

## X-Linked Retinoschisis – A Promising Future

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**Abstract:** We report a case of X-linked retinoschisis (XLRS) in a Malaysian Chinese family of four male siblings aged 11, 9, 2 and 6-months old. The two younger siblings had an eye assessment and subsequently diagnosed with XLRS. The eldest never had an eye examination as he had no visual complaint. However, the second son already underwent bilateral retinal surgeries three years ago for retinal detachment / retinoschisis, but his vision remained poor. The third son also had retinal detachment and subsequently underwent a retinal surgery in our Centre. The youngest is on follow up conservatively with regular examination under anaesthesia.

**Keywords:** X-linked retinoschisis, familial retinoschisis, retinal detachment, male, children, gene therapy, carbonic anhydrase inhibitor

### INTRODUCTION

The retina is microscopically divided into ten distinct layers. They are grouped into the pigmented layer (outermost layer) and the neurosensory layer (nine inner layers). A retinal detachment is defined as a separation of the neurosensory layer from the pigmented layer, whereas retinoschisis is a separation within the neurosensory layer.

X-linked retinoschisis (XLRS) is a recessive degenerative disease of the central retina and almost always affect males with worldwide prevalence estimated at 1/5000-1/20000 [1].

Diagnosis is usually made during childhood by characteristics features include variable central vision loss, radial streaks arising from foveal schisis, splitting of neurosensory layer in the peripheral retina, and a negative (b wave more reduced than a wave) electroretinogram (ERG). Features of foveal schisis are seen in all patients whereas less than half presents with peripheral retinoschisis [2]. In 1977 Sauer et al identified the RS1 gene responsible for XLRS. The RS1 gene encodes the production of an essential retinal protein called retinoschisin. Retinoschisin is expressed and secreted mainly by the photoreceptor and a lesser extent the bipolar cells, acts to bind these cells together. It was thought to bind to Na/K ATPase and help regulate fluid balance between intracellular and extracellular environment [2]. Mutation to this gene causes disruption to cellular binding, function and interaction, leading to characteristic Optical Coherent Tomography (OCT) appearances of schisis and cystic cavities.

Although mainly affecting males, female carriers usually have normal retinal function and rarely any retinal abnormalities [2]. Best corrected visual acuity (BCVA) normally ranges from 20/50 to 20/120 and remains stable up to sixth decade of life [3].

Disease progression and severity of each individual is highly variable even within families and common secondary complications such as retinal detachment and vitreous hemorrhage can occur, leading to a poor outcome [1]. The treatment and management of XLRS has been challenging but numerous studies in the recent years have made progress in the treatment and management of this disease.

### Objective

To report a rare case of X-linked retinoschisis in a Malaysian Chinese family.

### Method

Observational case report

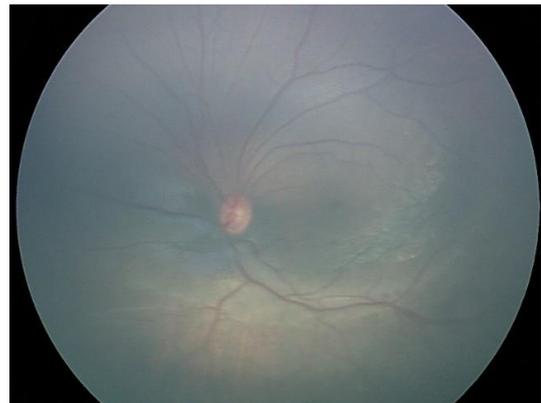
### CASE DESCRIPTION

Here we report a case of two male Chinese children aged 6-months and 2 years old with X-linked retinoschisis. According to mother's observation, unlike other children, her 2-year-old son was not looking straight. She described the child as "seeing using his side vision". She did not observe any squint and there was no history of knocking into things. The family brought the child for an eye examination and on fundus examination showed right retinoschisis and left macula-

off retinoschisis with retinal detachment. He subsequently underwent left eye vitrectomy with tamponade. He is still under follow up.

His youngest brother, a 6-month-old baby boy had an eye screening the same day and was incidentally found to have bilateral suspicious retinal detachment. He was subsequently planned for an examination under anesthesia (EUA) which revealed bilateral inferior retinoschisis with inner leaf lifted inferiorly in both eyes, involving the macula (Fig. 1-2). There was no retinal tear in the outer layers. He was followed up conservatively with regular EUA.

Further family history revealed that the eldest son, aged 11 never had an eye examination by ophthalmologist as he had no visual complaint. However, the second son, aged 9 already had bilateral retinal surgeries done three years ago for retinal detachment / retinoschisis, but his visual acuity remained poor. Both parents had no visual complaint and had normal fundus examinations. There was no history of consanguineous marriage and no family history of retinal diseases. (See chart below).



**Fig-2: Inferior retinoschisis of the left eye involving the macula**

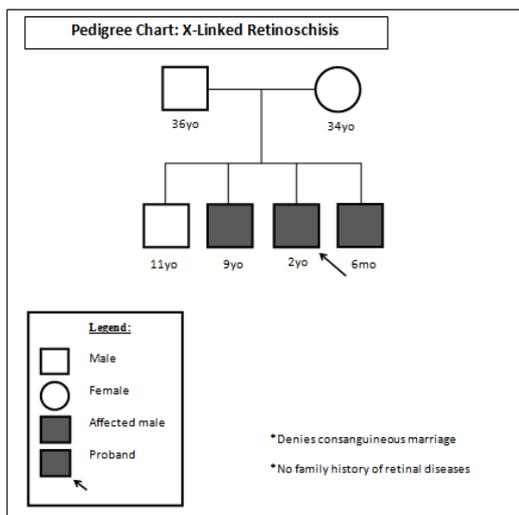
**DISCUSSION**

The RS1 gene encodes retinoschisin, a 224 amino acid protein containing a discoidin domain as the major structural unit, an N-terminal cleavable signal sequence, and regions responsible for subunit oligomerization [2]. Over 190 disease-causing mutations in the RS1 gene are known with most mutations occurring as non-synonymous changes in the discoidin domain [2]. The most common type of mutation was a missense mutation (80%) followed by small frameshifting insertions/deletions (10%), intronic splice site mutations (5%) and exon deletions (5%) [4] This may explain the variability in disease severity and presentation in different individual.

XLRS may be a slow progressing disease, however regular follow up is important to monitor for progression and complications from the disease. In the past decade significant progress has been made to improve clinical diagnosis, genetic analysis, understanding of disease process and treatment [2].

Clinical diagnosis and disease progression monitoring has been greatly improved using Spectral Domain OCT. An OCT study has shown that visual acuity is correlated with outer segment thickness and not the total retinal thickness [4]. Other investigation modalities such as fundus autofluorescence, fluorescein angiography, ERG, electro-oculography, colour vision and visual field test is useful but has limited diagnostic value [2].

The use of carbonic anhydrase inhibitor (CAI) has been reported in a few studies. The results show that CAI was able to promote resolution of cystic fluid in the fovea and maintain stability of the disease [4]. However the respond is not seen in all patients and the mechanism of action is still unclear [4] CAI may be used as a non-invasive management; however more studies are needed to determine its role as a treatment option.



**Chart: Shows the pedigree of the effected individuals in this case report.**



**Fig-1: Inferior retinoschisis of the right eye involving the macula**

Gene therapy using Recombinant adeno-associated virus (rAAV) mediated delivery of the normal RS1 gene to the retina of young knockout mice result in long-term retinoschisin expression and improvement of retinal structure and function [2]. Seok et al has shown that expression of retinoschisin postinjection starts as early as 2 weeks and a normal ERG result is only detected after 3 months [5]. Gene therapy has created a new hope and may be soon the treatment for XLRS in the future.

Regular but complete fundus examination should be performed carefully at each follow-up visits. Vitreous haemorrhage or retinal detachment complicates approximately 5% of all affected males [2]. Complications as such however would require surgical management such as pars plana vitrectomy as reported in this case.

### **CONCLUSION**

XLRS is a slow progressing hereditary eye disease usually affecting male offspring, characterized with foveoschisis or peripheral retinoschisis. Genetic testing and counseling are important for future family planning while regular eye examination is crucial for early detection and treatment of complications such as vitreous haemorrhage and retinal detachment. The increasing focus on gene therapy shows promising results and may soon be an effective treatment option in the near future.

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