Familial Exudative Vitreoretinopathy and Systemic Abnormalities in Patients With *CTNNB1* Mutations

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Purpose. Familial exudative vitreoretinopathy (FEVR) is an inherited vitreoretinopathy. This study aimed to analyze the ocular phenotypes and systemic features of patients with *CTNNB1* mutations.

Methods. Whole exome sequencing was performed in the probands, and Sanger sequencing was used to verify the mutations and perform segregation analysis in the available family members. A luciferase assay was used to assess the effect of the mutant β-catenin on transcription. Comprehensive ocular examinations were performed on the probands and family members. Systemic features were evaluated and followed up.

Results. A total of 763 FEVR families were enrolled. Seven different *CTNNB1* mutations, including 5 novels and 2 known mutations, were detected in 8 families, accounting for 1.05% of all FEVR families. Compared to wild-type *CTNNB1*, the *CTNNB1* mutants failed to induce luciferase reporter activity in SuperTopFlash (STF) cells. Among the 16 eyes of the 8 probands, 2 (12.5%) eyes were classified as stage 2 FEVR, 8 (50.0%) as stage 4, and 6 (37.5%) as stage 5. All the patients had varying degrees of systemic abnormalities and presented with motor, speech, and developmental delays over time. Among the eight families with *CTNNB1* mutations, seven were de novo mutations, and one proband inherited the mutation from his asymptomatic mother.

Conclusions. This study provides detailed descriptions of the ocular phenotypes of patients with *CTNNB1* mutations that presented as severe FEVR, and accompanied with other systemic abnormalities. Five novel mutations identified in this study, expanded the mutation spectrum of *CTNNB1*-associated FEVR.

Keywords: familial exudative vitreoretinopathy, *CTNNB1*, systemic abnormalities

Familial exudative vitreoretinopathy (FEVR) was first described by Criswick and Schepens in 1969.[1] It is an inherited vitreoretinopathy disease characterized by abnormal retinal vascular development. The main clinical manifestations of FEVR are supernumerary branching of retinal vessels, neovascularization, vitreoretinal traction, vitreous hemorrhage, retinal fold, and retinal detachment.[2] In a previous study, we found that congenital/developmental diseases were the most common etiologies of pediatric nontraumatic rhegmatogenous retinal detachment in China, and that FEVR accounted for most of the congenital/developmental anomalies.[3] To date, the following 6 genes have been found to be associated with the development of FEVR: low-density lipoprotein receptor-related protein 5 (*LRP5*; MIM: 603506),[4] frizzled class receptor 4 (*FZD4*; MIM: 604579),[5] tetraspanin 12 (*TSPAN12*; MIM: 613138),[6] norrin cystine knot growth factor (*NDP*; MIM: 300658),[7] zinc finger protein 408 (*ZNF408*; MIM: 616454),[8] and kinesin family member 11 (*KIF11*; MIM: 148760).[9] In addition, new candidate genes are constantly being reported, such as catenin α-1 (*CTNNA1*; MIM: 116805),[10] catenin β-1 (*CTNNB1*; MIM: 116806),[11] jagged 1 (*JAG1*; MIM: 601920),[12] discs large MAGUK scaffold protein 1 *(DLG1;* MIM: 601014),[13] low-density lipoprotein receptor-related protein 6 (*LRP6*; MIM: 603507),[14] transforming growth factor-beta receptor 2 (*TGFBR2*; MIM: 190182),[15] and catenin delta 1 (*CTNND1*, MIM: 601045).[16] However, these studies are mostly case reports.

Seven of the genes associated with FEVR development (*LRP5*, *FZD4*, *TSPAN12*, *NDP*, *CTNNA1*, *CTNND1*, and *CTNNB1*) are related to the Norrin/Wnt signaling pathway, which is involved in the regulation of various vascular diseases as well as cell proliferation, differentiation, migration, polarization, and apoptosis.[17,18] This study focused on *CTNNB1*, which has 16 exons, spans 23.2 kb,[19,20] and is mapped to the 3p21 chromosome region. It encodes β-catenin, which plays an important role in the Norrin/Wnt signaling pathway.[21] β-catenin was first described as an adherens junction protein. Subsequently, it was found that when the Wnt/β-catenin pathway is activated by Wnt ligands, β-catenin can translocate to the nucleus and activate β-catenin/TCF-4-dependent transcription.[22] β-catenin comprises three regions: an unstructured N-terminal domain, a conserved region consisting of 12 armadillo repeats, and an unstructured C-terminal domain (CTD).[19]

Although some studies have described the FEVR phenotype in patients with *CTNNB1* mutations, they did not fully evaluate the systemic conditions of these patients nor conduct follow-ups.[11,23–25] Therefore, this study aimed to

comprehensively analyze and report on the ocular manifestations, systemic conditions, and follow-up data of eight families with *CTNNB1* mutations.

Methods

This study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University (2014MEKY048) and conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all adult patients and the parents or guardians of the children.

A total of 763 FEVR probands were recruited from patients and their family members referred to our hospital from January 2014 to October 2022. The clinical diagnostic criteria of FEVR were based on previous reports,[26,27] and staging of FEVR was performed according to Trese et al.[26] Any potential participants with a gestational age of fewer than 32 weeks, a birth weight of less than 2000 g, or a history of oxygen inhalation were excluded. All probands and their family members underwent complete ophthalmic examinations, as described in our previous study.[28] Patients who could not cooperate with the examination were examined while under sedation. The anterior segment was examined using a handheld slit lamp (Keeler, Malvern, PA, USA), and the fundus was examined via RetCam wide-field fundoscopy (Clarity Medical Systems, Pleasanton, CA, USA).

DNA samples were extracted from peripheral whole blood or saliva samples. Proband samples were subjected to whole exome sequencing (WES), and their family members' samples were then subjected to Sanger sequencing for validation and segregation analysis in the families. The WES analysis was performed as previously described.[29] The transcript ID of *CTNNB1* (NM_001904.4) was used for reference. The dbNSFP is used for functional prediction and annotation of all potential non-synonymous single-nucleotide variants.[30] The splice site was predicted by in silico prediction based on the methods of adaptive boosting (ada_score) and random forests (rf_score).[31]

SuperTopFlash (STF) cells were transfected with 200 ng DNA mix and 1.5 mL Lipofectamine TM 2000 Transfection Reagent (Invitrogen, Carlsbad, CA, USA) in 24-well plates. The STF cells were transiently transfected with wild-type (WT) or mutant (c.1723G>A, c.888_889dup, c.1707del, and c.2138-4_2140del) expression constructs. Luciferase reporter assays were carried out as previously reported.[32] Forty-eight hours after transfection, the transfected cells were washed with phosphate buffered saline (PBS) three times, and luciferase reporter activity was assayed using a dual-luciferase assay kit following the manufacturer's instructions (Promega, Madison, WI, USA). Each assay was performed in triplicate. A representative result from three independent experiments is shown. Each test was performed in triplicate.

Results

Mutations

In this study, among 763 FEVR probands and their family numbers, 7 heterozygous *CTNNB1* mutations were detected in 8 probands, which accounted for 1.05% of all the FEVR probands. Two of the probands had the same mutation (Table 1).[33,34] Five of the 7 *CTNNB1* mutations were found to be novel, namely, c.888_889dup (p.Thr297Ilefs*9), c.1707del (p.Ile569Metfs*12), c.2138-4_2140del, c.1543C>T (p.Arg515*), and c.2137+5G>T. Two of the 7 *CTNNB1* mutations were already known: c.1723G>A (p.Gly575Arg) and c.1981C>T (p.Arg661*). Seven of the eight mutations were de novo mutations (Fig. 1).

To analyze the effect of the mutations on the Wnt pathway, a luciferase assay was performed with the c.888_889dup, c.1707del, c.1723G>A, and c.2138-4_2140del mutants. Compared to the WT *CTNNB1*, all four of the tested *CTNNB1* mutants failed to induce luciferase reporter activity in STF cells ($P < 0.0001$, Fig. 2).

The Ocular Manifestation in the Patients

The eight probands included four girls and four boys. In each case, onset occurred within the first few months after birth (the probands were 2 to 6 months old at the time of the initial visit, median of 3 months old). However, the age of onset was not accurate and difficult to define. Instead, the time at which each proband was found to not chase light was observed. An extremely shallow anterior chamber (anterior chamber nearly disappearing) was noted in five eyes (31.25%), a shallow anterior chamber was noted in five eyes (31.25%), an irregular pupil and synechiae were noted in one eye (6.25%), and five eyes were unremarkable. A cloudy cornea was detected in two eyes. All the patients had stage 4 or stage 5 FEVR in at least one eye. Retinal detachment was detected in eight eyes (50.0%) of five patients, and retinal folds were detected in six eyes (37.5%) of four patients (Table 2, Fig. 3). Two (DX590 and

Table 1. Identified Variants in *CTNNB1* Gene 0

ID	cDNA Change	Protein Change	Location (hg19)	Exon	SIFT	Polyphen-2	REVEL	gnomAD	Inheritance	Reference
DX304	c.888_889dup	p.Thr297Ilefs*9	chr3:41267303	6	_	_	_	0	de novo	Novel
DX516	c.1707del	p.Ile569Metfs*12	chr3:41277237	11	_	_	_	0	de novo	Novel
DX590	c.1723G>A	p.Gly575Arg	chr3:41277254	11	Damaging	Probably damaging	0.716	0	de novo	33,37
DX739	c.2138-4_2140del	_	chr3:41280620	15	_	_	_	0	de novo	Novel
DX774	c.1543C>T	p.Arg515*	chr3:41275648	10	_	_	_	_	de novo	Novel
DX787	c.1981C>T	p.Arg661*	chr3:41278105	13	_	_	_	0	de novo	34
DX797	c.1723G>A	p.Gly575Arg	chr3:41277254	11	Damaging	Probably damaging	0.716	0	de novo	33,37
DX839	c.2137+5G>T	_	chr3:41279572	intron 14	_	_	_	0	autosomal dominant	Novel

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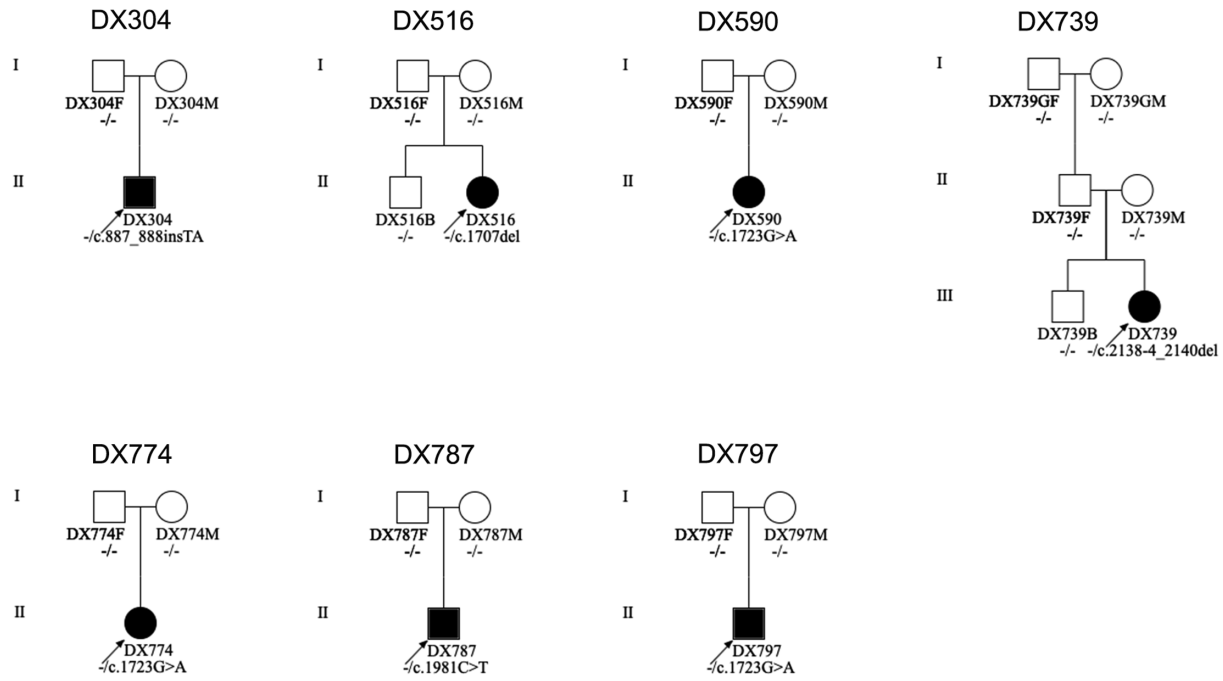

Figure 1. The pedigrees of the seven families with the identified de novo *CTNNB1* mutations.

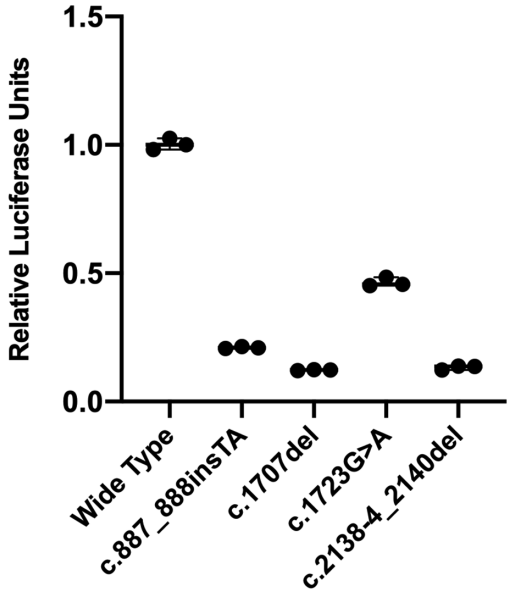

Figure 2. Results of the luciferase assays conducted using mutated *CTNNB1*. SuperTopFlash (STF) cells were transiently transfected with wild-type (WT) or mutant β-catenin (c.1723G>A, c.888_889dup, c.1707del, and c.2138-4_2140del) expression constructs along with an STF luciferase plasmid, and luciferase activity was measured 48 hours later. The dots represent the luciferase ratios for the different constructs. The results are from three independent experiments performed in triplicate. $P < 0.0001$ between the WT and all the mutations.

DX774) of the 8 probands had asymmetric conditions, with a bilateral FEVR stage difference greater than 1 (Fig. 4). The rest of the probands had symmetric conditions, with a bilateral FEVR stage difference less than or equal to 1. The 2 probands with the same mutation (c.1723G>A) had varying phenotypes: one presented with stage 2 and stage 4 FEVR, and the other presented with stage 4 and stage 5 FEVR.

Systemic Findings in the Patients

All 8 probands had systemic symptoms of varying severity at the initial visit to the ophthalmic center, which occurred when they were 2 to 15 months old. The self-reported and medically recorded systemic abnormalities were motor delays, developmental delays, microcephaly, and occult spina bifida (see Table 3). As the probands got older, more systemic problems were detected. The age at the last follow-up varied from 7 months to 36 months. Only one of the 8 probands could walk independently and speak fluently at the age of 36 months. The remaining seven patients could not walk or talk (see Table 3). The phenotypic severity could not be compared across the probands because of the young age of some of the probands and the difference in age among the probands at the last follow-up.

The Family With the Autosomal Dominant Inheritance Trait

In this study, seven of the patients had de novo *CTNNB1* mutations. However, one proband (DX839) and his elder sister (DX839S1) inherited the c.2137+5G>T mutation from their mother (DX839M). The mutation was predicted to be splice-altering with the ada_score of 0.999 and rf_score of 0.974. DX839 had vitreous hemorrhage and retinal detachment in the right eye, and retinal fold in the left eye. His mother and elder sister were asymptomatic with bilateral best corrected visual acuity of 20/20; however, supernumerary branches were detected in scanning laser ophthalmoscope (SLO) and

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Table 2. Ocular Features of the Probands With *CTNNB1* Mutations

ID	Variants	Gender	Age Onset (Mo)	Age at Exam (Mo)	First Symptom	Anterior Segment OD[§]	Anterior segment OS[‖]	Fundus OD	Fundus OS	FEVR Stage (OD/OS)
DX304	c.887_888insTA	M	2	5	Not chasing	ESAC[*]	ESAC	RD[‡]	RD	5/5
DX516	c.1707del	F	6	7	Not chasing	Unremarkable	Unremarkable	Retinal fold	Retinal fold	4/4
DX590	c.1723G>A	F	5	15	Not chasing	Unremarkable	Unremarkable	Ridge	Retinal fold	2/4
DX739	c.2138-4_2140del	F	3	5	Not chasing	ESAC, cloudy cornea	ESAC, cloudy cornea	RD	RD	5/5
DX774	c.1543C>T	F	6	12	Not chasing	Unremarkable	Irregular pupil, synechia	Ridge	RD	2/5
DX787	c.1981C>T	M	2	2	Not chasing	SAC[†]	SAC	Retinal fold	Retinal fold	4/4
DX797	c.1723G>A	M	2	12	Not chasing	SAC	ESAC	RD	RD	4/5
DX839	c.2137+5G>T	M	3	15	Not chasing	SAC	SAC	RD	Retinal fold	4/4

[*] Extremely shallow anterior chamber (ESAC).
[†] Shallow anterior chamber (SAC).
[‡] Retinal detachment (RD).
[§] Right eye.
[‖] Left eye.

fundus fluorescein angiography (FFA). In DX839S1, FFA also revealed peripheral straightening of retinal vessels (Fig. 5).

Discussion

Eight probands with *CTNNB1* mutations and their families were recruited for this study, accounting for 1.05% of all FEVR families. All the probands had severe FEVR and systemic abnormalities. During follow-up, the systemic abnormalities were determined to be developmental, motor, and speech delays. Among the probands, seven had de novo mutations, and one inherited the mutation from his asymptomatic mother. Seven different *CTNNB1* mutations were detected, including five novel mutations.

The Known *CTNNB1* Mutations and Associated Phenotypes

All 8 patients presented with severe ocular manifestations and stage 4 and stage 5 FEVR, except 2 eyes (2/16 eyes) that had stage 2 FEVR, which was coincident with the findings of a previous study.[35] FEVR caused by *CTNNB1* mutation was first described by Dixon,[23] and in that study, the patients presented with stage 4 FEVR in one

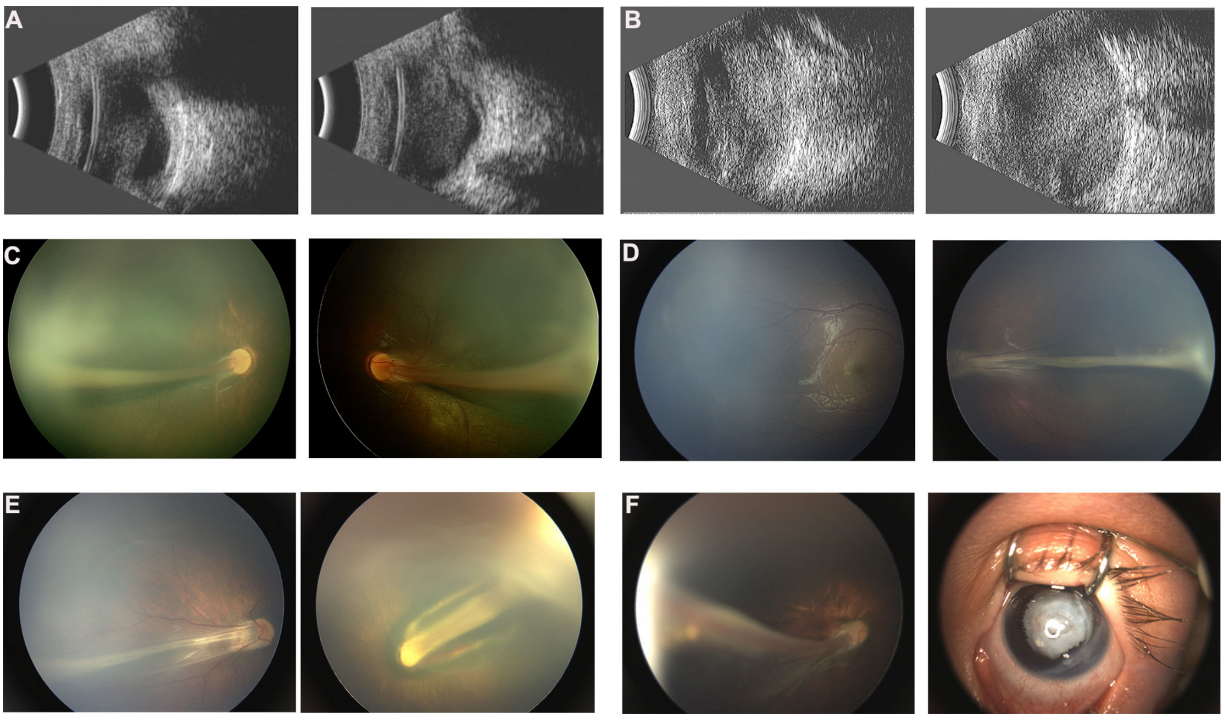

Figure 3. The fundus images of the families with the de novo *CTNNB1* mutations. The B scans revealed total retinal detachment in both eyes of DX304 (**A**) and DX739 (**B**). Retcam revealed bilateral retinal folds in the eyes of DX516 (**C**), stage 2 FEVR of the right eye and retinal fold of the left eye of DX590 (**D**), and bilateral retinal folds of DX787 (**E**). (**F**) Retcam revealed retinal fold and tractional retinal detachment of the right eye and total retinal detachment of the left eye of DX797.

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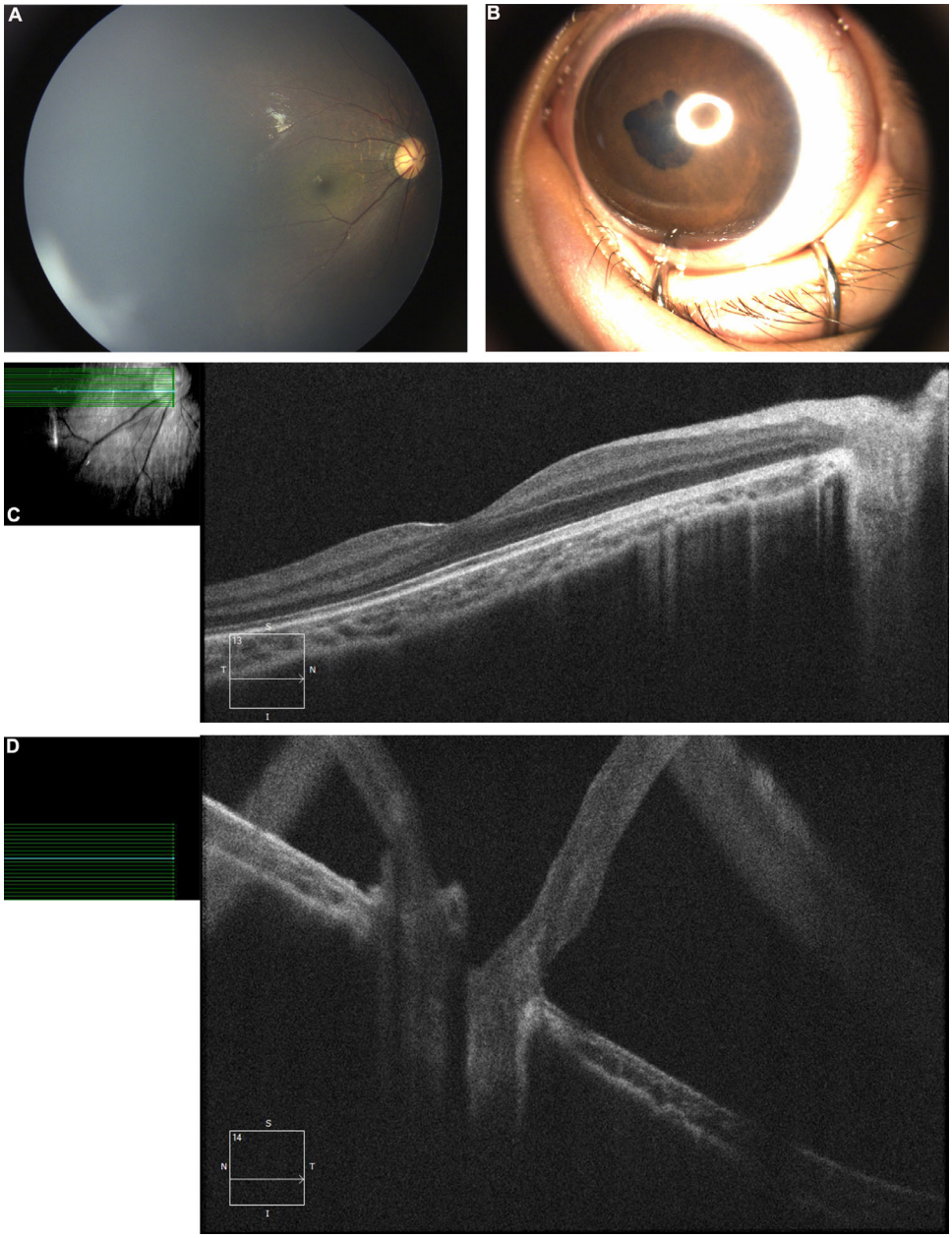

Figure 4. Asymmetry in patient DX774. (**A**) Retcam image showing stage 2 FEVR in the right eye. (**B**) The image shows an irregular pupil and synechiae in the left eye. (**C**) Optical coherence tomography (OCT) shows normal retinal structure in the macular area of the right eye. (**D**) OCT shows retinal detachment of the left eye.

Table 3. Systemic Abnormalities of the Probands With *CTNNB1* Mutations

ID	Age Onset (Mo)	Age at Exam (Mo)	Systemic Abnormalities	Age at Follow Up (Mo)	Systemic Abnormalities
DX304	2	5	Microcephaly, developmental delays, axial hypotonia	NA	NA
DX516	6	7	Developmental delay	27	Can't walk independently, can't talk
DX590	5	15	Microcephaly	36	Walking independently, can talk
DX739	3	5	Microcephaly, developmental delay	15	Can't sit independently, can't talk
DX774	6	12	Microcephaly, occult spina bifida, axial hypotonia	35	Sit independently, can't walk, can't talk
DX787	2	2	Motor delays	7	Can't sit independently
DX797	2	12	Microcephaly, developmental delay	18	Can't sit independently, can't talk
DX839	3	15	Motor delays	19	Sitting at 8-mo, walking independently for 3-4 steps at 18 mo, can't talk

NA, not applicable.

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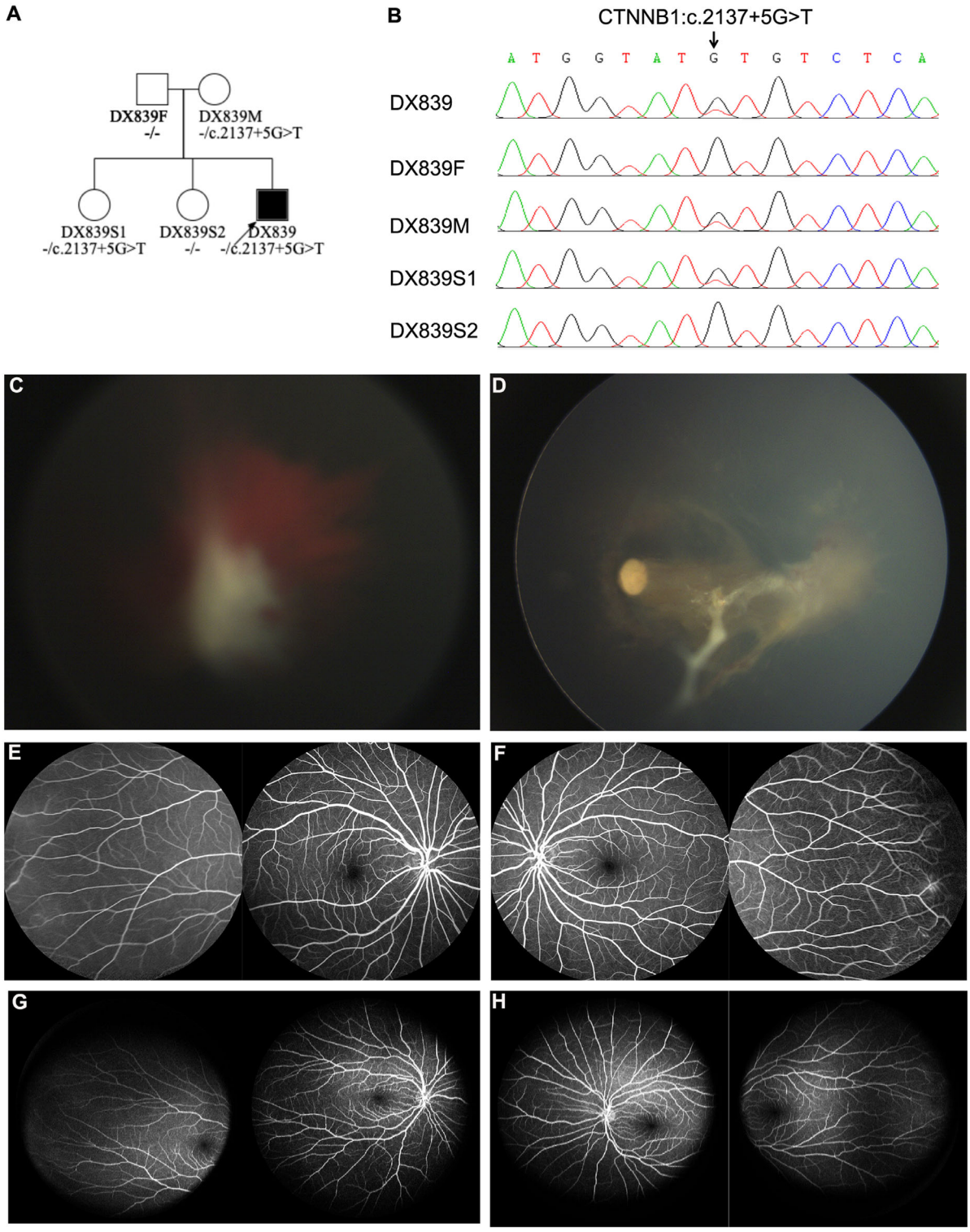

Figure 5. The fundus changes in the family members of DX839. (**A**) Pedigree of the family of DX839. (**B**) Segregation analysis of the family of DX839 via Sanger sequencing. (**C**) Fundus image showing vitreous hemorrhage and retinal detachment of the right eye of DX839. (**D**) Fundus image showing retinal fold of the left eye of DX839. (**E**, **F**) Fundus fluorescein angiography (FFA) of DX839M showing supernumerary vascular branching. (**G**, **H**) FFA of DX839S1 showing supernumerary vascular branching and peripheral straightening of retinal vessels.

eye and stage 1 FEVR in the contralateral eye. In our study, all eight probands were identified after they were observed to not be chasing light in the first few months after birth. This symptom was also noted in patients with *NDP* mutations, which also cause severe FEVR, and in patients with Norrie disease at the very beginning of life.[7] *CTNNB1*-associated FEVR accounts for only a small proportion of FEVR cases, and case reports of *CTNNB1*-associated

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FEVR proved its early onset and severity.[11,25,36] Two known mutations c.1723G>A (p.Gly575Arg) and c.1981C>T (p.Arg661*) have been detected in this study, in which, c.1723G>A was reported in 2 patients, one with epilepsy and the other one with retinal detachment bilaterally secondary to FEVR and gross and fine motor delays, and c.1981C>T was reported in a patient with deciphering developmental disorders.[33,34,37]

The De Novo and Autosomal Dominant Inheritance Trait

In this study, we analyzed the data from a family with an autosomal dominant inheritance trait. The proband had severe FEVR, whereas his mother and elder sister were asymptomatic with mild retinal vascular abnormalities. Most of the patients included in previous studies were found to have de novo *CTNNB1* mutations,[38] and families with autosomal dominant traits have rarely been reported in FEVR studies. Unlike probands with de novo *CTNNB1* mutations with severe FEVR, phenotype severity has been found to vary in family members with the same mutations,[24] and some have been reported to be asymptomatic, like the patients in our study. Family members with different phenotype severity is a common occurrence in *CTNNB1*-associated FEVR,[24] and has also been observed in FEVR associated with other genes, such as *FZD4*.[28] The reason for this is unknown, and thus further study is needed to determine the mechanism.

The Genotype–Phenotype Correlation

Genotype–phenotype correlations were not analyzed in this study. However, it was noted that all the patients had severe FEVR and other systemic abnormalities, and that the patients' mutations were located in exons 6, 10, 11, 13, and 15, and intron 14 of *CTNNB1*. Previous studies have reported the FEVR phenotype to be associated with mutations located in exons 3, 4, 6, 7, 8, 9, 10, 11, 13, and 14.[11,24,25,36] These findings indicate that there is no mutation hotspot in *CTNNB1* specifically associated with the FEVR phenotype. Furthermore, a study demonstrated that patients with nonsense and missense mutations in exons 14 and 15 had only ocular abnormalities,[39] whereas those with frameshift mutations had severe disease phenotypes. Panagiotou indicated that non-syndromic FEVR is a milder phenotype caused by mutations in the CTD of β-catenin.[24] However, two patients with deletion and splicing mutations in the CTD region had FEVR and developmental delays in this study. It should be noted that it was difficult to determine whether the patients had non-syndromic FEVR or *CTNNB1*-associated neurodevelopmental disorders because of their young age. Panagiotou also reported that one patient was diagnosed with non-syndromic FEVR at 4 weeks old; however, at the age of 3 years, the patient displayed many clinical features associated with syndromic intellectual disability.[24] The patients recruited in this study were a few months old, and eye abnormalities were their main symptoms. During follow-up, developmental, speech, and motor delays were found, and severe FEVR was the main symptom observed among the young patients. In this study, the luciferase reporter activity revealed the relative luciferase activity was decreased in mutations, however, which decreased less in the missense mutations than the truncation mutations, which coincided with the previous studies.[24,25] However, no specific correlation between the mutation type and the disease severity has been built.

Conclusion

This study analyzed and described in detail the ocular phenotype of patients with *CTNNB1* mutations who presented with severe FEVR. The FEVR was the main ocular symptom, which was accompanied with other systemic disabilities. Thus, lifelong monitoring of these patients is needed. Five novel mutations were also identified in this study, which expanded the mutation spectrum of *CTNNB1*.

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References

1. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. *Am J Ophthalmol*. 1969;68(4):578–594.
2. Tian T, Chen C, Zhang X, Zhang Q, Zhao P. Clinical and genetic features of familial exudative vitreoretinopathy with only-unilateral abnormalities in a Chinese cohort. *JAMA Ophthalmol*. 2019;137(9):1054–1058.
3. Chen C, Huang S, Sun L, et al. Analysis of etiologic factors in pediatric rhegmatogenous retinal detachment with genetic testing. *Am J Ophthalmol*. 2020;218:330–336.
4. Jiao X, Ventruto V, Trese MT, Shastry BS, Hejtmancik JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. *Am J Hum Genet*. 2004;75(5):878–884.
5. Robitaille J, MacDonald ML, Kaykas A, et al. Mutant frizzled-4 disrupts retinal angiogenesis in familial exudative vitreoretinopathy. *Nat Genet*. 2002;32(2):326–330.
6. Nikopoulos K, Gilissen C, Hoischen A, et al. Next-generation sequencing of a 40 Mb linkage interval reveals TSPAN12 mutations in patients with familial exudative vitreoretinopathy. *Am J Hum Genet*. 2010;86(2):240–247.
7. Chen ZY, Battinelli EM, Fielder A, et al. A mutation in the Norrie disease gene (NDP) associated with X-linked familial exudative vitreoretinopathy. *Nat Genet*. 1993;5(2):180–183.
8. Collin RW, Nikopoulos K, Dona M, et al. ZNF408 is mutated in familial exudative vitreoretinopathy and is crucial for the development of zebrafish retinal vasculature. *Proc Natl Acad Sci USA*. 2013;110(24):9856–9861.
9. Li JK, Fei P, Li Y, et al. Identification of novel KIF11 mutations in patients with familial exudative vitreoretinopathy and a phenotypic analysis. *Sci Rep*. 2016;6:26564.
10. Zhu X, Yang M, Zhao P, et al. Catenin alpha 1 mutations cause familial exudative vitreoretinopathy by overactivating Norrin/beta-catenin signaling. *J Clin Invest*. 2021;131(6):e139869.
11. Sun W, Xiao X, Li S, Jia X, Wang P, Zhang Q. Germline mutations in CTNNB1 associated with syndromic FEVR or Norrie disease. *Invest Ophthalmol Vis Sci*. 2019;60(1):93–97.
12. Zhang L, Zhang X, Xu H, et al. Exome sequencing revealed Notch ligand JAG1 as a novel candidate gene for familial exudative vitreoretinopathy. *Genet Med*. 2020;22(1):77–84.

13. Zhang S, Li X, Liu W, et al. Whole-exome sequencing identified DLG1 as a candidate gene for familial exudative vitreoretinopathy. *Genet Test Mol Biomarkers*. 2021;25(5):309–316.
14. Li S, Yang M, He Y, et al. Variants in the Wnt co-receptor LRP6 are associated with familial exudative vitreoretinopathy. *J Genet Genomics*. 2022;49(6):590–594.
15. Asano T, Oku K, Kondo H. Familial exudative vitreoretinopathy with TGFBR2 mutation without signs of Loeys-Dietz syndrome. *Ophthalmic Genet*. 2021;42(5):637–640.
16. Yang M, Li S, Huang L, et al. CTNND1 variants cause familial exudative vitreoretinopathy through the Wnt/cadherin axis. *JCI Insight*. 2022;7(14):e158428.
17. Klaus A, Birchmeier W. Wnt signalling and its impact on development and cancer. *Nat Rev Cancer*. 2008;8(5):387–398.
18. Reis M, Liebner S. Wnt signaling in the vasculature. *Exp Cell Res*. 2013;319(9):1317–1323.
19. Nollet F, Berx G, Molemans F, van Roy F. Genomic organization of the human beta-catenin gene (CTNNB1). *Genomics*. 1996;32(3):413–424.
20. Kraus C, Liehr T, Hulsken J, et al. Localization of the human beta-catenin gene (CTNNB1) to 3p21: A region implicated in tumor development. *Genomics*. 1994;23(1):272–274.
21. Dunach M, Del Valle-Perez B, Garcia de Herreros A. p120-catenin in canonical Wnt signaling. *Crit Rev Biochem Mol Biol*. 2017;52(3):327–339.
22. He S, Tang S. WNT/beta-catenin signaling in the development of liver cancers. *Biomed Pharmacother*. 2020;132:110851.
23. Dixon MW, Stem MS, Schuette JL, Keegan CE, Besirli CG. CTNNB1 mutation associated with familial exudative vitreoretinopathy (FEVR) phenotype. *Ophthalmic Genet*. 2016;37(4):468–470.
24. Panagiotou ES, Sanjurjo Soriano C, Poulter JA, et al. Defects in the cell signaling mediator beta-catenin cause the retinal vascular condition FEVR. *Am J Hum Genet*. 2017;100(6):960–968.
25. He Y, Yang M, Zhao R, et al. Novel truncating variants in CTNNB1 cause familial exudative vitreoretinopathy. *J Med Genet*. 2023;60(2):174–185.
26. Kashani AH, Brown KT, Chang E, Drenser KA, Capone A, Trese MT. Diversity of retinal vascular anomalies in patients with familial exudative vitreoretinopathy. *Ophthalmology*. 2014;121(11):2220–2227.
27. Ranchod TM, Ho LY, Drenser KA, Capone A, Jr., Trese MT. Clinical presentation of familial exudative vitreoretinopathy. *Ophthalmology*. 2011;118(10):2070–2075.
28. Lu J, Huang L, Sun L, et al. FZD4 in a large Chinese population with familial exudative vitreoretinopathy: Molecular characteristics and clinical manifestations. *Invest Ophthalmol Vis Sci*. 2022;63(4):7.
29. Chen C, Sun L, Li S, et al. Novel variants in familial exudative vitreoretinopathy patients with KIF11 mutations and the Genotype-Phenotype correlation. *Exp Eye Res*. 2020;199:108165.
30. Liu X, Jian X, Boerwinkle E. dbNSFP: A lightweight database of human nonsynonymous SNPs and their functional predictions. *Hum Mutat*. 2011;32(8):894–899.
31. Jian X, Boerwinkle E, Liu X. In silico prediction of splice-altering single nucleotide variants in the human genome. *Nucleic Acids Res*. 2014;42(22):13534–13544.
32. Xu Q, Wang Y, Dabdoub A, et al. Vascular development in the retina and inner ear: Control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair. *Cell*. 2004;116(6):883–895.
33. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med*. 2016;18(9):898–905.
34. Kharbanda M, Pilz DT, Tomkins S, et al. Clinical features associated with CTNNB1 de novo loss of function mutations in ten individuals. *Eur J Med Genet*. 2017;60(2):130–135.
35. Yang J, Xiao X, Li S, et al. Severe exudative vitreoretinopathy as a common feature for CTNNB1, KIF11 and NDP variants plus sector degeneration for KIF11. *Am J Ophthalmol*. 2022;235:178–187.
36. Coussa RG, Zhao Y, DeBenedictis MJ, Babiuch A, Sears J, Traboulsi EI. Novel mutation in CTNNB1 causes familial exudative vitreoretinopathy (FEVR) and microcephaly: Case report and review of the literature. *Ophthalmic Genet*. 2020;41(1):63–68.
37. Rossetti LZ, Bekheirnia MR, Lewis AM, et al. Missense variants in CTNNB1 can be associated with vitreoretinopathy-Seven new cases of CTNNB1-associated neurodevelopmental disorder including a previously unreported retinal phenotype. *Mol Genet Genomic Med*. 2021;9(1):e1542.
38. Ho SKL, Tsang MHY, Lee M, et al. CTNNB1 neurodevelopmental disorder. In: Adam MP, Everman DB, Mirzaa GM, et al. eds. *GeneReviews((R))*. Seattle, WA; GeneReviews: 1993.
39. Mirosevic S, Khandelwal S, Susjan P, et al. Correlation between phenotype and genotype in CTNNB1 syndrome: A systematic review of the literature. *Int J Mol Sci*. 2022;23(20):12564.

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