

## EXTENDED REPORT

# Clinical features of X linked juvenile retinoschisis associated with new mutations in the XLR51 gene in Italian families

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**Aims:** To describe the clinical phenotype of X linked juvenile retinoschisis in eight Italian families with six different mutations in the XLR51 gene.

**Methods:** Complete ophthalmic examinations, electroretinography and A and B-scan standardised echography were performed in 18 affected males. The coding sequences of the XLR51 gene were amplified by polymerase chain reaction and directly sequenced on an automated sequencer.

**Results:** Six different XLR51 mutations were identified; two of these mutations Ile81Asn and the Trp122Cys, have not been previously described. The affected males showed an electronegative response to the standard white scotopic stimulus and a prolonged implicit time of the 30 Hz flicker. In the families with Trp112Cys and Trp122Cys mutations we observed a more severe retinoschisis (RS) clinical picture compared with the other genotypes.

**Conclusion:** The severe RS phenotypes associated with Trp112Cys and to Trp122Cys mutations suggest that these mutations determine a notable alteration in the function of the retinoschisin protein.

Congenital retinoschisis is a rare bilateral vitreoretinal disorder characterised by vitreous degeneration and splitting of the retina between the nerve fibre and ganglion cell layers. The patients have typically a cystic-like stellate maculopathy or a foveal schisis,<sup>1</sup> and in 50% of cases bilateral inferotemporal retinoschisis.<sup>1,2</sup> The electroretinogram is beneficial in the diagnosis of juvenile retinoschisis. The scotopic amplitudes are more severely affected than the photopic amplitudes. The a-wave can be of normal or reduced amplitude in this disorder,<sup>3</sup> whereas the amplitude of the b-wave is appreciably reduced,<sup>4,5</sup> giving a negative wave tracing.

The disease is transmitted as an X linked recessive trait, occurring almost exclusively in males, although a few affected female carriers have also been identified, some having a family history of consanguinity,<sup>6,7</sup> supporting homozygosity of X locus.

The cloned retinoschisis gene (XLR51) maps to the distal short arm of the X chromosome (Xp22).<sup>8</sup> The expression is restricted to the photoreceptors and bipolar cells<sup>9-11</sup> and the protein contains a conserved region found in other proteins that participate in cell-cell interactions.<sup>8</sup>

Some reports have been published describing the clinical features in families with defined mutations in the XLR51 gene.<sup>7,12-15</sup>

In this study we describe six different mutations, two of which have not been previously described, in the XLR51 gene and we determine the clinical phenotype associated with these genotypes in eight Italian families.

## PATIENTS AND METHODS

Five families with X linked retinoschisis (XLR5) diagnosed at the department of ophthalmology, Seconda Università di Napoli, one at the department of ophthalmology, Università "Federico II" di Napoli, and two XLR5 families diagnosed at the department of ophthalmology HSR, Università di Milano, Italy, were included in this study (Fig 1). The research procedures were carried out in accordance with institutional guidelines and the Declaration of Helsinki. Informed consent was

obtained from all patients and controls after the nature of the procedures was fully explained.

Complete ophthalmic examinations were performed in 18 affected male (mean age 23 (SD 9) years) and 14 female (mean age 40 (SD 6) years) obligate carriers. The clinical examinations included best corrected visual acuity with Snellen visual chart, slit lamp biomicroscopy, fundus examination, fundus photography, fluorescein angiography, A and B scan, standardised echography, and electroretinography.

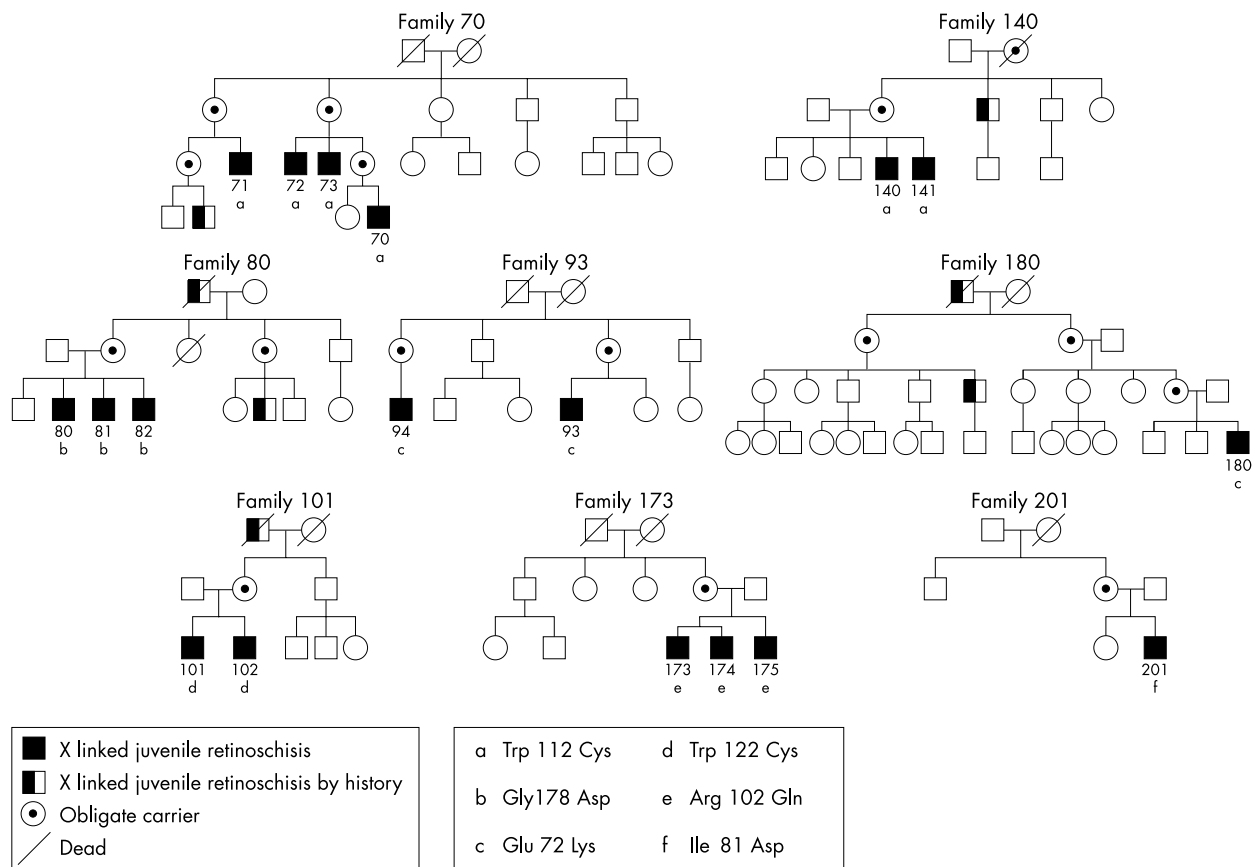
The electroretinogram (ERG) was recorded by means of corneal contact lens electrodes with a Ganzfeld stimulator according to international clinical standards.<sup>16</sup> The ERG results from the XLR5 patients were compared with those of 20 control subjects with normal vision, whose ages ranged from 15-33 years; we defined "reduced" as values below mean -2 SD of controls values.

The diagnostic criteria in XLR51 male patients included macular abnormalities defined as typical foveal schisis, blunted foveal reflex, pigmentary demarcation lines or retinal pigment atrophy with or without peripheral retinoschisis, reduced ERG b-wave, and a history of bilateral visual impairment since childhood.<sup>1,17</sup>

Blood samples from 18 retinoschisis patients belonging to eight families were collected. Genomic DNA was isolated from lymphocytes by standard methods. The coding sequences of the XLR51 gene were amplified by polymerase chain reaction (PCR) and directly sequenced on an automated sequencer (ABI 3100; Applied Biosystem, Foster City, CA, USA) using the ABI-PRISM big dye terminator cycle sequencing ready reaction kit (Applied Biosystem). The pathogenic effect of the mutations identified was confirmed by excluding their presence in 100 normal X chromosomes.

## RESULTS

Six different XLR51 mutations were identified (Table 1). Similar to previous reports,<sup>18</sup> all the mutations were missense mutations and were clustered in exons 4, 5, and 6 encoding the discoidin motif. To the best of our knowledge, two of these



**Figure 1** Pedigrees of families with X linked juvenile retinoschisis and identified mutations in the XLR51 gene.

mutations have not been previously described—namely, the Ile81Asp and the Trp122Cys. Both these mutations affect amino acids that are highly conserved in the discoidin motif across evolution, changing them to residues never found at this position in related proteins.<sup>18</sup>

The clinical data of patients are reported in Table 2. The mean age at the onset of disease in the 18 XLR51 male patients was 5.6 (SD 2.3) years and the symptoms at the onset were photophobia and/or hemeralopia, nystagmus, and reduced visual acuity, but in a few cases the patients were asymptomatic and diagnosed after ophthalmological screening. Best corrected visual acuity varied from 20/20 to light perception (mean values 20/60 (SD 20/100)); the refractive spherical errors ranged from  $-4.50$  to  $+5$  dioptres (mean values  $-0.1$  (SD 2.3)). Hypermetropia in our patients, unlike in the reports of other studies,<sup>19–21</sup> was not the most frequent refractive error; the mean value of the axial length calculated with immersion standardised A-scan echography was 22.9 (SD 0.91).<sup>22</sup>

The vitreous abnormalities observed ophthalmoscopically were vitreous veils in 18 eyes (51.4%), vitreoretinal tractions in

18 eyes (51.4%), and falciform folds in three eyes (8.6%). All patients who underwent A and B-scan standardised echographic examination showed vitreoschisis in both eyes, with the hyaloid adherent to the underlying retina, while two patients, who had previously undergone eye surgery for retinal detachment, showed posterior vitreous detachment, a probable consequence of surgery.<sup>23</sup>

Macular abnormalities were present in all affected patients; 27 eyes (77.1%) showed a typical foveal schisis, a cystic-like stellate alteration, five eyes (14.3%) showed macular atrophy and in three eyes macular coloboma, macular scarring, and healthy macula were present, respectively.

Macular abnormalities were not related to any genotype. The presence of bone spicule pigmentation was evident only in pedigree 140 but not in pedigree 70 with the same mutation.

Peripheral retinoschisis was evident in the temporal sector in 17 of the 35 eyes studied (48.6%) and 10 of these (58.8%) also showed retinal detachment; the families with Trp112Cys, Trp122Cys, and Arg102Gln mutations showed peripheral retinoschisis.

Moreover, in all patients we noted an increased thickness of the retinal choroid layer in the macular region (2 (SD 0.2) mm; in normal controls, the value is  $<1.5$  mm).<sup>24</sup> This increased macular thickness (Fig 2) is due not only to macular schisis, but also to a thickening of the choroid. The increased thickness of the choroid is present only in the posterior pole.

Electroretinography was performed for 11 patients (Table 3), as five patients refused the examination and two patients showed an ERG performed in another eye clinic before ocular surgery for retinal detachment. In all pedigrees the typical response to white single flash was seen with a reduction of the b-wave amplitude and a relative preservation of the a-wave amplitude, causing a reduced b/a ratio. The b/a ratio was reduced ( $<1.1$ ) in nine patients (81.8%) while two patients

**Table 1** Identified mutations in the XLR51 pedigrees

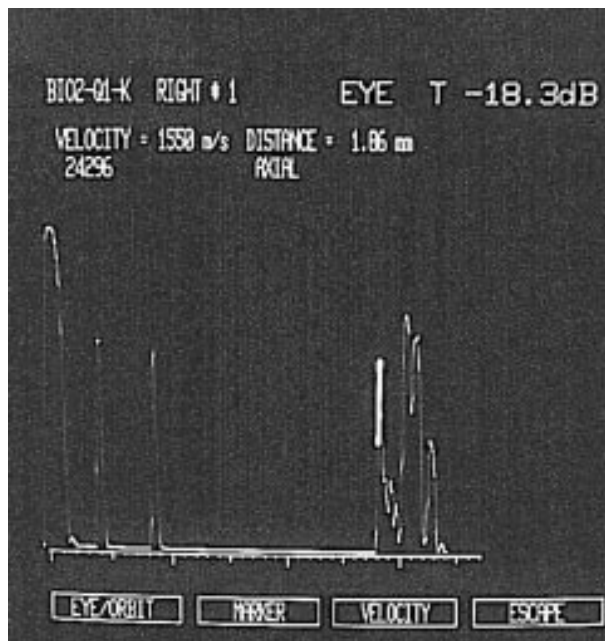
Pedigree	Exon	Mutation	Protein
70	5	336 G>T	Trp 112Cys
140	5	336 G>T	Trp 112Cys
80	6	533 G>A	Gly178Asp
93	4	214 G>A	Glu 72 Lys
180	4	214 G>A	Glu 72 Lys
101	5	366 G>C	Trp 122 Cys*
173	4	305 G>A	Arg 102 Gln
201	4	242 T>A	Ile 81 Asp*

\*New mutation.

**Table 2** Clinical data of XLR51 families

Pedigree	Subject	Mutation	Age (years)	Age at onset (years)	R/L	VA	Refractive spherical error (D)	Axial length (mm)	Vitreous abnormalities			Peripheral retinoschisis	Retinal detachment
									Ophthalmoscopy	Echography	Macular abnormalities		
70	70	Trp112Cys	9	4	R	20/60	-	22.3	-	vitreoschisis	foveal schisis	yes	no
					L	20/60	+1	21.6	-	vitreoschisis	foveal schisis	yes	no
-	71	Trp112Cys	27	4	R	20/1000	+5	21.3	vitreoretinal traction	posterior vitreous detachment	foveal schisis	yes	yes
					L	20/100	+5	20.7	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
-	72	Trp112Cys	26	5	R	20/100	+1	24.2	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
					L	20/1000	-	23.4	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
-	73	Trp112Cys	28	3	R	20/40	-0.75	23	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
					L	20/1000	+0.5	23.4	vitreoretinal traction	posterior vitreous detachment	foveal schisis	yes	yes
140	140	Trp112Cys	24	6	R	20/60	+0.75	22.1	vitreous veils, falciform fold, vitreoretinal traction	vitreoschisis	foveal schisis, bone spicule pigmentation	yes	no
					L	20/200	+2	21.6	vitreoretinal traction	vitreoschisis	retinal pigment atrophy, bone spicule pigmentation	no	no
-	141	Trp112Cys	20	6	R	LP	-	23.6	falciform fold, vitreoretinal traction	vitreoschisis	retinal pigment atrophy, bone spicule pigmentation	no	no
					L	20/200	-4.50	24	falciform fold, vitreous veils, vitreoretinal traction	vitreoschisis	foveal schisis, bone spicule pigmentation	yes	no
80	80	Gly178Asp	32	6	R	20/100	-	23.2	vitreous veils	vitreoschisis	foveal schisis	no	no
					L	20/100	-	23.3	-	vitreoschisis	foveal schisis	no	no
-	81	Gly178Asp	28	6	R	20/100	+0.50	22.6	vitreous veils, vitreoretinal traction	vitreoschisis	foveal schisis	no	no
					L	20/100	-1.50	23	vitreous veils, vitreoretinal traction	vitreoschisis	foveal schisis	yes	no
-	82	Gly178Asp	20	6	R	20/100	-2	22.1	vitreous veils, vitreoretinal traction	vitreoschisis	foveal schisis	no	no
					L	20/100	-0.50	22.7	vitreous veils, vitreoretinal traction	vitreoschisis	foveal schisis	yes	no
93	93	Glu72Lys	-	-	R	20/90	-	23.9	vitreous veils	vitreoschisis	foveal schisis	no	no
					L	20/40	-	22.5	vitreous veils	vitreoschisis	foveal schisis	no	no
-	94	Glu72Lys	10	4	R	20/40	-2	22.9	vitreous veils	vitreoschisis	foveal schisis	no	no
					L	20/30	-2	23.3	vitreous veils	vitreoschisis	foveal schisis	no	no
180	180	Glu72 Lys	19	5	R	20/33	-0.50	23.6	vitreous veils	vitreoschisis	foveal schisis	no	no
					L	20/33	-	23.3	vitreous veils	vitreoschisis	foveal schisis	no	no
101	101	Trp122Cys	24	5	R	20/25	-	23.9	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
					L	enucleation	-	-	-	-	-	-	-
-	102	Trp122Cys	27	6	R	20/20	-	24.2	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
					L	20/25	-	24	vitreoretinal traction	vitreoschisis	foveal schisis	yes	yes
173	173	Arg102Gln	37	5	R	20/22	-	23.4	vitreous veils	vitreoschisis	-	yes	no
					L	20/100	-2	23.6	vitrectomy	-	retinal pigment atrophy	yes	yes
-	174	Arg102Gln	37	5	R	20/50	-	22.7	vitreous veils	vitreoschisis	macular scarring	no	no
					L	20/50	-	22.6	vitreous veils	vitreoschisis	retinal pigment atrophy	no	no
-	175	Arg102Gln	31	5	R	20/25	-2	23.6	vitreous veils	vitreoschisis	retinal pigment atrophy	no	no
					L	20/1000	-	23.4	vitreous veils	vitreoschisis	macular coloboma	no	no
201	201	Ile81Asp	12	6	R	20/100	-	23	-	vitreoschisis	foveal schisis	no	no
					L	20/100	-	23.4	-	vitreoschisis	foveal schisis	no	no

R= right eye; L= left eye; VA= visual acuity; LP= light perception.



**Figure 2** Echographic examination recorded in an affected XLR5 male, showing an increased thickness of retinal choroid layer in the macular region.

(18.2%) had a reduction in both the a and b-wave amplitudes, with a normal b/a ratio. Moreover, the amplitude of the a-wave was reduced in four patients and this reduction did not appear to be related to the duration of the disease. These patients showed a Trp112Cys mutation of the XLR5 gene. The scotopic blue flash response was reduced in seven patients (<275  $\mu$ V) and extinct in four patients. The photopic b-wave amplitude was reduced in eight patients (<124  $\mu$ V) while three patients had extinct responses. The genotype of the patients with extinct scotopic or photopic ERG was Trp112Cys. The 30 Hz flicker amplitude was reduced in three patients (<34  $\mu$ V) and extinct in the patient with Glu72Lys genotype. The implicit time of the 30 Hz flicker was prolonged in six patients.

## DISCUSSION

A study of the genotype/phenotype correlation in XLR5 is complicated because of the low number of XLR5 patients and because most mutations take place within the discoidin domain, which probably results in a similar effect on the function of this protein.

Although a great number of mutations have been identified in the XLR5 gene,<sup>18, 25-28</sup> there are few clinical data relating to the different genotypes.<sup>7, 12-15</sup>

This is the first study reporting a genotype-phenotype correlation on XLR5 in Italian patients in which we found two mutations not previously described.<sup>18</sup>

In Glu72Lys XLR5 families, we showed typical foveal schisis without peripheral schisis and the presence of vitreoschisis and vitreous veils in all patients, something not described in the families studied by Scinoida.<sup>14</sup>

The phenotype associated with the Gly178Asp genotype showed a similar clinical picture in brothers, with foveal schisis, vitreous veils, vitreoretinal tractions, vitreoschisis, and peripheral schisis. Moreover, in this pedigree, in accordance with what has been reported by Sieving<sup>13</sup> in a XLR5 subject of 80 years of age with the same mutation, the ERG findings showed the classic alteration of the inner retina with a sparing of the a-wave function, resulting in the reduction of the b/a ratio to the maximal ERG response.

In the families with Trp112Cys and Trp122Cys mutations we observed a more severe RS clinical picture compared with the other genotypes. The Trp112Cys families showed a typical foveal retinoschisis with peripheral retinoschisis, vitreoretinal tractions, retinal detachment, and a severe reduction of the retinal function, as evident from the reduced amplitude of both the a and b-waves to the maximal scotopic ERG and from the extinct scotopic and photopic tracing in most of the subjects, despite the same duration of the disease as the other families. The phenotype associated with the novel mutation Trp122Cys, which is typical foveal retinoschisis with peripheral schisis, also showed a severe phenotype, as evident from the need for surgery for retinal detachment and from the marked alteration in the electrophysiological results performed 2 years before surgery which suggested extensive retinal impairment, not consistent with congenital retinoschisis.

No clinical phenotype is distinguished but we note that some ERG changes are associated with certain mutations. In fact, Trp 112 Cys is associated with very poor b-wave amplitudes (4/4 patients) and reduced a wave amplitudes in 2/4 patients tested. Trp 122 Cys is associated with reduced b and a wave amplitudes in 2/2 patient tested. Other mutations showed the more classical reduced b-wave with preservation of the a-wave (Table 3).

The severe XLR5 phenotypes associated with Trp112Cys and Trp122Cys mutations suggest that these mutations determine a dramatic alteration in the function of the retinoschisin protein. The tryptophan residues involved in these mutations are highly conserved in other discoidin domains,<sup>18</sup> indicating that these two amino acid residues have an important role in the function of this domain and, consequently, of the retinoschisin protein. It is also important to note that the replacement of

**Table 3** Electrophysiological data of XLR5 families

Pedigree	Subject	Mutation	Age (years)	Scotopic (blue flash) b-wave ( $\mu$ V)	Photopic b-wave ( $\mu$ V)	Scotopic (white flash)			30 Hz flicker	
						b-wave ( $\mu$ V)	a-wave ( $\mu$ V)	b/a ratio	Amplitude ( $\mu$ V)	Implicit time (ms)
70	70	Trp112Cys	9	45,8	23	77	55	1.4	10.5	26
-	71	Trp112Cys	27	extinguished	extinguished	142	187	0.8	43.7	27
-	72	Trp112Cys	26	extinguished	26	65	102	0.6	17.7	38
-	73	Trp112Cys	28	extinguished	90	182	219	0.8	37.5	33
140	140	Trp112Cys	24	extinguished	extinguished	36	46	0.8	11.1	43
-	141	Trp112Cys	20	71,5	extinguished	67	50	1.3	35.9	33
80	80	Gly178Asp	32	58,2	66	238	261	0.9	-	-
-	81	Gly178Asp	28	106	79	279	288	0.9	44.3	30
-	82	Gly178Asp	20	28,7	73	160	186	0.9	39.2	34
93	94	Glu72Lys	10	112	71	223	195	1.1	extinguished	-
180	180	Glu72Lys	19	97,5	105	205	232	0.9	57.9	27
				379 (104)*	210 (86)*	377 (113)*	238 (84)*	1.7 (0.6)*	90 (56)*	>24 <27*

\*Mean values (2 SD) in controls.

a large hydrophobic residue such as tryptophan with a smaller and more hydrophilic residue such as cysteine will result in a corresponding alteration in the protein structure of the discoidin domain. Since this domain is a protein-protein interaction module, it is conceivable that a disruption will impair the ability of retinoschisin to interact properly with its putative partners yet to be identified.

The molecular elucidation of X-linked juvenile retinoschisis may serve as a key to understanding the pathogenesis and, perhaps, provide a better tool for use in clinical diagnosis, prognosis, and genetic counselling.

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