# Analysis of Etiologic Factors in Pediatric Rhegmatogenous Retinal Detachment With Genetic Testing

CHONGLIN CHEN, SIJIAN HUANG, LIMEI SUN, SONGSHAN LI, LI HUANG, ZHIRONG WANG, XIAOLING LUO, AND XIAOYAN DING

• PURPOSE: **The purpose of this study was to investigate the etiology and clinical features of nontraumatic rhegmatogenous retinal detachment (RRD) in children.**
• DESIGN: **Consecutive, cross-sectional study.**
• METHODS: **In this study, 112 operative eyes of 102 patients ≤18 years of age with nontraumatic RRD were included. Comprehensive ophthalmic examinations were performed in all patients. Genetic testing was performed in 34 patients with hereditary congenital/developmental diseases. The etiology of RRD was analyzed.**
• RESULTS: **The average age was 12.2 ± 4.5 years (range, 1-18 years). The percentages of male and female patients were 74.5% (76/102) and 25.5% (26/102), respectively. The most common etiologic factors were congenital/developmental anomalies (51/102, 50%), followed by simple myopia (34/102, 33.3%) and previous intraocular surgery (6/102, 5.9%). More than half (31/51, 60.8%) of the patients with congenital/developmental anomalies had familial exudative vitreoretinopathy. Further analysis of the underlying etiologic factors based on age revealed that the most common etiology of RRD in patients ≤12 years of age was congenital/developmental anomalies (28/48, 58.3%); however, simple myopia was the major etiologic factor in patients > 12 years of age (27/54, 50%).**
• CONCLUSIONS: **Congenital/developmental diseases were the most common etiologies of pediatric nontraumatic RRD in China. Familial exudative vitreoretinopathy accounted for most of the congenital/developmental anomalies.** **(Am J Ophthalmol 2020;218:330–336. © 2020 Elsevier Inc. All rights reserved.)**

RHEGMATOGENOUS RETINAL DETACHMENT (RRD) IS more rare in children compared with adults, accounting for about 1.7%-12.6% of all RRD cases.[1,2] Despite the low incidence, RRD is a major cause of blindness in children.[1,3] Although RRD is often associated with poor visual outcomes,[4–8] careful ophthalmologic examination and evaluation of the affected children can preserve their vision and improve their quality of life.

The reported predisposing factors for pediatric RRD include myopia, trauma, congenital/developmental abnormalities, and previous intraocular surgery.[5,7,8] Associated congenital/developmental abnormalities include familial exudative vitreoretinopathy (FEVR), Stickler syndrome, Marfan syndrome, morning glory syndrome (MGS), and retinopathy of prematurity (ROP).[3] The etiologic factors, clinical features, and prognosis of RRD in children differ from those in adults, which poses a challenge to ophthalmologists.[8,9]

Different classifications of nontraumatic pediatric RRD have been reported.[8,10,11] To our knowledge, our study was the first to analyze the etiologic and clinical characteristics of nontraumatic pediatric RRD based on genetic testing.

## PATIENTS AND METHODS

THIS WAS A CONSECUTIVE CASE SERIES OF PATIENTS ≥18 years of age who underwent primary surgical repair for RRD at the Pediatric Retinal Department by a single ophthalmologist at our hospital between January 1, 2014 and December 31, 2018. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University. Informed consent was obtained from the parents of all patients. The exclusion criteria were tractional and exudative retinal detachment or a history of penetrating or blunt trauma.

Complete ophthalmic examination was performed in children with RRD and their parents and any siblings, including the visual acuity test, intraocular pressure test, slit-lamp biomicroscopy, and binocular indirect ophthalmoscopy. The retina of the affected eyes was assessed under mydriatic conditions with a Goldmann 3-mirror contact lens. Ophthalmic findings at presentation included lens and vitreous statuses, type and location of retinal holes, status of the macula (on or off), and extent of retinal detachment. Digital fundus photography (Topcon Retinal Camera TRC-50DX, Tokyo, Japan), scanning laser ophthalmoscopy (SLO; Optos PLC Daytona, Dunfermline,

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Feb 13, 2020.
From the State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.
Inquiries to Xiaoyan Ding, Sun Yat-sen University, State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, 54 Xianlie S Rd, Guangzhou 510060, China; e-mail: dingxiaoyan@gzzoc.com



0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.02.015

**TABLE 1.** Demographic Information for 112 Operated Eyes from 102 Pediatric Patients with Nontraumatic Rhegmatogenous Retinal Detachment

| Variants | N = 112 |
|---|---|
| Age, years | |
| Mean ± SD | 12.2 ± 4.5 |
| Range | 1-18 |
| Gender, n (%) | |
| Male | 76 (74.5) |
| Female | 26 (25.5) |
| Laterality, n (%) | |
| Unilateral | 84 (82.4) |
| Bilateral | 18 (17.6) |
| Surgery-needed RRD | 10 (9.8) |
| End stage RRD without any treatment | 6 (5.9) |
| Previous successful RD surgeries | 2 (1.9) |
| Right eye | 58 (51.8) |
| Left eye | 54 (48.2) |
| Lens status, n (%) | |
| Cataract | 4 (3.6) |
| Lens subluxations or dislocation | 3 (2.7) |
| Aphakia | 5 (4.5) |
| Pseudophakia | 4 (3.6) |
| Types of retinal breaks, n (%) | |
| Round holes | 78 (69.6) |
| Horseshoe tear | 13 (11.6) |
| Giant retinal tear | 3 (2.7) |
| Dialysis | 3 (2.7) |
| Not stated in chart | 15 (10.7) |
| Macula off, n (%) | 68 (60.7) |
| Four-quadrant retinal detachment | 26 (23.2) |

RRD = rhegmatogenous retinal detachment; SD = standard deviation.

**TABLE 2.** Risk Factors of Pediatric Nontraumatic Rhegmatogenous Retinal Detachment in 102 Patients

| Risk Factors | N = 102 |
|---|---|
| Myopia, n (%) | 48 (47.1) |
| Mild to moderate (<6 diopters) | 16 (15.7) |
| High (>6 diopters) | 32 (31.4) |
| Congenital/developmental anomalies, n (%) | 51 (50) |
| Previous intraocular surgery, n (%) | 12 (11.8) |
| Previous cataract surgery | 8 (7.8) |
| Previous RD surgery | 3 (2.9) |
| Previous glaucoma surgery | 1 (1.0) |
| Vitreous proliferation and retinal traction, n (%) | 12 (11.8) |
| Lattice degeneration, n (%) | 33 (32.4) |
| Positive family history (from parent) of RD-associated ocular abnormalities, n (%) | 3 (2.9) |
| Multiple factors, n (%) | 20 (19.6) |
| Myopia with congenital/developmental anomalies | 14 (13.7) |
| Myopia with previous intraocular surgery | 2 (2.0) |
| Congenital/developmental anomalies with previous intraocular surgery | 4 (3.9) |

RD = retinal detachment.

United Kingdom), and fundus fluorescein angiography (FFA; Heidelberg HRA SPECTRALIS/HRA2, Heidelberg Engineering, GmbH, Dossenheim, Germany) were performed. In patients with bilateral RRD, data from only the operated eyes were used.

Clinical data were collected, including age at presentation, gender, refractive errors, axial length, family history, and ocular findings in their family members. The risk factors for pediatric RRD included presence of myopia, congenital/developmental ocular diseases, and previous intraocular surgery. Patients with developmental anomalies of the eye involving the retinal vasculature, retina, choroid, and vitreous and proven congenital syndrome involving the posterior segment of the eye, including FEVR, Stickler syndrome, Marfan syndrome, MGS, X-linked retinoschisis, and ROP were categorized under the congenital/developmental anomaly. Patients with >1 risk factor for RRD were categorized as having multiple factors.

In our study, genetic testing was performed in patients with clinically diagnosed hereditary congenital/developmental diseases from January 1, 2015. Panel-based targeted next-generation sequencing was performed for pediatric retinal diseases[12] between January 1, 2015 and December 31, 2017, and whole-exome sequencing was performed between January 1, 2018 and December 31, 2018. Genetic testing was offered to all patients and their families with hereditary congenital/developmental diseases, but 33% (17/51) declined testing. Peripheral whole-blood DNA samples were extracted, and identified mutations were validated through Sanger sequencing of family members. The Human Gene Mutation Database, Genome Aggregation Database, and Exome Aggregation Consortium were used to identify the reported pathogenic variants. Online algorithms, including MutationTaster, Protein Variation Effect Analyzer, and Polymorphism Phenotyping v2, were used to estimate the pathogenicity of missense mutations.

We analyzed the etiologic factors of RRD in children. In the current study, simple myopia was identified in those myopic patients without any congenital/developmental factors, such as FEVR, Stickler syndrome, and Marfan syndrome. FEVR, Stickler syndrome, Marfan syndrome, or other possible hereditary ocular diseases were diagnosed according to previous studies.[13–16] Patients without any aforementioned predisposing factors for RRD were included in the unknown group. Statistical analyses were performed using SPSS software (v 23, SPSS, Inc., Chicago, Illinois, USA). The $\chi^2$ or Fisher exact test was used for categorical data. Statistical significance was defined as $P < .05$.

**TABLE 3.** Causative Mutations Identified in Patients with Inherited Congenital Anomalies

| Patient ID | Disease | Gene | Nucleotide | Protein Change | Allele Frequency | Polyphen2 | MutationTaster | PROVEAN | Sequencing Method | Source |
|---|---|---|---|---|---|---|---|---|---|---|
| RD5 | FEVR | *LRP5* | 266A>G | Gln89Arg | 0.00921 | Benign | Disease causing | Neutral | NGS | Lin and associates[17] |
| RD16 | FEVR | *LRP5* | 1942G>A | Val648Ile | 0 | Benign | Disease causing | Neutral | NGS | Tang and associates[12] |
| RD124 | FEVR | *LRP5* | 1800C>T | Val600= | 0.0004319 | — | Disease causing | — | NGS | Novel |
| RD175 | FEVR | *TSPAN12* | 352G>T | Glu118Ter | 0 | — | — | — | WES | Novel |
| RD140 | FEVR | *FZD4* | CNV (exon1-2) | — | — | — | — | — | WES | Novel |
| RD166 | FEVR | *JAG1* | 506C>T | Thr169Met | 0 | Possibly damaging | Disease causing | Damaging | WES | Novel |
| RD132 | Stickler | *COL2A1* | 3597+1G>C | — | 0 | — | — | — | NGS | Novel |
| RD169 | Stickler | *COL2A1* | 25_26delinsTA | Thr9Ter | 0 | — | — | — | NGS | Novel |
| RD3 | Stickler | *COL2A1* | 1693C>T | Arg565Cys | 0 | Probably damaging | Disease causing | Neutral | NGS | Wang and associates[18] |
| RD83 | Stickler | *COL2A1* | 2356-1G>A | — | 0 | — | — | — | NGS | Novel |
| RD139 | Stickler | *COL2A1* | 251_252delAG | Glu84ValfsTer8 | 0 | — | — | — | WES | Novel |
| RD183 | Stickler | *COL2A1* | 925-1G>T | — | 0 | — | — | — | WES | Novel |
| RD182 | Stickler | *COL9A2* | 899C>T | Thr300Met | 0 | Probably damaging | Polymorphism | Damaging | WES | Richards and associates[19] |
| RD75 | Choroidal Coloboma | *COL11A1* | 560C>T | Thr187Met | 0.00004957 | Probably damaging | Disease causing | Damaging | NGS | Miyagawa and associates[20] |
| RD109 | VHL | *VHL* | 233A>G | Asn78Ser | 0 | Probably damaging | Disease causing | Damaging | NGS | Chen and associates[21] |
| RD181 | RP | *C2orf71* | 3002G>A | Trp1001Ter | 0.000255 | — | — | — | WES | Audo and associates[22] |
| RD181 | RP | *C2orf71* | 1978_1984del | Ser660ProfsTer83 | 0 | — | — | — | WES | Novel |

FEVR = familial exudative vitreoretinopathy; NGS = next-generation sequencing; RP = retinitis pigmentosa; WES = whole-exome sequencing.

**TABLE 4.** Distribution of Etiologies for Patients with Nontraumatic Rhegmatogenous Retinal Detachment by Age Range

| Etiologic Factors | n (%) | Subgroup Analysis | |
|---|---|---|---|
| | | 1-12 Years of Age | 13-18 Years of Age |
| Total | 102 (100) | 48 (47.1) | 54 (52.9) |
| Congenital/developmental anomalies | 51 (50) | 28 (58.3) | 23 (42.6) |
| Familial exudative vitreoretinopathy | 31 | 16 | 15 |
| Stickler syndrome | 11 | 7 | 4 |
| Marfan syndrome | 2 | 1 | 1 |
| Morning glory syndrome | 2 | 2 | 0 |
| X-linked retinoschisis | 1 | 1 | 0 |
| Retinopathy of prematurity | 1 | 1 | 0 |
| Choroidal coloboma | 1 | 0 | 1 |
| Others | 2 | 0 | 2 |
| Simple myopia | 34 (33.3) | 7 | 27 |
| Previous intraocular surgery | 6 (5.9) | 4 | 2 |
| Unknown | 11 (10.8) | 9 | 2 |

## RESULTS

A TOTAL OF 120 EYES WITH NONTRAUMATIC RRD WERE identified in 102 patients. The average age was 12.2 ± 4.5 years (range 1-18 years). The number of men and women was 76 (74.5%) and 26 (25.5%), respectively (male:female ratio 2.9:1). Bilateral retinal detachment was presented in 18 children, including end-stage RRD without any treatment value in 6 eyes, and reattached retina contributed to previous successful RD surgeries in 2 eyes. Bilateral treatment-needed RRD were noted in 10 children. Therefore, a total of 112 eyes with nontraumatic RRD in 102 patients, which received retinal surgical treatment were included in the study. Table 1 summarizes the demographics of the pediatric patients.

• **RISK FACTORS FOR NONTRAUMATIC RRD IN CHILDREN:** Risk factors for nontraumatic RRD in children included a congenital/developmental disease in 51 (50%) patients, myopia in 48 (47.1%) patients, and previous intraocular surgery in 12 (11.8%) patients. The intraocular surgery included previous congenital cataract removal in 8 patients, previous RD surgery in 3 patients, and previous glaucoma surgery in 1 patient. Positive fundus findings in at least one of the parents were detected in 43 (42.2%) families, including 13 (12.7%) families with myopia, 27 families with posterior and peripheral leakage, and 3 families with previous RD. Multiple risk factors were detected in 20 (19.6%) patients, including myopia with congenital/developmental anomalies (14/102, 13.7%), myopia with intraocular surgery (2/102, 2.0%, the 2 with previous RD surgery), and congenital/developmental anomalies with intraocular surgery (4/102, 3.9%; 3 were with previous cataract surgery and 1 was with previous RD surgery) (Table 2, Supplemental Figure 1).

• **CAUSATIVE MUTATIONS IDENTIFIED IN PATIENTS WITH HEREDITARY CONGENITAL/DEVELOPMENTAL ANOMALIES:** Genetic testing was performed in 34 patients with hereditary congenital/developmental anomalies. Potentially pathogenic mutations were identified in 16 patients. Seventeen causative mutations were identified in 16 patients, including compound heterozygous mutations in *C2orf71* (3002G>A, 1978_1984del) in 1 patient. Among the 17 pathogenic mutations, 10 were novel (Table 3). Schematic pedigrees of the families with novel causative mutations are shown in Supplemental Figure 2.

Among the 31 patients with FEVR in our study, 18 underwent genetic testing, and 6 potentially pathogenic mutations were identified in 6 patients. Seven potentially pathogenic mutations were identified in 7 patients with Stickler syndrome.

• **ANALYSIS OF ETIOLOGIC FACTORS FOR NONTRAUMATIC RRD IN CHILDREN:** At least 1 etiologic factor could be identified in majority of the patients (91, 89.2%), a congenital/developmental disease in 51 (50.0%) patients, simple myopia in 34 (33.3%) patients, and a single previous intraocular surgery in 6 (6/102, 5.9%) patients ($P < .001$). Congenital/developmental anomalies included FEVR (31/51, 60.8%), Stickler syndrome (11/51, 21.6%), Marfan syndrome (2/51, 3.9%), MGS (2/51, 3.9%), X-linked retinoschisis (1/51, 2.0%), ROP (1/51, 2.0%), choroidal coloboma (1/51, 2.0%), Von Hippel–Lindau disease (1/51, 2.0%), and retinitis pigmentosa (1/51, 2.0%). More than half (31/51, 60.8%) of patients in the congenital/developmental anomalies group had FEVR (Table 4).

Subgroup analysis according to the patients' age at RRD onset revealed that the most common etiology of RRD in patients <12 years of age was congenital/developmental anomalies (28/48, 58.3%); however, simple myopia was the major etiologic factor in patients >12 years of age

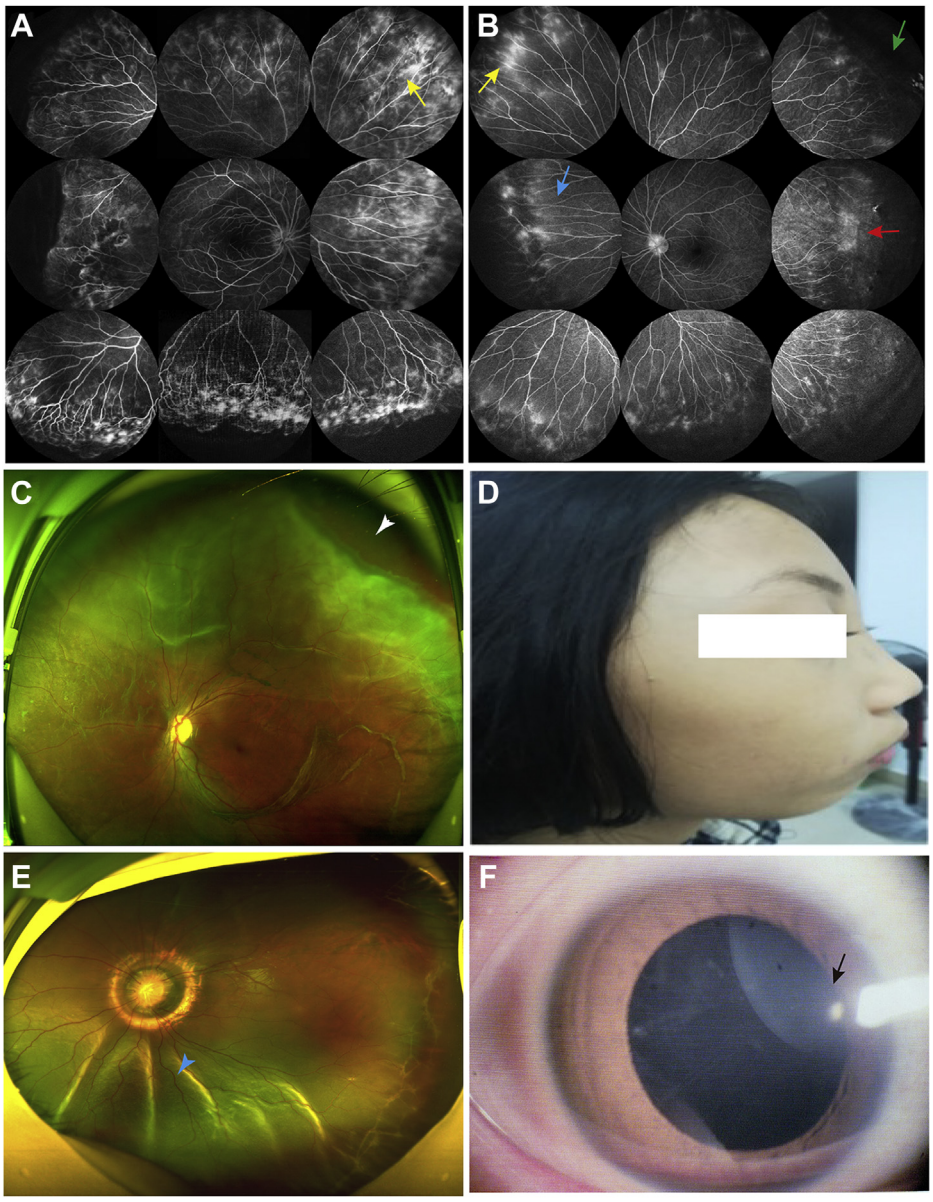


**FIGURE. Representative clinical findings in patients with congenital/developmental anomalies. (A and B) Images of representative fundus fluorescein angiography of a patient with familial exudative vitreoretinopathy–associated rhegmatogenous retinal detachment. The novel *TSPAN12* mutation of nucleotide 352G > T was identified in a 13-year-old boy who has retinal detachment in the inferior temporal quadrant of the right eye. Fundus fluorescein angiography shows typical familial exudative vitreoretinopathy manifestations, including straightened vessel branches in the peripheral retina (blue arrow, B), an avascular zone (green arrow, B), V-shaped degeneration (red arrow, B), and peripheral vascular leakage (yellow arrow, A and B). (C) Representative clinical features of Stickler syndrome in a 12-year-old boy (*COL2A1*, 925-1G > T) with retinal dialysis in the superior temporal quadrant of the left eye (white arrowhead, C). (D) Classic nasal bone and mandibular malformations in a 7-year-old girl with Stickler syndrome (*COL2A1*, 2356-1G > A). (E) Scanning laser ophthalmoscopy of a 3-year-old boy with morning glory syndrome in the left eye. Retinal detachment in the inferior nasal quadrant of the left eye (blue arrowhead, E) is observed. F. Rhegmatogenous retinal detachment in the right eye of a 17-year-old girl with Marfan syndrome. Subluxations are observed in lens of the right eye (black arrow).**

(27/54, 50%). There was a statistically significant difference in etiology between patients <12 years of age compared with patients >12 years of age ($P < .001$; Table 4).

• **SUBGROUP ANALYSIS IN PATIENTS WITH CONGENITAL/DEVELOPMENTAL ANOMALIES:** The most common etiologies were FEVR (31/51, 60.8%) and Stickler syndrome (11/51, 21.6%). In the FEVR group, round retinal hole(s)

(single or multiple) were noted in 74.2% (23/31) of the eyes. Retinal holes located in the temporal periphery were detected in 71.0% (22/31) of the affected eyes. Figure shows the most common manifestations in patients with FEVR, including posterior and peripheral leakage, avascular zone, V-shaped degeneration, and straightened vessel branches in the peripheral retina. In the Stickler syndrome group, retinal dialysis was observed in 3 of 11 patients (2 of them with bilateral retinal dialysis). Systemic findings in the Stickler syndrome group were flat face, and abnormal nasal bone and mandibular development (Figure). Figure also shows the epresentative clinical characteristics of MGS and Marfan syndrome.

## DISCUSSION

RRD HAS AN ANNUAL INCIDENCE OF APPROXIMATELY 1.2 cases per 10,000 people.[6,11,23] Because of the low incidence in this age group, only a few series of RRD in children have been reported.[5,10,11,24] In this study including 102 pediatric patients with RRD, at ≥1 contributing etiology could be identified in 89.2% (91/102) of patients. In previous studies, myopia, which has an incidence of 34% in the United States[23] and 9.4% in Iran,[7] has been commonly reported as an independent factor for pediatric RRD. Myopia is more prevalent in Eastern Asian patients,[25,26] which was reported as the major etiologic factor for RRD in children, and studies from Chang and associates[5] and Chen and associates[11] reported higher incidence rates of myopia in pediatric RRD, ranging from 23% to 37.5%. In our series, the incidence of myopia as an etiologic factor for nontraumatic pediatric RRD was 33.3% (34/102), similar to previous studies. However, myopia is also a feature of many congenital/developmental anomalies as Stickler syndrome or Marfan syndrome. If only simple myopia (ie, no associated predisposing factor) is considered, then myopia is no longer among the leading causes of pediatric RRD. We suggest that myopia should be considered differently in the clinical diagnosis, follow-up, therapy, and outcome with Stickler syndrome or other congenital diseases.

In our study, we examined not only the phenotype of the fellow eye in children with RRD but also performed screening of the family members, which could aid the clinical diagnosis. With these, some patients with both myopia and other ocular abnormalities were regrouped into the congenital/developmental disorders. As a result, in the present study, congenital/developmental anomalies were the most common etiologic factor for nontraumatic RRD in children. In our study, the frequency of congenital/developmental anomalies was 50% (51/102). Previous studies from Eastern Asia reported incidence rates ranging from 16.6%-39.5%.[8,10] Our data showed that congenital/developmental anomalies play a primary role in pediatric RRD.

One of strengths of our study is that the etiology of pediatric RRD was analyzed based on genetic testing, which could help distinguish patients with myopia combined with congenital/developmental diseases. In Western countries, ROP is the most common congenital/developmental anomaly, while in the Middle East and western countries, Stickler syndrome is the most common.[7,24] In contrast, FEVR accounted for most of the congenital/developmental anomalies in Japan.[4,27] In the present study, 60.8% (31/51) of the patients in the congenital/developmental anomalies group had FEVR. Among the 31 FEVR patients, 27 of them were boys. Therefore, we suggest that the male predominance in nontraumatic pediatric patients with RRD was mainly associated with the male predominance in FEVR patients. Furthermore, pediatric patients with FEVR-associated RRD reportedly had a similar genetic make-up as that of classical FEVR patients,[28] similar to our previous studies.[12,29] FEVR is frequently asymptomatic and presents with diverse signs, and therefore it is often undetected and can resemble other ocular conditions.[14,30,31] Genetic testing is important. Conducting genetic testing in children with RRD can help diagnose patients with congenital/developmental diseases, and genetic counseling is necessary for family planning services.

There were several limitations to our study. First, because nontraumatic pediatric RRD is rare, the number of patients was limited. Second, because our hospital is a tertiary referral institute for pediatric retinal diseases, referral biases might be present. Third, not all the patients underwent genetic testing, as it was not available between January 1, 2014 and January 1, 2015. Fourth, whole-genome sequencing may now be better equipped to evaluate FEVR genes for pathogenic mutations, but it was not available in our laboratory at the time of our study.

In summary, we analyzed the etiology of pediatric RRD based on genetic testing and found that congenital/developmental anomalies are the most common reasons. In our study, FEVR was more common as an etiology of pediatric RRD than reported earlier.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**CHONGLIN CHEN:** CONCEPTUALIZATION, INVESTIGATION, Formal analysis, Writing - original draft. **Sijian Huang:** Resources, Data curation. **Limei Sun:** Investigation. **Songshan Li:** Resources, Investigation. **Li Huang:** Formal analysis. **Zhirong Wang:** Resources. **Xiaoling Luo:** Data curation. **Xiaoyan Ding:** Conceptualization, Writing - review & editing, Supervision.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST.
Funding/Support: Supported by grants from the Fundamental Research Funds of State Key Laboratory of Ophthalmology, research funds of Sun Yat-sen University (grant number 15ykjxc22d; Guangzhou, Guangdong, China), and the Science and Technology Program Guangzhou, China (grant number 201803010031; Guangzhou, Guangdong, China). The sponsors and funding organizations had no role in the design or conduct of this research.
Financial Disclosures: The authors report no financial disclosures.

## REFERENCES

1. Soliman MM, Macky TA. Pediatric rhegmatogenous retinal detachment. *Int Ophthalmol Clin* 2011;51(1):147–171.
2. Al-Zaaidi S, Al-Rashaed S, Al-Harthi E, et al. Rhegmatogenous retinal detachment in children 16 years of age or younger. *Clin Ophthalmol* 2013;7:1001–1014.
3. Wenick AS, Baranano DE. Evaluation and management of pediatric rhegmatogenous retinal detachment. *Saudi J Ophthalmol* 2012;26(3):255–263.
4. Akabane N, Yamamoto S, Tsukahara I, et al. Surgical outcomes in juvenile retinal detachment. *Jpn J Ophthalmol* 2001;45(4):409–411.
5. Chang PY, Yang CM, Yang CH, et al. Clinical characteristics and surgical outcomes of pediatric rhegmatogenous retinal detachment in Taiwan. *Am J Ophthalmol* 2005;139(6):1067–1072.
6. Gonzales CR, Singh S, Yu F, et al. Pediatric rhegmatogenous retinal detachment: clinical features and surgical outcomes. *Retina* 2008;28(6):847–852.
7. Soheilian M, Ramezani A, Malihi M, et al. Clinical features and surgical outcomes of pediatric rhegmatogenous retinal detachment. *Retina* 2009;29(4):545–551.
8. Huang YC, Chu YC, Wang NK, et al. Impact of etiology on the outcome of pediatric rhegmatogenous retinal detachment. *Retina* 2019;39(1):118–126.
9. Rumelt S, Sarrazin L, Averbukh E, et al. Paediatric vs adult retinal detachment. *Eye (Lond)* 2007;21(12):1473–1478.
10. Wang NK, Tsai CH, Chen YP, et al. Pediatric rhegmatogenous retinal detachment in East Asians. *Ophthalmology* 2005;112(11):1890–1895.
11. Chen SN, Jiunn-Feng H, Te-Cheng Y. Pediatric rhegmatogenous retinal detachment in Taiwan. *Retina* 2006;26(4):410–414.
12. Tang M, Sun L, Hu A, et al. Mutation spectrum of the LRP5, NDP, and TSPAN12 genes in chinese patients with familial exudative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 2017;58(13):5949.
13. Yuan M, Ding X, Yang Y, et al. Clinical features of affected and undetached fellow eyes in patients with FEVR-associated rhegmatogenous retinal detachment. *Retina* 2017;37(3):585–591.
14. Yuan M, Yang Y, Yu S, et al. Posterior pole retinal abnormalities in mild asymptomatic FEVR. *Invest Ophthalmol Vis Sci* 2014;56(1):458–463.
15. Fincham GS, Pasea L, Carroll C, et al. Prevention of retinal detachment in Stickler syndrome: the Cambridge prophylactic cryotherapy protocol. *Ophthalmology* 2014;121(8):1588–1597.
16. Lee SY, Ang CL. Results of retinal detachment surgery in Marfan syndrome in asians. *Retina* 2003;23(1):24–29.
17. Lin Y, Gao H, Chen C, et al. Clinical and next-generation sequencing findings in a Chinese family exhibiting severe familial exudative vitreoretinopathy. *Int J Mol Med* 2018;41(2):773–782.
18. Wang X, Jia X, Xiao X, et al. Mutation survey and genotype-phenotype analysis of COL2A1 and COL11A1 genes in 16 Chinese patients with Stickler syndrome. *Mol Vis* 2016;22:697–704.
19. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17(5):405–424.
20. Miyagawa M, Naito T, Nishio SY, et al. Targeted exon sequencing successfully discovers rare causative genes and clarifies the molecular epidemiology of Japanese deafness patients. *PLoS One* 2013;8(8):e71381.
21. Chen F, Kishida T, Yao M, et al. Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. *Hum Mutat* 1995;5(1):66–75.
22. Audo I, Lancelot ME, Mohand-Said S, et al. Novel C2orf71 mutations account for approximately 1% of cases in a large French arRP cohort. *Hum Mutat* 2011;32(4):E2091–E2103.
23. Fivgas GD, Capone A Jr. Pediatric rhegmatogenous retinal detachment. *Retina* 2001;21(2):101–106.
24. Smith JM, Ward LT, Townsend JH, et al. Rhegmatogenous retinal detachment in children: clinical factors predictive of successful surgical repair. *Ophthalmology* 2019;126(9):1263–1270.
25. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet* 2012;379(9827):1739–1748.
26. He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA* 2015;314(11):1142–1148.
27. Oono Y, Uehara K, Haruta M, Yamakawa R. Characteristics and surgical outcomes of pediatric rhegmatogenous retinal detachment. *Clin Ophthalmol* 2012;6:939–943.
28. Salvo J, Lyubasyuk V, Xu M, et al. Next-generation sequencing and novel variant determination in a cohort of 92 familial exudative vitreoretinopathy patients. *Invest Ophthalmol Vis Sci* 2015;56(3):1937–1946.
29. Chen C, Wang Z, Sun L, et al. Next-generation sequencing in the familial exudative vitreoretinopathy-associated rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci* 2019;60(7):2659.
30. Yuan M, Yang Y, Yan H, et al. Increased posterior retinal vessels in mild asymptomatic familial exudative vitreoretinopathy eyes. *Retina* 2016;36(6):1209–1215.
31. Lyu J, Zhang Q, Wang SY, et al. Ultra-wide-field scanning laser ophthalmoscopy assists in the clinical detection and evaluation of asymptomatic early-stage familial exudative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol* 2017;255(1):39–47.