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X-linked juvenile retinoschisis: Clinical diagnosis, genetic analysis, and molecular mechanisms

Robert S. Molday [a,*,1], Ulrich Kellner [b,1], Bernhard H.F. Weber [c,1]

[a] Department of Biochemistry and Molecular Biology, Centre of Macular Research, University of British Columbia, 2350 Health Sciences Mall, Vancouver, B.C. V6T 1Z3, Canada
[b] Center of Rare Retinal Disease, AugenZentrum Siegburg, MVZ ADTC Siegburg GmbH, Europaplatz 3, D-53721 Siegburg, Germany
[c] University of Regensburg, Institute of Human Genetics, Franz-Josef-Strauss-Allee 11, D-97053 Regensburg, Germany

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ABSTRACT

X-linked juvenile retinoschisis (XLRS, MIM 312700) is a common early onset macular degeneration in males characterized by mild to severe loss in visual acuity, splitting of retinal layers, and a reduction in the b-wave of the electroretinogram (ERG). The *RS1* gene (MIM 300839) associated with the disease 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. Retinoschisin is secreted from retinal cells as a disulphide-linked homo-octameric complex which binds to the surface of photoreceptors and bipolar cells to help maintain the integrity of the retina. Over 190 disease-causing mutations in the *RS1* gene are known with most mutations occurring as non-synonymous changes in the discoidin domain. Cell expression studies have shown that disease-associated missense mutations in the discoidin domain cause severe protein misfolding and retention in the endoplasmic reticulum, mutations in the signal sequence result in aberrant protein synthesis, and mutations in regions flanking the discoidin domain cause defective disulphide-linked subunit assembly, all of which produce a non-functional protein. Knockout mice deficient in retinoschisin have been generated and shown to display most of the characteristic features found in XLRS patients. 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 rescue of retinal structure and function providing a 'proof of concept' that gene therapy may be an effective treatment for XLRS.

Contents

* Corresponding author. Tel.: +1 604 822 6173; fax: +1 604 822 5227.
E-mail address: molday@mail.ubc.ca (R.S. Molday).

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1. Introduction

X-linked juvenile retinoschisis (XLRS, MIM 312700) is a relatively common early onset retinal degenerative disease that affects males early in life. Characteristic features include mild to severe loss in central vision, radial streaks arising from foveal schisis, splitting of inner retinal layers in the peripheral retina, and a negative electroretinogram (ERG) arising from a marked reduction in b-wave amplitude (George et al., 1995; Tantri et al., 2004). Disease progression and severity is highly variable even within families. During the course of the disease, secondary complications including retinal detachment and vitreous hemorrhage can occur leading to a poor outcome. Female carriers are asymptomatic although detailed clinical examination can reveal minor retinal abnormalities (Kim et al., 2007).

XLRS was first thought to arise as a result of inherited defects in Müller cells. This was based on the b-wave response which was originally thought to directly involve Müller cells and histological examination of retina tissue from deceased patients showing filamentous material merging with Müller cell membrane and splitting of the nerve fiber layer (Condon et al., 1986; Gass, 1999; Miller and Dowling, 1970; Yanoff et al., 1968). Identification of the gene responsible for XLRS in 1997 by Sauer et al. (1997) and the subsequent analysis of gene and protein expression in the retina, however, have directly implicated photoreceptors and bipolar cells, and not Müller cells, in the disease process (Grayson et al., 2000; Molday et al., 2001; Mooy et al., 2002; Reid et al., 1999). The *RS1* gene encodes a 24 kDa discoidin-domain containing protein which is secreted as a homo-oligomeric complex (Sauer et al., 1997; Wu et al., 2005). This complex binds tightly to the surface of photoreceptors and bipolar cells where it helps to maintain the cellular organization of the retina and structure of the photoreceptor-bipolar synapse.

Over the past 15 years significant progress has been made in understanding XLRS at a clinical, genetic, molecular, and cellular level. To date 191 different mutations in the *RS1* gene are known to cause XLRS. Protein expression studies have provided insight into the mechanisms by which specific mutations affect the expression, structure and secretion of retinoschisin and lead to a pathogenic state. Mice deficient in retinoschisin have been developed and used to obtain insight into the role of retinoschisin in retina structure, function and pathology. Finally, the delivery of the normal *RS1* gene to knockout mice deficient in endogenous retinoschisin has resulted in significant restoration of retinal structure and function. In this chapter, we review our current knowledge of retinoschisin and its role in XLRS pathology from a clinical, genetic and molecular perspective.

2. Clinical findings of congenital XLRS

2.1. Clinical manifestations

XLRS was first described in 1898 in two affected brothers by the Austrian ophthalmologist Josef Haas (Haas, 1898). Since then, XLRS has been shown to be one of the more frequent inherited retinal disorders affecting macular function in males with an estimated prevalence ranging between 1:5000 to 1:20,000 (George et al., 1995). The name derives from an internal splitting of the retina mostly affecting the temporal periphery of the fundus. This peripheral retinoschisis occurs in less than 50% of affected individuals, whereas foveal involvement is present in all affected patients. Foveal involvement is usually associated with moderate visual loss. Therefore, XLRS is frequently diagnosed prior to school age suggesting a juvenile onset. Several cases of severe retinoschisis have been described in the first year of age suggesting that XLRS indeed is present at birth (Lee et al., 2009; Prasad et al., 2006; Renner et al., 2008; Sieving, 1998). These severe cases as well as the absence of acute visual loss in the majority of cases indicates that the onset of XLRS is congenital, but the diagnosis is delayed because small infants are not affected in their daily tasks by moderate visual loss.

Multiple studies reporting clinical features of XLRS in a series of families have been reported world-wide (Apushkin et al., 2005b; Atchaneeyasakul et al., 2010; Eksandh et al., 2000; Forsius et al., 1963; George et al., 1995, 1996; Hewitt et al., 2005; Kellner et al., 1990; Lesch et al., 2008; Pimenides et al., 2005; Renner et al., 2008; Riveiro-Alvarez et al., 2009; Shinoda et al., 2000; Shukla et al., 2007; Simonelli et al., 2003; Vainio-Mattila et al., 1969; Xu et al., 2011). The penetrance of XLRS is almost complete but clinical expression is highly variable (Sieving, 1998). In our series of 100 XLRS patients the manifestations ranged from almost complete retinoschisis at the age of 3 months in both eyes to normal visual acuity with mild pigmentary macular abnormalities and a negative full-field electroretinogram (ERG) (Kellner et al., 1990; Renner et al., 2008). The expression of the disease is usually symmetrical in both eyes, however, a marked asymmetry of visual function can be present especially in cases where additional complications occur (Tantri et al., 2004). Visual acuity is reduced to 20/100 in most patients although it may vary greatly. On ophthalmoscopy, foveal retinoschisis presents as a spoke-wheel pattern and peripheral retinoschisis as a sharply delineated detachment of the inner retinal sheet usually limited to the periphery or mid-periphery (Fig. 1). Peripheral retinoschisis may extend from the periphery to the macula including the fovea in some cases; in rare instances marked retinoschisis might involve nearly the complete retina. If the inner