CTNNB1 and the Eyes

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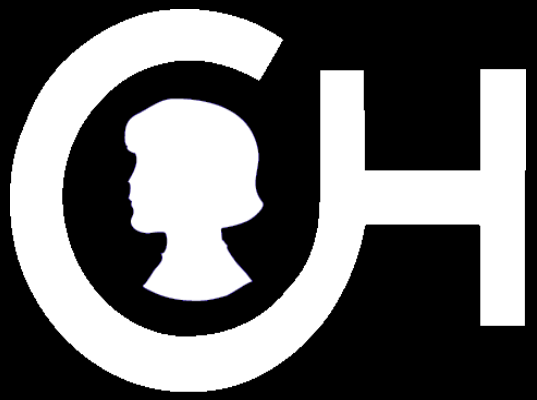


Motivation

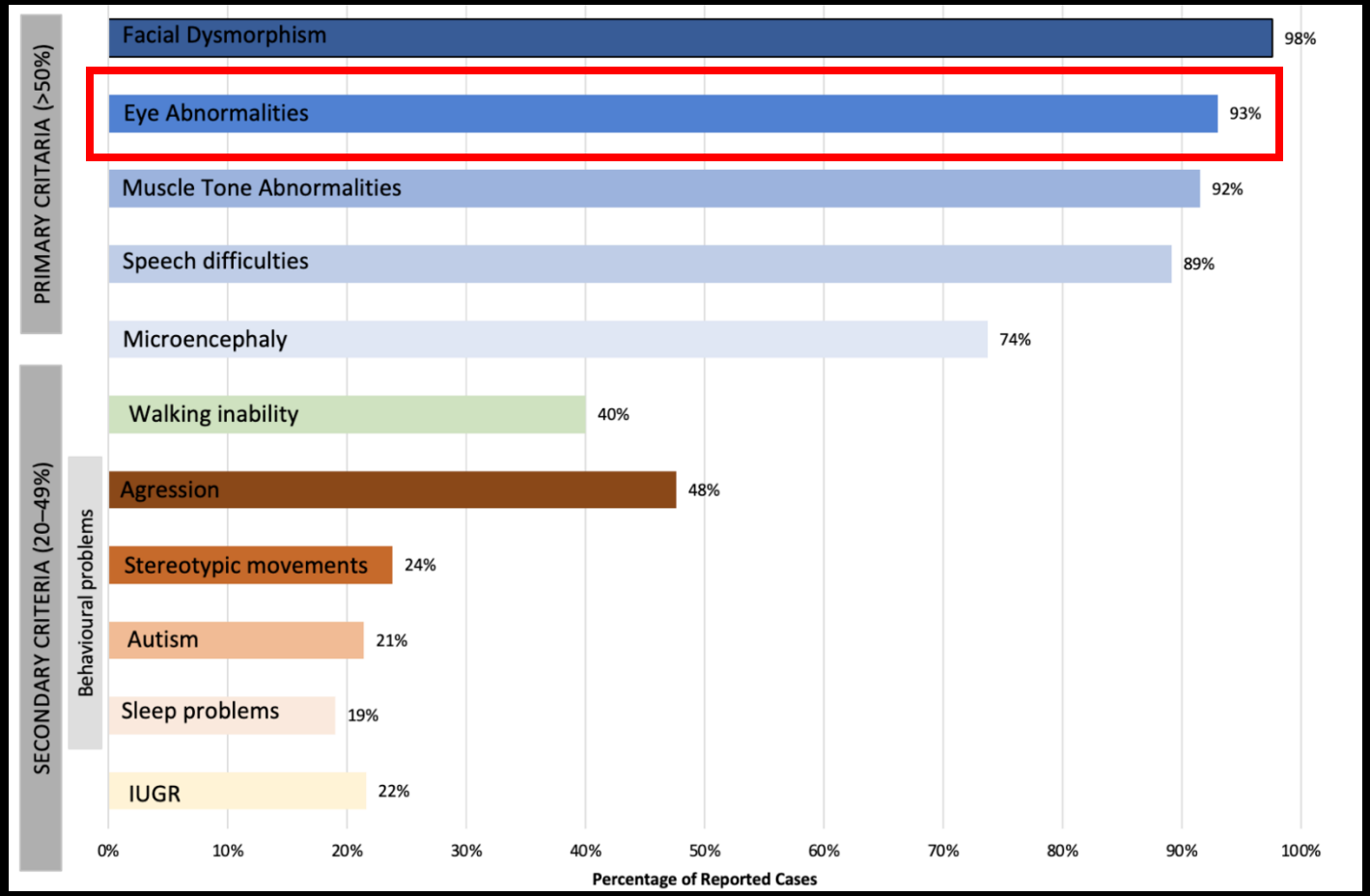
Would it be possible with your knowledge and information correlated to CTNNB1 and FEVR write a recommendation to the eye doctors from Leuven that [redacted] and [redacted] need the correct check on FEVR.
I don't know how I could convince the doctors they need the propper check.
You could pass the recommendation by me.

heard your speech at the research conference back in June and I am wanting [redacted] to be tested for FEVR. We have had two opinions here in MN that both doctors have told us her retinas look good and to not move forward with the fluorescein angiography test. My fear in all this, is the 'what if' and to know it can be tested for and potentially treated, feels like a

for CTNNB1 syndrome. Following your presentation at the last two conferences, we suggested to our ophthalmologist the possibility of performing a fluorescein angiography on [redacted], arguing based on your intervention. The examination turned out positive for FEVR (stage 1 right eye and stage 2 left eye) and he was treated with laser immediately afterwards.

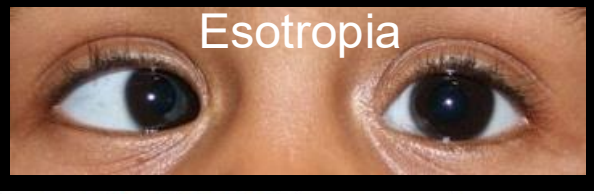
Introduction

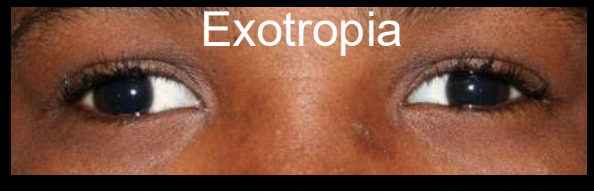
- Majority of CTNNB1 patients diagnosed with ophthalmic disease.
- Severity ranges from mild to blindness at birth.
- Risk of progression not fully understood.
- Genotype-Phenotype relationships not fully understood.

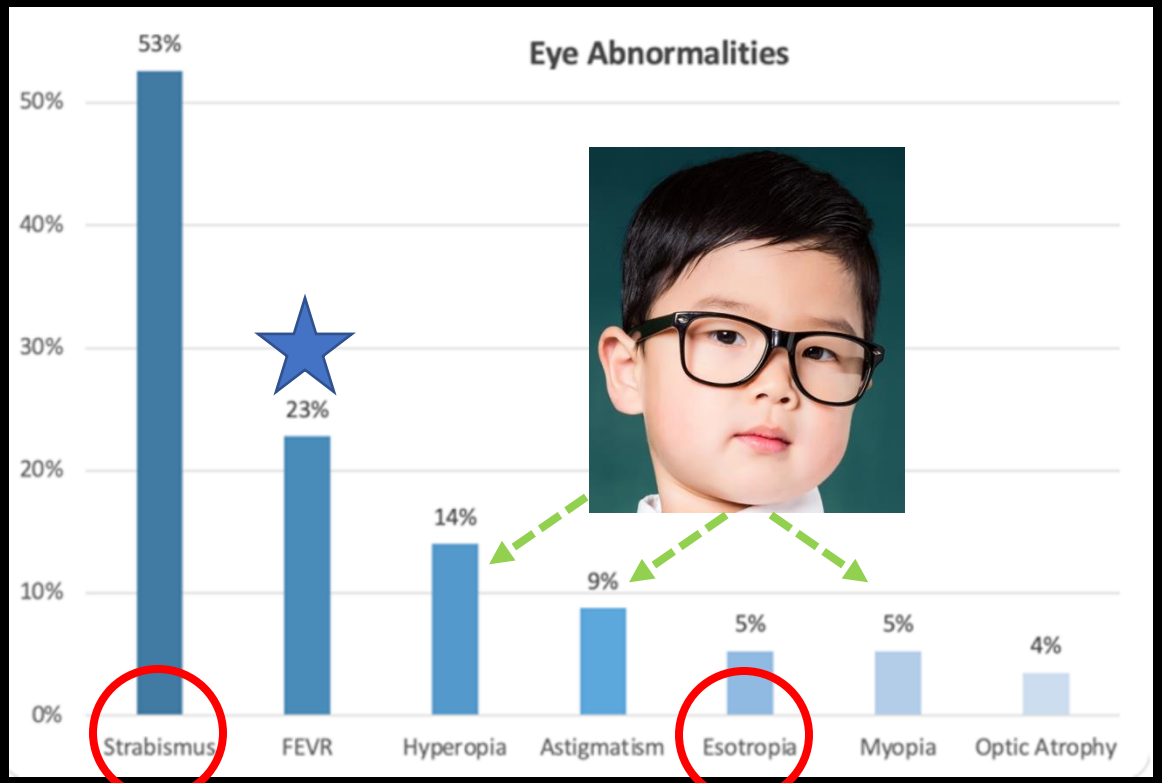


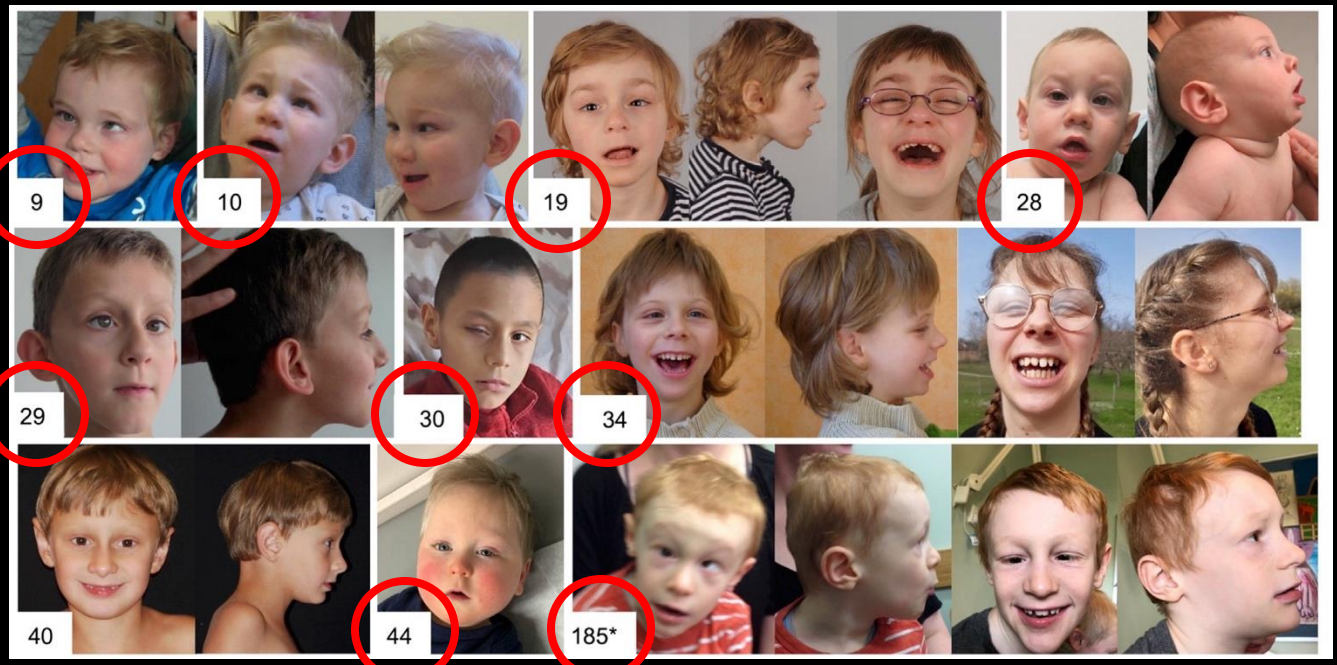
Mirošević, Š. *et al.* Correlation between Phenotype and Genotype in CTNNB1 Syndrome: A Systematic Review of the Literature. *Int J Mol Sci* **23**, doi:10.3390/ijms232012564 (2022).

Ocular presentations in CTNNB1







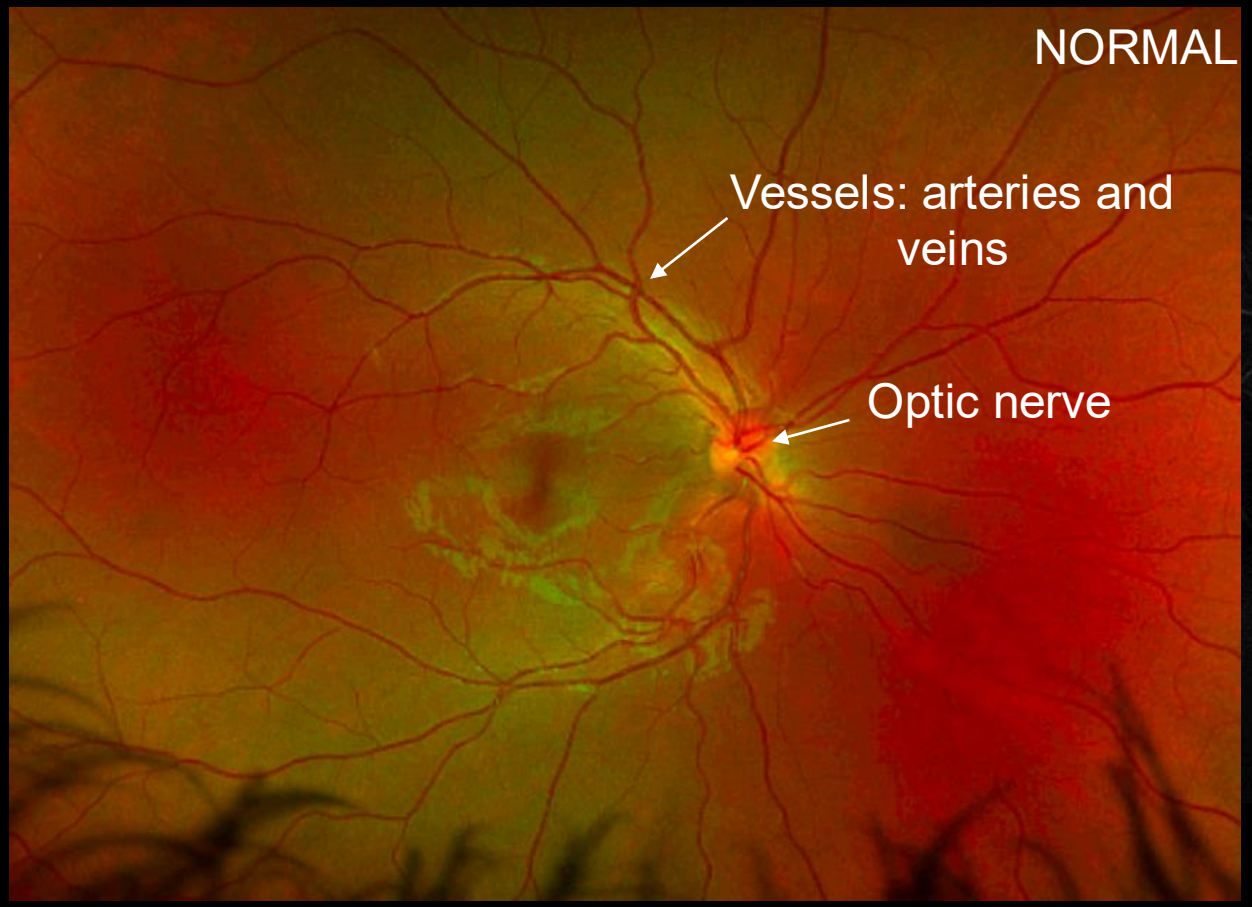


Miroševič, Š. *et al.* Correlation between Phenotype and Genotype in CTNNB1 Syndrome: A Systematic Review of the Literature. *Int J Mol Sci* **23**, doi:10.3390/ijms232012564 (2022).

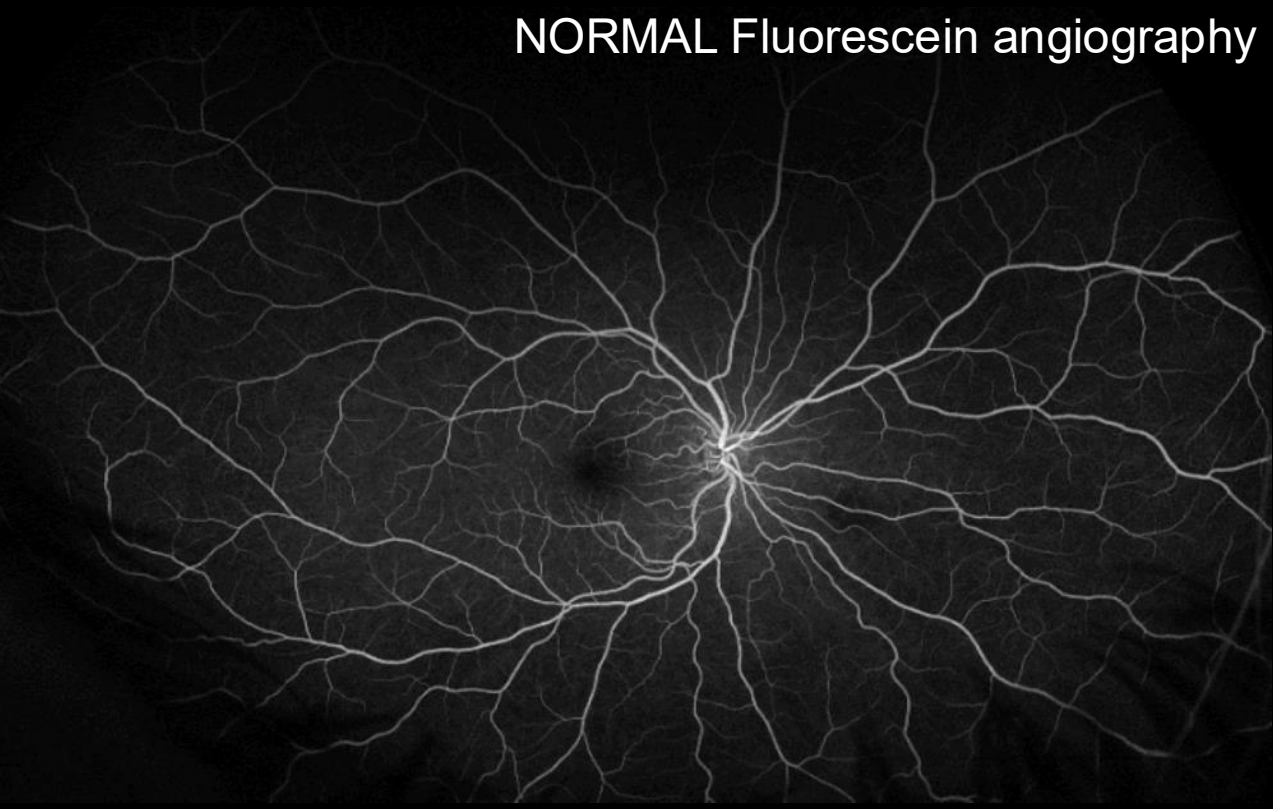
Kayumi, S. *et al.* Genomic and phenotypic characterization of 404 individuals with neurodevelopmental disorders caused by CTNNB1 variants. *Genet Med* **24**, 2351-2366, doi:10.1016/j.gim.2022.08.006 (2022).

What is FEVR?

Familial exudative vitreoretinopathy



NORMAL Fluorescein angiography



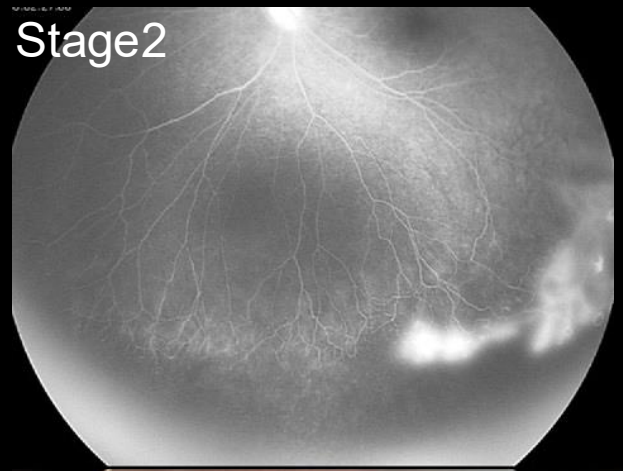
What is FEVR?

Familial exudative vitreoretinopathy

NORMAL

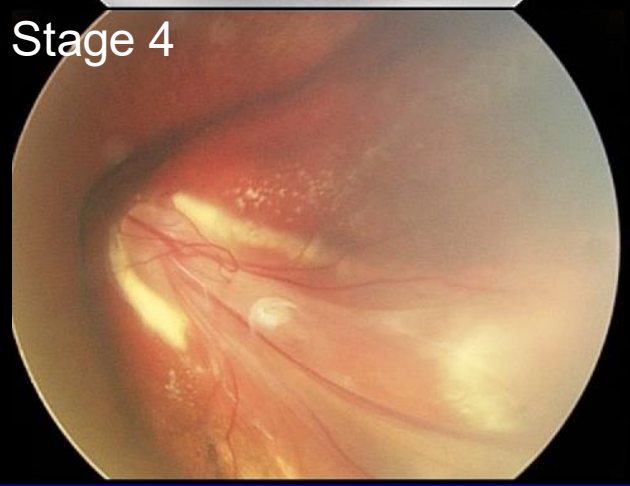
Stage 1

Stage2



Stage 3

Stage 4

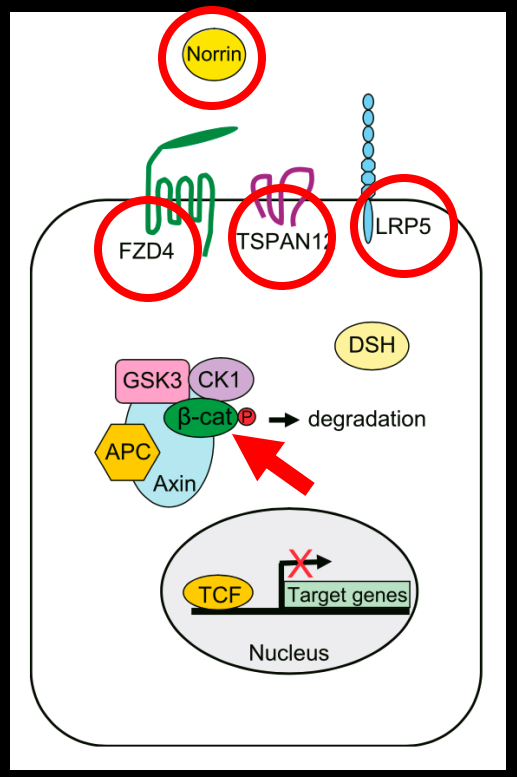


Stage 5

Ranchod, T. M., *et al.* & Trese, M. T. Clinical presentation of familial exudative vitreoretinopathy. *Ophthalmology* **118**, 2070-2075, doi:10.1016/j.ophtha.2011.06.020 (2011).

What causes FEVR? *Genetics*

OFF



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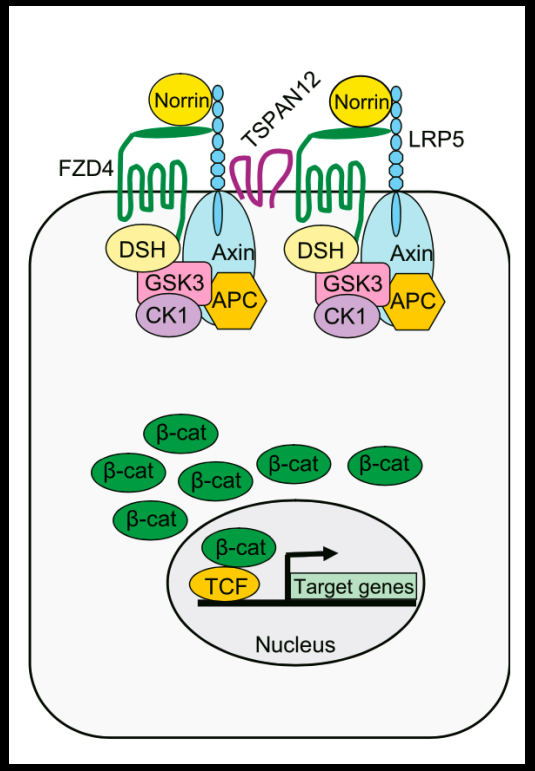


- 6 previously identified genes responsible for the majority of FEVR. All suspected critical for retinal vessel development.
  - **LRP5, FZD4, TSPAN12, NDP**, ZN408, KIF11
- No genetic cause identified for up to 50% of clinically suspected FEVR
- CTNNB1 thought to be < 5% of FEVR

Panagiotou, E. S. *et al.* Defects in the Cell Signaling Mediator beta-Catenin Cause the Retinal Vascular Condition FEVR. *American journal of human genetics* **100**, 960-968, (2017).

FEVR severity in CTNNB1

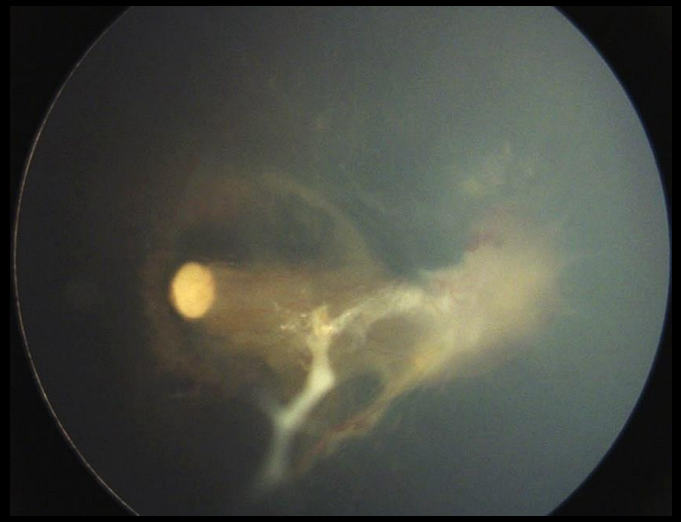
Worst disease presents earliest.

Huang *et al.* 16 eyes: 50% Stage 4, 38% Stage 5

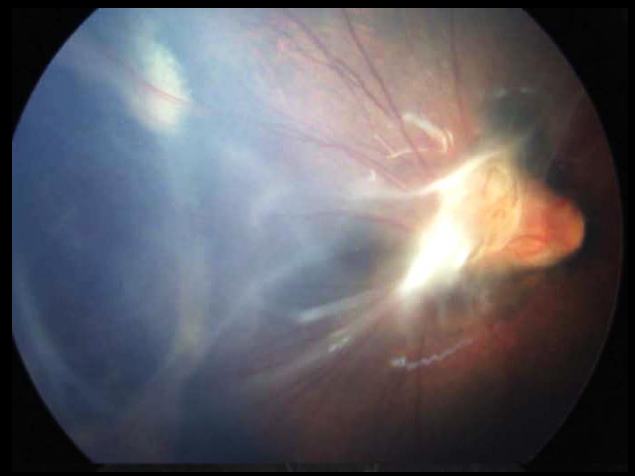
He *et al.* 6 eyes: 100% Stage 5

Dixon *et al.* 2 eyes: Stage 4 / Stage 2

Tipsuriyaporn *et al.* 2 eyes: Stage 4 / Stage 3



Huang, L., *et al.* Familial Exudative Vitreoretinopathy and Systemic Abnormalities in Patients With CTNNB1 Mutations. *Investigative Ophthalmology & Visual Science* **64**, 18-18, (2023).



Tipsuriyaporn, B. *et al.* CTNNB1 (beta-CATENIN) VITREORETINOPATHY: IMAGING CHARACTERISTICS AND SURGICAL MANAGEMENT. *Retin Cases Brief Rep* **16**, 259-262 (2022).

Were we underdiagnosing FEVR in CTNNB1?

Yes

CHOP Study

- Case series
- Retrospective review of children with **normal** in-office exam who subsequently underwent exam under anesthesia with fluorescein angiography.
- 11 patients
- Average age at diagnosis of CTNNB1 syndrome was 2 years (range 1-5)
- Average age at exam was 6 years (range 2-11)
- 82% (9/11) of patients had a diagnosis of strabismus, and 55% (5/11) had undergone strabismus surgery.

Bedoukian, E.C., G. Forbes, and D. Scoles, *Vitreoretinopathy in Asymptomatic Children With CTNNB1 Syndrome.* JAMA Ophthalmol, 2024.

Results

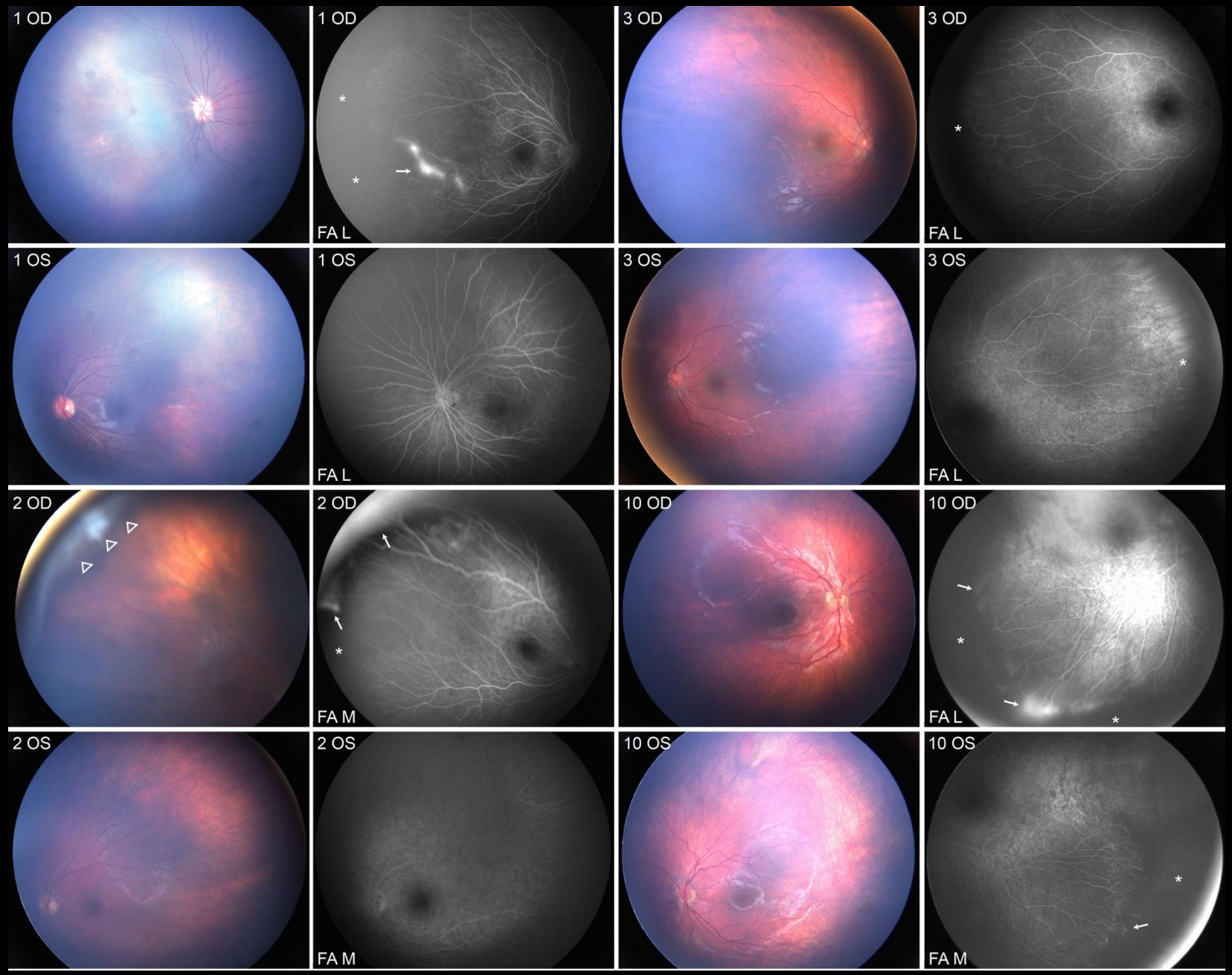
FEVR was present in **46%** (5/11) of patients and **38%** (9/22) of eyes

Vitreoretinopathy requiring treatment was identified in **27%** (6/22) of eyes including **one retinal detachment**

*Update, now screened 16 pts**

*FEVR was present in **63%** (10/16) of patients and **53%** (17/32) of eyes*

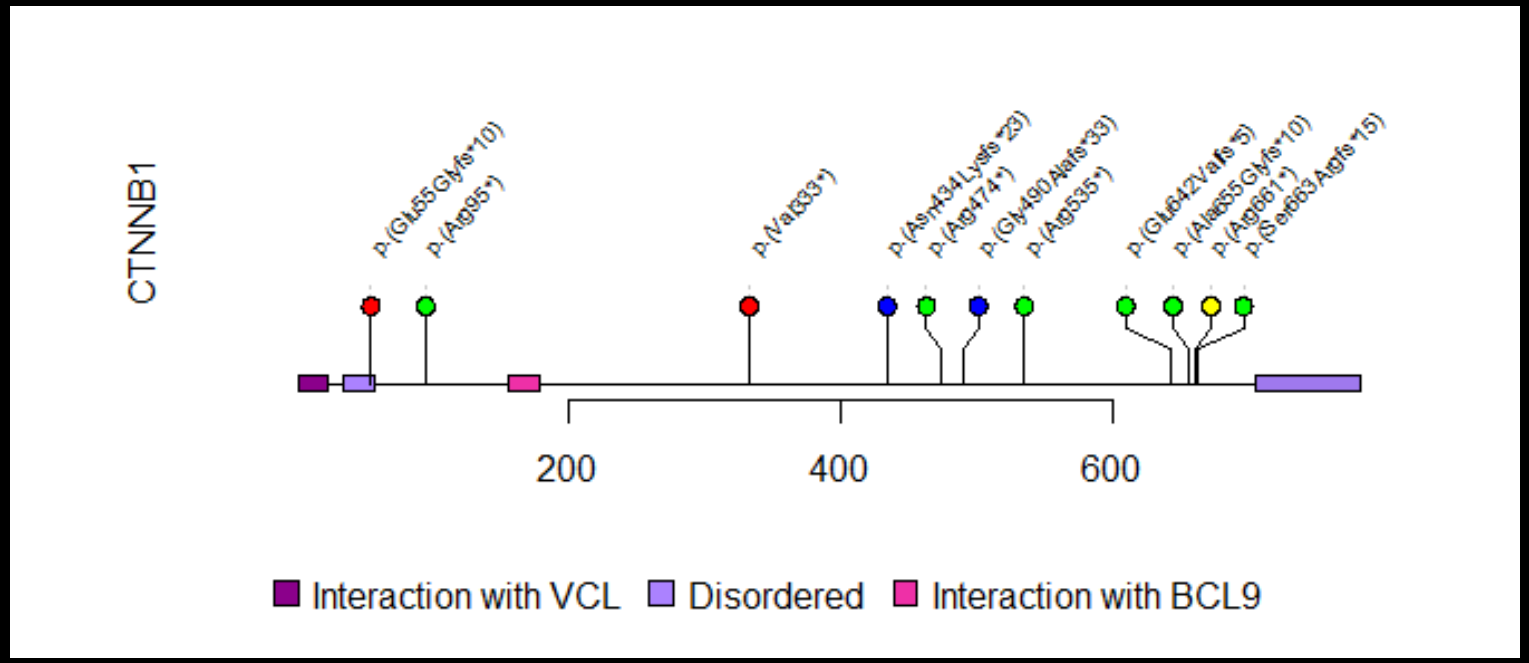
*Treatment in **31%** (10/32) eyes*



Results

FEVR stage in worse eye per patient vs variant location on CTNNB1 gene

Stage 0
Stage 1
Stage 2
Stage 3



Bedoukian, E.C., G. Forbes, and D. Scoles, *Vitreoretinopathy in Asymptomatic Children With CTNNB1 Syndrome.* JAMA Ophthalmol, 2024.

Utah CTNNB1 Cohort

TABLE 1

Demographic, Ocular, and Systemic Characteristics of Patients

Characteristic	1	2	3	4	5	6	7
Sex	F	F	M	F	F	M	M
Age at first eye clinic visit	5 m	5 m	9 m	14 m	5 y	3 y	15 m
Age at FEVR diagnosis (y)	8	4	8	9	19	7	N/A
Age at last follow–up (y)	9	5	8	10	20	8	6
No. of eye clinic visits	32	11	8	19	24	9	12
Strabismus	+	+	–	+	+	–	+
Nasolacrimal duct obstruction	–	+	–	+	–	–	–
Nystagmus	–	–	+	–	–	–	–
Amblyopia	+	+	+	+	–	+	+
Clinically significant refractive error	+	+	+	+	+	+	–
Retina referral for vision loss from FEVR	–	–	+	–	+	–	–
Retina referral for FEVR screening	+	+	–	+	–	+	+
FEVR diagnosed by clinic examination	–	–	+	–	+	–	N/A
FEVR diagnosed by wide-angle FA	+	+	+	+	+	+	N/A
FEVR stage at diagnosis (right/left)	1A/0	2B/2B	4B/3B	2A/2A	0/2B	1B/1B	0/0
Treatment for FEVR	–	+	+	+	+	+	–
Microcephaly	–	+	+	–	–	–	+
Hyoptony	+	–	–	–	–	+	–
Spasticity	–	+	–	–	–	–	–
Developmental delay	+	+	+	+	+	+	+

FA = fluorescein angiography; FEVR = familial exudative retinopathy; N/A = not available

"patients in our cohort required treatment for FEVR despite repeatedly normal dilated examinations in clinic over multiple years."

Review of published cases:

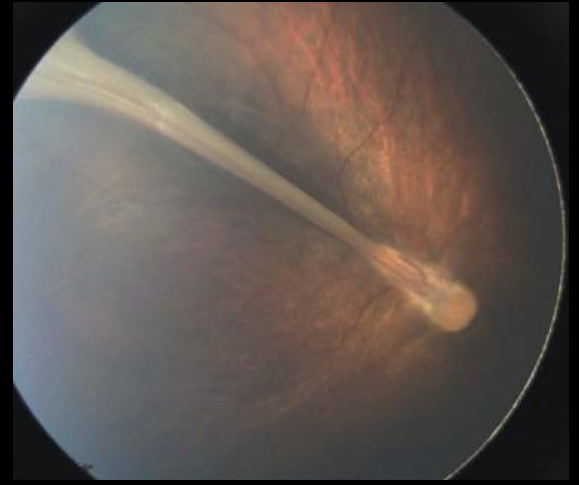
136 patients, of which 37 had FEVR (27%)

22% had stage 1 or 2

70% had stage 3 or higher

Requejo Figueroa, G.A., et al., *Utility of Fluorescein Angiography for Early Detection of Familial Exudative Vitreoretinopathy in Neurodevelopmental Disorder With Spastic Diplegia and Visual Defects due to CTNNB1 Variants*. J Pediatr Ophthalmol Strabismus, 2024: p. 1-7.

Screening: early is better



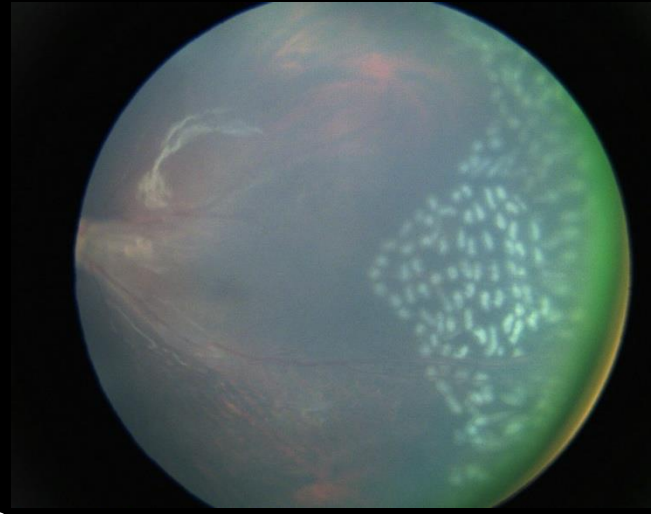
Visual development

WHO?	**Pediatric Ophthalmologist**
WHAT	Strabismus Refractive error Amblyopia Cataract Glaucoma etc

FEVR

WHO?	**Pediatric Ophthalmologist or Pediatric Retina Specialist**
WHAT	Fluorescein angiography Exam under anesthesia Repeat frequency determined by disease stage

Treatment: earlier is better



Visual development

WHO?	**Pediatric Ophthalmologist**
WHAT	Glasses Strabismus surgery Patching Cataract Surgery Glaucoma Surgery etc

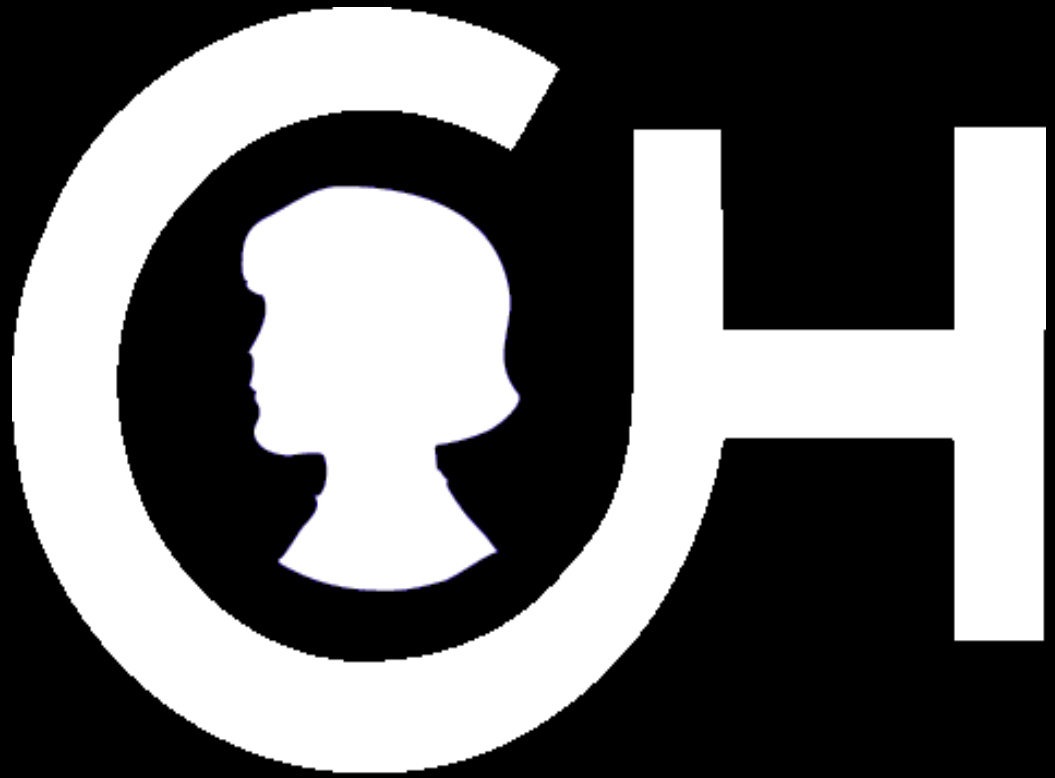
FEVR

WHO?	**Pediatric Retina Specialist**
WHAT	Observation Laser Scleral buckle Vitrectomy

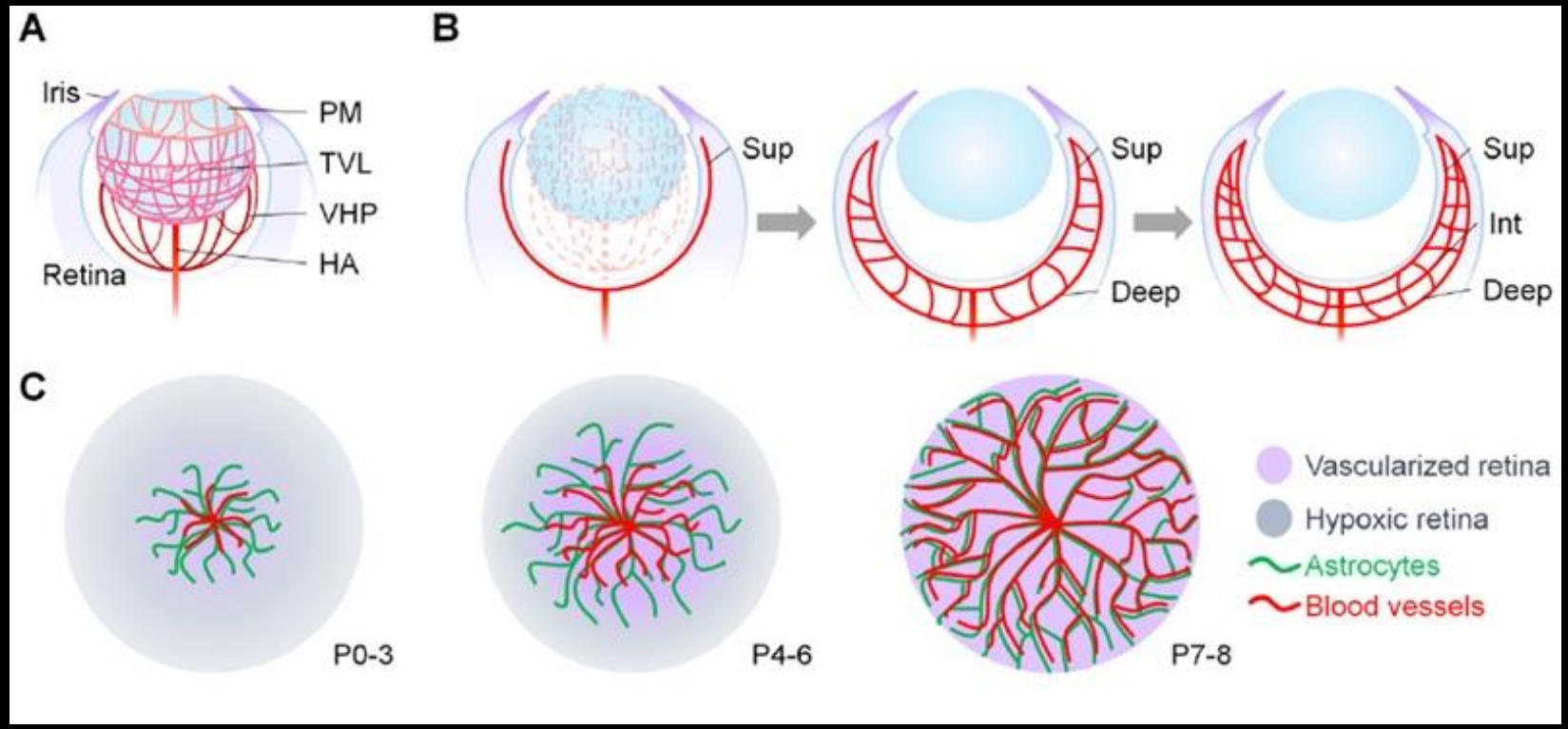
Conclusions

- CTNNB1 is a complex multisystem disorder which frequently involves the eyes and threatens vision
  - FEVR ~ 40%
- Visual expectations CTNNB1?
  - Very challenging to predict but overall good
    - Heterogeneity of phenotype
    - Vision is multifactorial when considering children with developmental delay
- Next Steps
  - Continue to build or understanding of CTNNB1 and the eyes

Thank you!



What causes FEVR? *Pathophysiology*



Norrin secreted by retinal glia to trigger growth of blood vessels.

FEVR findings related to abnormal growth of retinal vessels and incomplete regression of the embryonic vessels of the eye.

- Supernumery (too many) vessels
- Neovascularization
- Vitreoretinal traction
- Retinal fold
- Retinal detachment

Wang, Z., *et al.* Wnt Signaling in vascular eye diseases. *Prog Retin Eye Res* **70**, 110-133, doi:10.1016/j.preteyeres.2018.11.008 (2019).