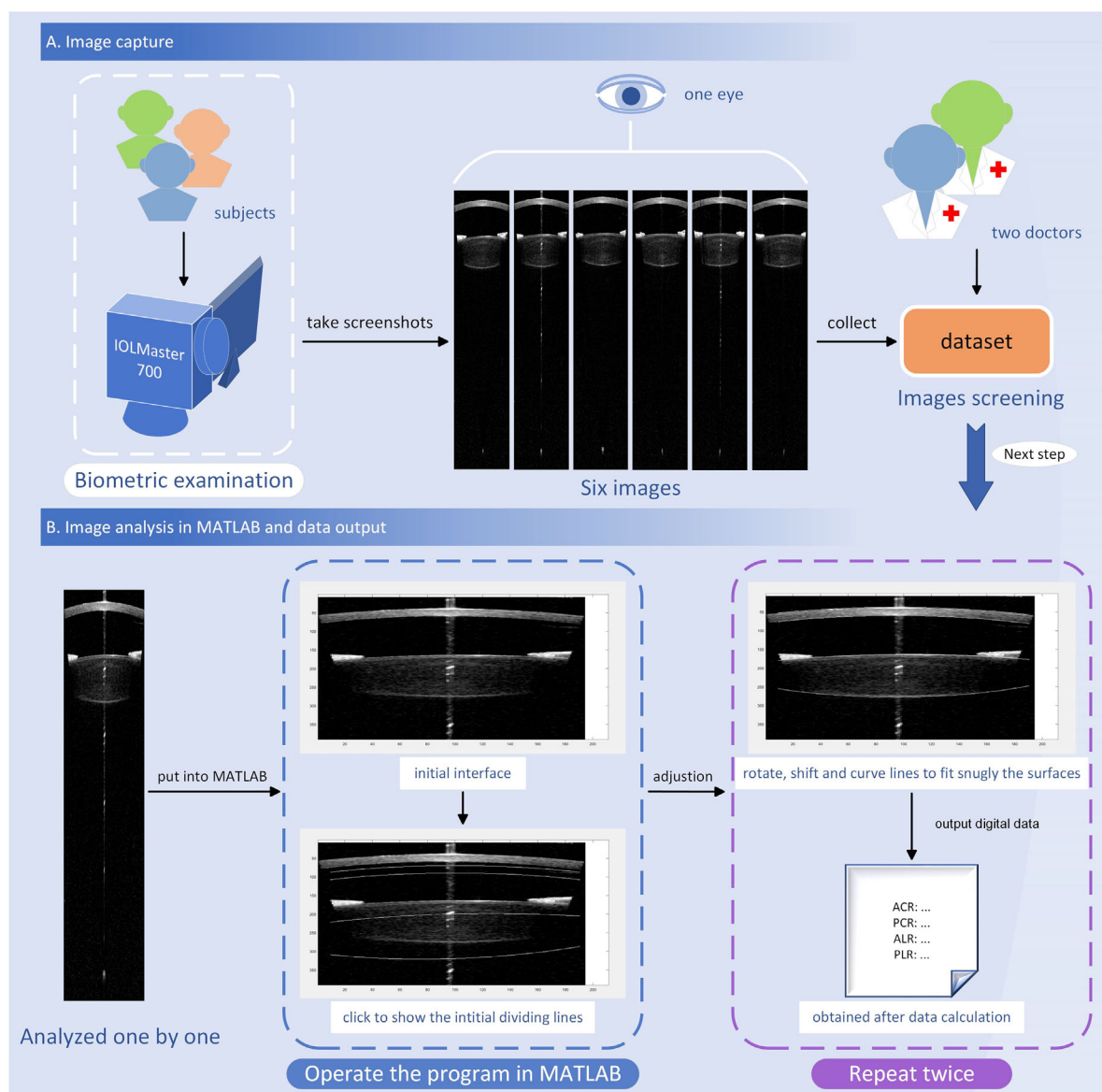

FIGURE. Analysis of the central anterior and posterior surface curvature of cornea and lens.

the accuracy of the biometric data, FEVR patients without reliable biometric measures due to nystagmus, retinal folds, or lack of patient cooperation were excluded.

Controls

The controls were screened from a large number of healthy children who visited the Shenzhen Eye Hospital for myopia assessment. Controls were matched with FEVR cases first by gender, followed by the spherical equivalent (SE) (matched the sphere, and cylinder, respectively) and age. Controls were matched to FEVR cases to make their differences in SE and age as small as possible. The cases and controls were matched with difference all within 1.00 D (42/50 had SE difference within 0.50 D) except for one case with an SE −22.75 D and the matched control had an SE of −19.0 D (e.g., difference of 3.75 D). The cases and controls were matched with age difference all within two years (41 pairs of cases and controls had same age, six pairs had age difference of one year, and three pairs had age difference of two years). While matching cases and controls, the data for ocular biometric measures were not accessed.

Biometric Measures

Children in the two groups underwent the same procedures for measuring refractive error and ocular biometrics. Refractive error was measured by experienced optometrists. After administering cycloplegia (0.5% tropicamide three times at five- to 10-minute intervals), the optometrists first confirmed that the pupils were dilated to 6 mm and unresponsive to light and then conducted the retinoscopy in a dark room. The refractive status was presented with SE, calculated as sphere + 1/2 cylinder. Myopia was defined as SE $\leq$ −0.5 diopter (D), and high myopia was defined as SE $\leq$ −5.00 D.[14,15] IOLMaster 700 (2018; Carl Zeiss Meditec AG, Jena, Germany) was used for measuring ocular biometrics including axial length (AL), white-to-white diameter (WTW), central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), and pupil diameter (PD). All biometric measures acquired from IOLMaster 700 were exported to an Excel spreadsheet, from where we selected the desired data for statistical analysis. Vitreous chamber depth (VCD) was calculated as VCD = AL − CCT − ACD − LT.[16,17]

To obtain additional ocular biometric measures, analysis of optical tomography images from IOLMaster 700 was performed in MATLAB (R2016a; MathWorks, Inc., Natick, MA, USA) by using a self-developed program.[18] Process of capturing and screening optical tomography images were shown in the "A" of the Figure, and the "B" showed the interfaces of image analysis through the program. In this image analysis, the positions of the four dividing lines were adjusted to fit snugly the anterior and posterior surfaces of the cornea and lens for obtaining the anterior corneal surface curvature radius (ACR), posterior corneal surface curvature radius (PCR), anterior lens surface curvature radius (ALR) and posterior lens surface curvature radius (PLR). The images used for this analysis were the same optical tomography images automatically acquired from the subjects when examined on the IOLMaster 700. Thus all the biometric measures were derived from the same images. Each eye had four to six images for image analysis, and the analysis of each image was repeated twice, the average of eight to 12 values was calculated for statistical analysis. The unit of all biometric measures was in millimeters (mm).

Statistical Analysis

Statistical analysis was performed using SPSS v22.0 software (SPSS, Inc., Chicago, IL, USA). Continuous measures were presented as mean $\pm$ standard deviation (*SD*) and categorical measures were summarized using count and percentage. The comparisons of age, SE and ocular biometric parameters between FVER cases and matched controls were performed using paired *t*-test. All comparisons were two-sided and $P < 0.05$ was considered statistically significant. Pearson correlation coefficient (*r*) was calculated to assess the correlation between SE and each biometric parameters for FEVR cases and controls separately because FEVR may have impact on the correlation between SE and biometric parameters.

RESULTS

Characteristics of Cases and Controls

The characteristics of FEVR cases (50 eyes from 33 patients) and 1:1 matched healthy controls (50 eyes from 46 children) were reported in Table 1. The cases and controls were similar in age (mean 7.6 years), gender (48% female), refractive error (mean SE = −5.3 D). In FEVR group, 80% eyes had myopia, and 48% eyes had high myopia. The mean PD after dilation at the time of ocular assessment were 6.17 $\pm$ 1.98 mm in cases and 5.99 $\pm$ 1.86 mm in controls ($P = 0.56$). None of their characteristics were statistically different between cases and controls (Table 1).

TABLE 1. Characteristics of FEVR Cases and Controls

Baseline Characteristics	FEVR	Control	*P*
Number of patients (eyes)	33 (50)	46 (50)	
Gender			
Female	24	24	
Male	26	26	
Age at the measurement of refraction and biometry (y)	7.64 $\pm$ 3.58	7.62 $\pm$ 3.59	0.85
SE (D)	−5.27 $\pm$ 5.20	−5.30 $\pm$ 5.07	0.71
% Myopia	80%	78%	
% High myopia	48%	46%	
PD (mm)	6.17 $\pm$ 1.98	5.99 $\pm$ 1.86	0.56

Myopia was defined as SE $\leq$ −0.5 D and high myopia was defined as SE $\leq$ −5.00 D. Paired *t*-test was used for the comparison of age, SE and PD between the two groups.

TABLE 2. Comparison of Biometric Measures Between Cases and Controls

Biometric Measures	FEVR (N = 50 Eyes)	Control (N = 50 Eyes)	P
AL (mm)	24.74 ± 2.07	25.12 ± 1.97	0.009*
Cornea-related parameters			
WTW (mm)	11.96 ± 0.54	12.26 ± 0.46	0.001*
CCT (mm)	0.56 ± 0.05	0.55 ± 0.04	0.02*
CCT: AL (%)	2.28 ± 0.25	2.18 ± 0.19	0.001*
ACR (mm)	7.24 ± 0.27	7.26 ± 0.20	0.74
PCR (mm)	6.34 ± 0.30	6.36 ± 0.23	0.62
ACD (mm)	2.88 ± 0.35	3.08 ± 0.25	<0.001*
ACD: AL (%)	11.68 ± 1.38	12.30 ± 1.17	0.001*
Lens-related parameters			
LT (mm)	3.60 ± 0.24	3.51 ± 0.19	0.01*
LT: AL (%)	14.68 ± 1.86	14.05 ± 1.32	0.003*
ALR (mm)	9.47 ± 1.54	9.87 ± 1.34	0.03*
PLR (mm)	5.27 ± 0.48	5.30 ± 0.41	0.66
VCD (mm)	17.70 ± 2.05	17.99 ± 1.91	0.052
VCD: AL (%)	71.36 ± 2.48	71.47 ± 2.16	0.66

* $P < 0.05$ from paired *t*-test.

TABLE 3. Correlations Between Spherical Equivalent and Each Ocular Biometric Measures

Biometric Measures	FEVR Group (N = 50 Eyes)		Control Group (N = 50 Eyes)	
	Pearson Correlation Coefficient	P	Pearson Correlation Coefficient	P
AL (mm)	−0.79	<0.001*	−0.82	<0.001*
Cornea-related parameters				
CCT (mm)	0.12	0.42	0.12	0.39
ACR (mm)	0.29	0.04*	0.02	0.90
PCR (mm)	0.33	0.02*	−0.07	0.61
ACD (mm)	0.08	0.57	0.12	0.40
Lens-related parameters				
LT (mm)	−0.08	0.58	−0.34	0.02*
ALR (mm)	0.12	0.42	0.29	0.04*
PLR (mm)	−0.18	0.21	0.07	0.65

* $P < 0.05$ from Pearson correlation coefficient.

Differences in Biometric Measures Between Cases and Controls

Compared to the controls, the FEVR cases had significantly smaller AL (24.74 vs. 25.12, $P = 0.009$), WTW (11.96 vs. 12.26, $P = 0.001$), ACD (2.88 vs. 3.08, $P < 0.001$) and ALR (9.47 vs. 9.87, $P = 0.03$) while had significantly larger CCT (0.56 vs. 0.55, $P = 0.02$) and LT (3.60 vs. 3.51, $P = 0.01$). The FEVR cases and controls were not significantly different in ACR, PCR, PLR, and VCD (all $P > 0.05$, Table 2)

In addition, compared to the controls, FEVR eyes had significantly smaller ACD/AL (11.68 vs. 12.30, $P = 0.001$), and significantly larger CCT/AL (2.28 vs. 2.18, $P = 0.001$) and LT/AL (14.68 vs. 14.05, $P = 0.003$). However, there were not significantly difference between the FEVR cases and controls in VCD/AL (71.36 vs. 71.47, $P = 0.66$, Table 2).

Correlation Between SE and Each Biometric Measures in the FEVR Cases and Controls

In the FEVR cases, SE had a negative correlation with AL ($r = -0.79$, $P < 0.001$), positive correlations with ACR ($r = 0.29$, $P = 0.04$) and PCR ($r = 0.33$, $P = 0.02$), while in the controls, SE had negative correlations with AL ($r = -0.82$, $P < 0.001$) and LT ($r = -0.34$, $P = 0.02$), but positive correlation with ALR ($r = 0.29$, $P = 0.04$) (Table 3). In both groups, there was no significant correlation between the SE and CCT, ACD and PLR (all $P > 0.20$).

DISCUSSION

In this study, the percentages of eyes with myopia in the FEVR group were 80%, significantly higher than in healthy children of similar ages 30.8% to 32.9% myopia (SE ≤ −0.5 D).[15,19,20] The prevalence of high myopia in the FEVR group were 48% (SE ≤ −5.00 D), significantly higher than that in the global population in 2020 (5.2%)[15] and in children aged 4–14 (4.2%).[19] Such a high prevalence of myopia in children with FEVR has been also observed in previous studies. A retrospective study reported that FEVR eyes (stage 1–3) had rate of myopia (SE ≤ −0.5 D) 100% (18/18) and rate of high myopia (SE ≤ −5.00 D) 94.4% (17/18),[2] whereas a cohort study reported myopia rate 56.3% (9/16) and high myopia rate of 50% (8/16) in FEVR eyes (stage 1-2).[3] Another cohort study reported myopia rate of 63.2% (24/38) in FEVR patients with pathogenic variants in TSPAN12.[4]

The refractive components of the eye including AL, CCT, corneal curvature, ACD, LT, and lens curvature all contribute to the refractive status of an eye. Therefore we conducted this matched case-control study to investigate the difference of each of these ocular biometric measures between FEVR cases and healthy controls, and determine correlations of spherical equivalent with each ocular biometric measures in cases and controls separately. The results suggested that FEVR eyes had significantly smaller AL, WTW, ACD and ALR, but had significantly larger CCT and LT. The SE was negatively correlated with AL and positively correlated with ACR

and PCR in FEVR eyes, but in healthy control eyes, SE was negatively correlated with AL and LT, and positively correlated with ALR.

A long-term follow-up study for 335 FEVR infants with single positive gene revealed significant correlation between stages of FEVR and AL, that is, the AL became shorter with the increase of FEVR severity.[21] This finding is consistent with our result that FEVR patients had shorter AL compared to controls. Qi et al.[3] carried out a study focusing on lens morphology of FEVR patients and observed that the center of the lens protruded backwards, increasing the posterior surface curvature and leading to the myopia. Similarly, our study suggested alterations in the lens shape and curvature, which might contribute to the myopia development. However, our study suggested that the anterior center of lens protruded into the anterior chamber based on our results of smaller ACD and ALR and larger LT in FEVR patients than controls. The differences in findings may be related to the different study subjects and methods in the two studies. In the study by Qi et al.[3] only children diagnosed with FEVR with unique lens changes were included (totally nine patients) and the lens morphology were assessed by slit lamp examination. However, in our study, we included all eyes with FEVR in stage 1-2 (50 eyes in total) and measured ocular biometrics with the IOLMaster 700.

Previous studies comparing FEVR patients to controls matched by age and gender found longer AL in the FEVR group.[8,22] This is inconsistent with our findings that FEVR patients had a shorter AL compared to healthy controls. This may be due to the different control group used in the two studies. In our study, SE was matched between cases and controls to minimize the effect of SE on AL, whereas in previous studies the SE was not matched in cases and controls. Chen et al.[8] also found no difference in ACD between FEVR and emmetropic control group, whereas we found a shallower anterior chamber in FEVR patients compared to myopic controls. This highlights the importance of our finding that after matching for SE, FEVR patients showed more changes in eye morphology compared to non-FEVR myopes, which may be considered as specific morphological contributors to myopia development.

ROP, a disorder of abnormal peripheral retinal vascularization that occurs in premature and low-birth-weight infants, is often mentioned together with FEVR because of their high similarity in phenotypes. A history of prematurity is the primary factor to distinguish between ROP and FEVR. ROP and FEVR share similar clinical features such as peripheral avascular retina, retinal neovascularization, retinal folds, and detachment, because their retinal complications are secondary to the arrest of normal retinal vascular development. Unlike FEVR, the biometric characteristics and refractive development in children with ROP have been studied by many investigators. The similarities and differences between FEVR and ROP patients are described as follows.

First, we investigated the ocular biometric characteristics of FEVR patients, just as many researchers have also conducted similar research in ROP. Their ROP studies have supported that premature infants with ROP have a delayed ocular development and a higher incidence of refractive errors, especially myopia.[23–28] Typically, ROP infants had abnormal ocular biometrics including lower AL and ACD, higher CCT, corneal curvature, LT and lens curvatures than premature infants without ROP and full-term infants. Interestingly, these biometric findings in ROP infants are very

similar to our findings in the FEVR patients. However, we found corneal curvature in FEVR patients showed no statistical difference as compared to healthy controls. The main reason for this difference may be due to two differences in the characteristics of our FEVR patients and ROP infants. First, the ROP studies for eye development generally focus on infancy or early childhood, while the FEVR patients of our study were children aged 3–14 years. Second, many ROP studies inevitably included infants with ROP treatment, whereas this FEVR study only included subjects with FEVR stage 1 or 2 who have not been treated for FEVR. The ROP treatment can have an impact on ocular growth,[29–31] and eyes with more severe ROP are more likely to require treatment and thus tend to have more significant changes in biometric characteristics compared to untreated ROP eyes.[13,21,25]

Second, we analyzed correlations of the spherical equivalent and each biometric measures in FEVR eyes and found that the SE was negatively correlated with the AL, the anterior and posterior corneal surface curvature. In this study, patients with FEVR, like healthy subjects, showed negative correlation between SE and AL. However, comparing to the controls with similar refractive error, patients with FEVR had significantly shorter AL, indicating that the AL increase fail to completely explain their severe ametropia (namely myopia). Therefore, we believe the increase in the corneal curvature contributes greatly to myopia development in FEVR patients, which also has been reported in ROP.[23,32,33] The possible reason is that the corneal curvature accounts for approximately two-thirds of the total refracting power to the eye. Therefore, in both FEVR or ROP, the change of corneal curvature could be smaller than that of other refractive elements (such as lens thickness or curvature) while having a larger impact on the overall refraction. Moreover, in this study, the increase in AL was considered most responsible for myopia in the control group, which is consistent with many previous reports on the refraction of healthy subjects.

The changes of biometric features in ROP-affected eyes are currently thought to arise mainly from the mechanical restriction on anterior sclera and preoptic segment secondary to its peripheral avascular zone[34] and altered neuroectodermal development.[35] This concept may provide the grounds to explore the cause for the unique eye morphology of FEVR patients who share similar clinical features, especially the peripheral retinal avascular zones.

FEVR is an inherited ocular disease and most of the FEVR-related genes identified, such as FZD4, LRP5, NDP and TSPAN12 are linked to the Wnt signaling pathway. We speculate that mutations in Wnt pathway impairs the normal development of eye structures, leading to the unique ocular morphology observed in FEVR patients. Because many studies have shown that the Wnt pathway has an important role on the development of cornea,[36,37] lens,[38–41] AL,[33,36,38] and other ocular biometric parameters.[36,38] These findings suggest that the development and structure of the cornea, lens, and anterior chamber in FEVR patients may differ from the healthy subjects. Genetic studies found associations between Wnt signaling pathway genes and the ROP development.[42–44] This could be one of the possible mechanisms to explain the similar ocular biometric characteristics of patients with ROP and FEVR.

We found that compared to myopic controls, patients at early stage of FEVR tend to have a shorter axial length, smaller cornea diameter, thicker cornea, steeper cornea curvature, shallower anterior chamber, thicker lens thick-

ness, which may be associated with ocular developmental arrest. This finding suggests that FEVR may be a disease that affects the whole eye and not just the retina. The unique ocular structure and mechanisms of myopia development in FEVR eyes means that approaches for prevention and control of myopia for healthy children may not be suitable for children with FEVR. Furthermore, these changes in ocular biological structure in FEVR patients might be helpful for developing screening and early detection tools for FEVR.

There are limitations in this study. First, as a retrospective study, this study may inevitably have selection bias in the included subjects. However, we matched the cases with the controls for age, gender, and spherical equivalent to minimize the effect of these possible confounders. Second, the differences in biometric characteristics between FEVR patients with stage 1 and patients with stage 2 were not investigated in this study, which will be explored in future studies. Third, although we evaluated the cross-sectional correlation between SE and biometric measures in FEVR patients, this cross-sectional correlation analysis cannot elucidate the mechanisms of myopia development in FEVR without using the longitudinal data from the follow-up of FEVR patients at different ages. By analyzing a variety of biometric parameters in FEVR patients and their matched healthy controls, our study provides new insights into FEVR pathophysiology and contributes for a better understanding of ocular morphological factors that may contribute to the myopia development.

In summary, this matched case-control study shows that individuals in early stage of FEVR demonstrate unique changes in ocular morphology resembling ocular development arrest, as characterized by lower AL, WTW, and ACD but higher CCT, LT, and lens curvature. Consistent with previous studies, we found a high prevalence of myopia in FEVR patients, and the myopic spherical equivalent was associated with an increase in corneal curvature. These findings may help develop screening and early detection tools for FEVR.

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