



Case report

Select pediatric vitreoretinal disease in the setting of Turner's syndrome

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ABSTRACT

Purpose: To report 2 cases of pediatric vitreoretinal disease in the setting of Turner's syndrome.

Observations: A 4-year-old girl with Turner's syndrome was referred for evaluation of a tractional retinal detachment in the right eye. Fundoscopic examination disclosed temporal dragging of the macula in the right eye, and vascular nonperfusion in the right and left eyes. Genetic testing revealed a novel frameshift mutation in the *LRP5* gene consistent with familial exudative vitreoretinopathy (FEVR). The patient was treated with laser. A 14-year-old girl with Turner's syndrome presented with nyctalopia. Dilated fundus exam disclosed peri-foveal pigmentary changes and peripheral bone spicules. Full-field electroretinography demonstrated decreased rod and cone responses, consistent with retinitis pigmentosa (RP).

Conclusions and importance: Vitreoretinal disease, including RP and FEVR, is rarely observed in patients with Turner's syndrome.

1. Introduction

Turner's syndrome is a sex chromosome disorder caused by complete or partial loss or structural abnormality of one X chromosome,¹ resulting in phenotypically female patients with ovarian dysgenesis and short stature.² The estimated incidence is approximately one in two to three thousand live female births.^{1,2} Some patients are found to have somatic mosaicism, in which some cells have Karyotype 45,X and some have 46,XX.²

Numerous ocular findings have been reported in patients with Turner's syndrome including strabismus, hypertelorism, blepharoptosis, and cataracts.³ Posterior segment abnormalities have been rarely reported and published accounts include patients with peripheral neovascularization (NV),³ Coats' disease,⁴ morning glory disc anomaly (MGDA),¹ retinitis pigmentosa (RP),² familial exudative vitreoretinopathy (FEVR)⁵ and unilateral⁶ and bilateral tractional⁷ retinal detachments.

FEVR, first described in 1969 by Criswick and Schepens, is a rare hereditary disorder characterized by avascularity of the peripheral retina.⁸ Clinical manifestations may be variable ranging from macular dragging to retinal neovascularization, vitreous hemorrhage and tractional retinal detachment.^{8,9} The disorder exists in various modes of inheritance, but an autosomal dominant pattern is most common. Genes known to be associated with autosomal inheritance include *FZD4*, *LRP5* and *TSPAN12*.¹⁰ More recently, *ZNF408* was found to also play a role in

the development of retinal vasculature.¹¹ A missense mutation in *ZNF408* resulted in abnormal retinal vasculogenesis and was found to be associated with autosomal dominant FEVR in a large Dutch family.^{11,12} X-linked FEVR is caused by mutations in the *NDP* gene – the causal gene in Norrie disease, which is an *NPD*-related retinopathy with overlapping features with X-linked FEVR.¹⁰

RP is a progressive rod-cone dystrophy characterized by a gradual increase in areas of bone spicule pigmentation in the peripheral retina, attenuation of retinal vessels, and waxy pallor of the optic disc.² Patients typically suffer from nyctalopia and progressive visual field loss. RP is associated with all modes of inheritance. X-linked RP in particular accounts for 10–20% of all RP cases, and is associated with a more severe phenotype.^{2,13}

We present two cases of patients with Turner's syndrome seen at Bascom Palmer Eye Institute—one with RP and one with FEVR—and a review of the literature.

2. Findings

2.1. Case 1

A 4-year-old girl with a diagnosis of Turner's syndrome (genotype 45X) was referred for evaluation of retinal detachments of both eyes. The patient was born at 40 weeks (1928 g) and had a history of hypoplastic left heart syndrome (resulting in two cardiac surgeries),

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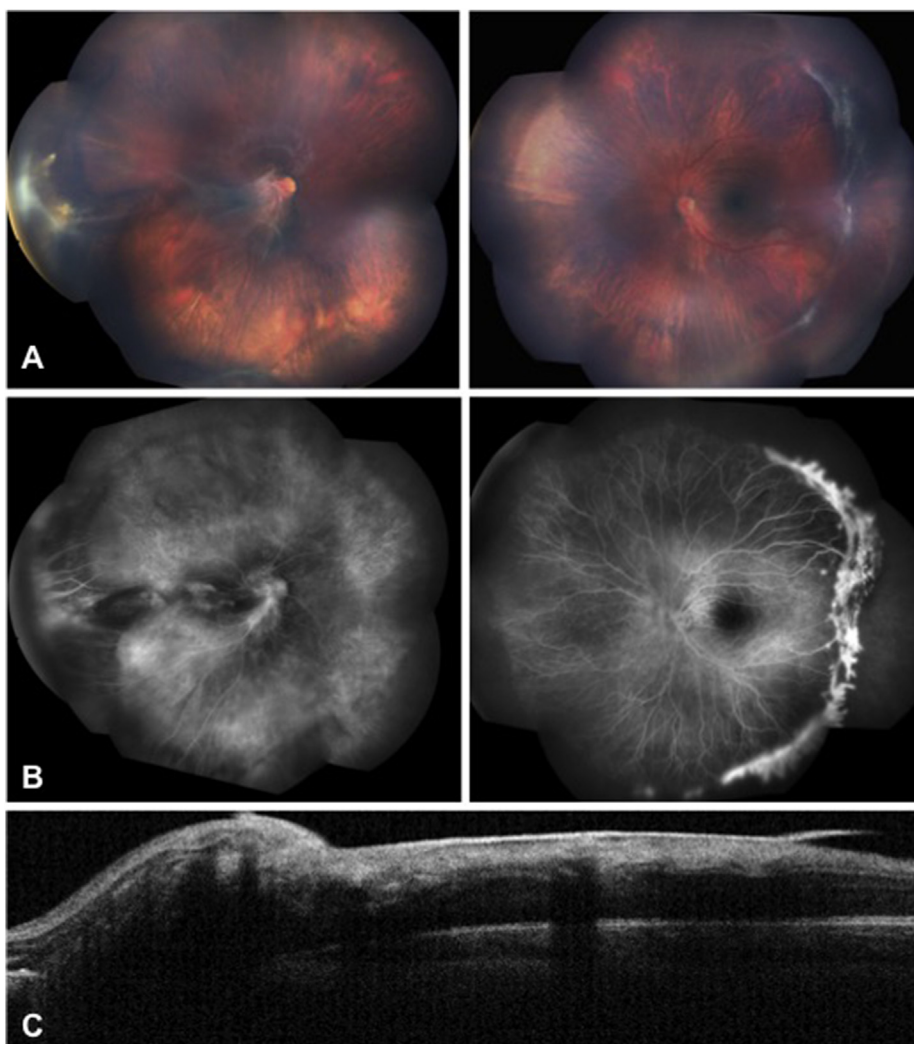


Fig. 1. A four-year-old female with Turner's syndrome and Familial Exudative Vitreoretinopathy. (A) Color fundus photos of the right and left eye demonstrate a tractional contracted posterior hyaloid with dragging of the macula and disc in the right eye, and peripheral pre-retinal fibrotic membranes in both eyes. (B) Fluorescein angiography (FA) of the right and left eye display 360-degree peripheral retinal non-perfusion in both eyes, with inferior and temporal late leakage in the left eye. (C) Optical coherence tomography (OCT) of the right eye demonstrates an extremely dense and contracted posterior hyaloid. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

recurrent urinary tract infection, and bladder reconstruction.

Anterior segment examination was unremarkable. Fundoscopic examination revealed extensive peripheral retinal non-perfusion of both eyes, left more than right, with a demarcation line and neovascularization in the left eye. There was a very dense, contracted posterior hyaloid in the right eye causing dragging of the macula and disc. Spectral domain optical coherence tomography (SD-OCT) again revealed an extremely dense and contracted posterior hyaloid the right eye and a relatively normal macular contour of the left eye. Fluorescein angiography (FA) of the right and left eye revealed 360-degree peripheral retinal non-perfusion with arterial tortuosity and peripheral capillary agenesia in both eyes, and inferior and temporal late leakage seen in the left eye (Fig. 1). Laser was performed in both eyes to the peripheral avascular retina, and sub-tenon triamcinolone was subsequently injected.

The patient underwent genetic testing for FEVR, and she was found to possess a novel heterozygous frameshift mutation in the *LRP5* (low-density lipoprotein receptor-related protein 5) gene, c.11delC.

She subsequently received additional laser in both eyes three times over six months. She also underwent additional sub-tenon triamcinolone injections, once in the left eye and twice in the right, over a six-month period. At 26-month follow up, the patient's Snellen best corrected visual acuity is has stabilized at 20/400 in the right eye and 20/60 in the left eye. Her dilated fundus exam is stable, and she has not required additional treatments.

2.2. Case 2

A 14-year-old girl with Turner's syndrome (mosaic genotype 46,XX/45,X) was referred to the retina service with nyctalopia. There was no known family history of retinal disease, however the patient's mother reported she has mild nyctalopia. On exam, Snellen best corrected visual acuity was 20/40 in both eyes. Anterior segment examination was unremarkable.

On dilated fundus exam, there was 2+ vitreous cell, optic nerve pallor, a ring of pigmentary changes surrounding the fovea extending peripherally with bone spicules and vascular attenuation in both eyes. SD-OCT revealed outer retinal atrophy with trace cystoid changes. Fundus autofluorescence (FAF) displayed a ring of hypoautofluorescence in both eyes (Fig. 2). Full field electroretinography (ERG) revealed reduced rod and cone responses in both eyes (Fig. 3). Based on imaging results, the patient has presumed RP. The patient and family declined genetic testing.

3. Discussion

Several ocular findings have been reported in patients with Turner's syndrome, none of which are considered pathognomonic for the disease. Posterior segment associations vary but are generally rarely encountered. In some reports, authors have hypothesized that the ocular findings are directly related to the chromosomal abnormality,² though very few have genetic testing to support this.

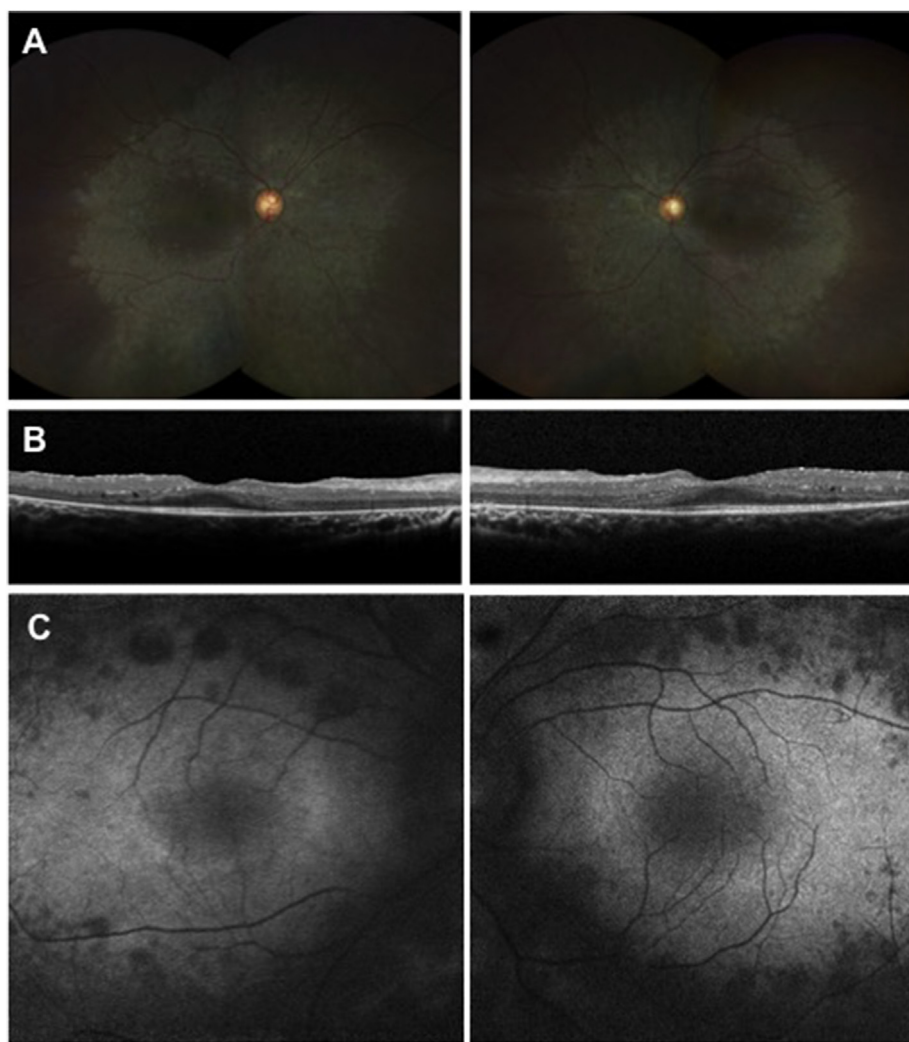


Fig. 2. A fourteen-year-old female with Turner's syndrome and presumed Retinitis Pigmentosa. (A) Color fundus photos of the right and left eye demonstrate a ring of pigmentary changes surrounding the fovea extending peripherally with bone spicules, and vascular attenuation. (B) Optical coherence tomography (OCT) of the right and left eye display outer retinal atrophy and cystoid changes. (C) Fundus autofluorescence (FAF) of the right and left eye demonstrate a ring of hypoautofluorescence. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Optic disc abnormalities have been rarely reported in Turner's syndrome. Sahni and colleagues presented a case of unilateral morning glory disc anomaly (MGDA) in an 11-year-old female with Turner's syndrome.¹ The authors emphasized that MGDA has been reported to occur with Aicardi syndrome, another X-linked condition, and that the underlying chromosomal abnormality in Turner's was likely responsible for the changes in the optic nerve.

Retinal detachment has been reported infrequently in Turner's syndrome. Khodadoust and Patron reported a unilateral retinal detachment in a 13-year-old patient with Turner's syndrome.⁶ However, it is relevant that this patient also had high myopia, and retinal detachment may have been more related to her refractive error. Another case report of a 2-month-old with Turner's syndrome described bilateral retinal detachments that resembled stage V retinopathy of prematurity (ROP) on clinical and ultrasound evaluation.⁷ The authors noted that the patient was born full term and was a normal birth weight (3000g), making ROP unlikely. They also noted that examination of family members showed no signs of FEVR, but genetic testing was not performed, and thus recessive or X-linked disease cannot be excluded.

Other cases of pediatric retinal vascular disease have been reported in Turner's syndrome. Peripheral non-perfusion and neovascularization were described in two infants – one born at 34 weeks and one at 33 weeks gestation.³ In both patients, only one eye showed peripheral

vascular abnormalities, while the fellow eyes appeared angiographically normal. Genetic testing was not performed, but the authors debated whether these cases represented ROP or FEVR. Of note, neither child had a family history of FEVR.

There is another case report of a 6-year-old girl with Turner's syndrome who had exam and imaging findings suggestive of FEVR, but also did not undergo genetic testing.⁵ She presented with total retinal detachment with temporal neovascularization (confirmed with angiography) in the left eye. Examination and angiographic evaluation of family members disclosed normal fundi of the mother and three siblings, but avascular temporal retina in both eyes of the patient's father. No genetic testing was performed to confirm the mutation or to evaluate if the condition was X-linked or autosomal.

All genes known to be associated with FEVR are components of the wingless (Wnt) pathway, and mutations affecting gene function result in abnormal formation of the retinal vasculature.¹⁰ We report the first case of FEVR in a patient with Turner's syndrome that was genetically confirmed. Our patient possesses the *LPR5* gene mutation. The *LPR5* gene is mapped to chromosome 11q13 in humans.¹⁴ In mice models, The *LPR5* gene plays a role in capillary lumen formation.¹⁴ Mutations in this gene are inherited in either an autosomal dominant or autosomal recessive fashion.¹⁰ In FEVR of X-linked inheritance, *NPD* gene mutations are most common.¹⁵ Thus, in our patient, this is a rare coincidence

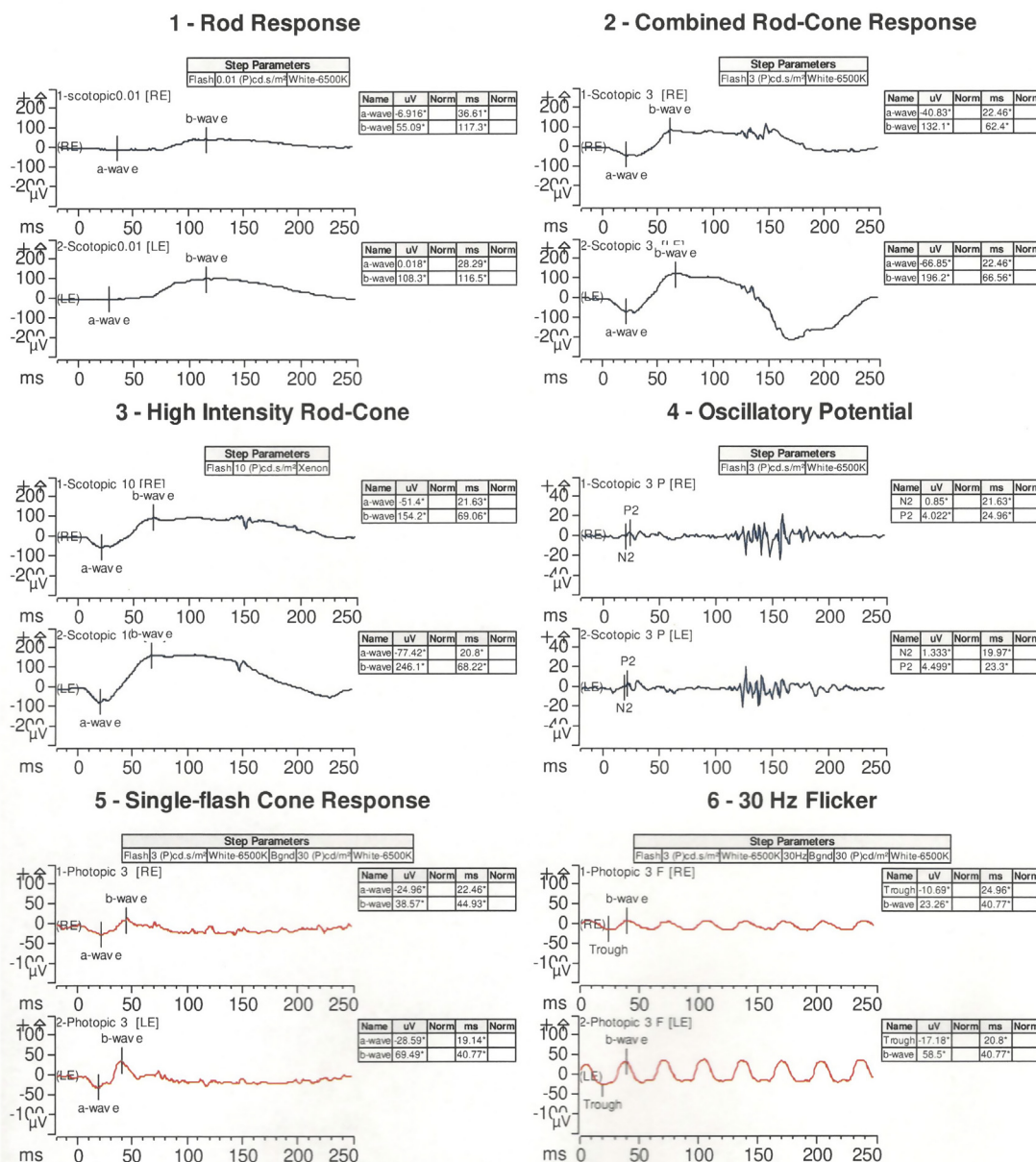


Fig. 3. Full field electroretinography (ERG) of a patient with presumed Retinitis Pigmentosa. Rod, combined rod and cone, and cone ERG amplitudes are reduced in both eyes. Right eye amplitudes are more significantly reduced than left eye.

of autosomal FEVR and Turner's syndrome.

There are only 4 prior case reports of patients with concurrent Turner's syndrome and RP, with only the most recent publication containing molecular genetic confirmation. In that report, a 28-year-old female with mosaic 45,X/46,XX Turner's syndrome was found to have RP confirmed by novel mutation in the *RPGR* gene – the mutation accounting for approximately 80% of all X-linked retinitis pigmentosa (XLRP) cases.² The authors noted that in most monosomy Turner syndrome patients, it is the paternal X chromosome that is lost. The patient's father did not carry the *RPGR* frameshift mutation. The authors of this report postulated that the mutant X chromosome was maternal given the mother had mild nyctalopia, though they did not have molecular genetic evidence of this. In this case, the patient's clinical presentation may have been a manifestation of an intact but mutated *RPGR* in the setting of lack of a normal paternal X chromosome.

Prior studies indicate that affected males with the *RPGR* mutation exhibit a more severe phenotype, whereas carrier females are more commonly asymptomatic or have mild disease with later onset.² This

may explain why patients with cells with a single X chromosome and XLRP might have more severe disease.

In our case, the patient and family declined genetic testing, and there was no known family history of retinal disease. The patients imaging and ERG, however, are very consistent with RP, and the patient's mother reported mild nyctalopia, similar to the case report cited above. We postulate that the patient's mother may be a carrier of the *RPGR* mutation with mild symptoms, and that our patient, with a single X chromosome, has XLRP with a similar clinical presentation to an affected male.

These cases shed light on the possibility that patient's with Turner's syndrome are more prone to other genetic abnormalities. Numerous co-occurring X-linked conditions have been reported including Fragile X syndrome, Duchenne muscular dystrophy, and hemophilia A and B.¹⁶ However numerous co-occurring autosomal disorders have also been described in case reports, including Neurofibromatosis Type 1, Cornelia de Lange syndrome, Long QT syndrome, Li-Fraumeni syndrome and 17 α hydroxylase deficiency.¹⁶ Without population based studies, it is

not possible to determine if these occur at a higher rate in patients with Turner's syndrome. Interestingly, literature review reveals that aneuploidies – notably Down syndrome, and trisomy 18, 13 and 8 – appear to be more common in Turner syndrome individuals.¹⁶ Furthermore, these autosomal aneuploidies were largely associated with non-mosaic karyotypes, indicating a meiotic error could have led to both disorders.¹⁶

4. Conclusions

In conclusion, we present two cases of Turner's syndrome: one with FEVR and one with RP. To our knowledge this is the first reported genetically confirmed case of FEVR in Turner's syndrome. This is the fifth reported case of RP and Turner's syndrome.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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