Identification of a Novel RPGR Exon ORF15 Mutation in a Family With X-linked Retinitis Pigmentosa

Zi-Bing Jin, MD, PhD; Feng Gu, PhD; Xu Ma, PhD; Nobuhisa Nao-i, MD

**Objective:** To investigate the phenotypic and genotypic characteristics of a novel mutation associated with X-linked retinitis pigmentosa (XLRP).

**Methods:** Six individuals in a family with XLRP were recruited, and clinical examinations were performed. All of the members were genotyped with microsatellite markers at loci that were considered to be associated with XLRP. The retinitis pigmentosa GTPase regulator gene (RPGR) was comprehensively screened using direct polymerase chain reaction sequencing.

**Results:** Genotyping analysis showed that the affected individuals in the family shared a common haplotype with selected markers. The patients demonstrated severe retinal degenerative phenotypes consistent with XLRP. Mutational screening of RPGR demonstrated a novel mutation, g.ORF15/H11001_1232_1233delGG.

**Conclusions:** We identified a novel mutation in the 3’ end of a highly repetitive region of exon open reading frame 15 (ORF15) and documented the detailed phenotypes of the patients with XLRP with the mutation. The clinical phenotype was consistent with XLRP, supporting the observation that the mutations in the 3’ end of the ORF15 coding sequence give rise to XLRP.

**Clinical Relevance:** The mutation in the 3’ end of the ORF15 coding sequence can lead to a spectrum of phenotypes, and the cone-predominant phenotype-related mutations can be located irregularly in exon ORF15.

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**RETINITIS PIGMENTOSA (RP) IS a clinically and genetically heterogeneous disease with progressive degeneration of retinal photoreceptors characterized by night blindness, progressive loss of peripheral vision, and typically the appearance of bone spicules in the retina. X-linked RP (XLRP) is the most severe among different heritable forms of RP. In affected males, rod and cone dysfunctions begin in early childhood and functions deteriorate rapidly. Female carriers display a wide spectrum of clinical features, ranging from normal to severe manifestations.**

To date, more than 32 genes responsible for RP have been cloned. Two of the most prevalent genes, the retinitis pigmentosa GTPase regulator gene (RPGR) and the retinitis pigment 2, X-linked gene (RP2), are known to be defective in 60% to 90% and 10% to 20% of families with XLRP, respectively. More recently, ORF15 mutations have been identified in X-linked cone-rod dystrophy (XLCORD). A study involving comprehensive molecular screening of a large number of families with XLRP and several families with XLCORD identified a number of mutations. The investigators assumed that mutations close to downstream of ORF15 implicate the early preferential loss of cone function with slight-to-moderate loss of rod function and downstream mutations are responsible for XLCORD. A recent study reported 2 nonsense mutations located at the 3’ end of the highly repetitive region (codons 143-468) of ORF15 (codons 365 and 392), supporting the idea that mutations toward the 3’ end of the highly repetitive region may cause cone-predominant dysfunction. Thus far, RPGR exon ORF15 is the only known gene responsible for XLCORD. A number of mutations in the 3’ end of the ORF15 coding sequence have been iden-
tified in families with XLRP, but few detailed phenotypic descriptions have been documented. Such data are important both for studying the genotype-phenotype correlation and for elucidating the distribution and contribution of the ORF15 mutations.

The aim of this study was to identify the mutation in a specific family with XLRP and to characterize the phenotypic changes in patients with the mutation. Through genotyping and mutational analysis, a novel mutation located at the 3’ end of the highly repetitive region of exon ORF15 was identified and the genotype-phenotype correlation was determined.

METHODS

FAMILY ASCERTAINMENT

This study followed the tenets of the Declaration of Helsinki. The protocol of this study was approved by the ethics committee of Miyazaki Medical College. Informed consent was obtained from all of the family members participating in this study. The study consisted of 6 members who were recruited for DNA testing (Figure 1). Blood samples were collected and genomic DNA was extracted by standard protocols (DNA Extractor WB Kit; Wako Pure Chemical Industries, Ltd, Osaka, Japan). Clinical examinations included routine ophthalmic examinations, Goldmann perimetry, electroretinography (ERG), and color fundus photography. The diagnosis of RP was confirmed by ophthalmologists (Z.-B.J. and N.N.). There was no history of other ocular or systemic abnormalities in the family.

GENOTYPING

Genotyping using microsatellite markers (DXS1068, DXS8025, DXS6810, DXS8054, and G10578) involved polymerase chain reaction amplification of the microsatellite region following standard methods and measurement of the size of the amplified fragment. The oligonucleotide primer sequences and the order of the markers were taken from NCBI and ENSEMBL databases. The genotypes were obtained.

Table 1. Summary of Clinical Findings for the Family With X-linked Retinitis Pigmentosa

<table>
<thead>
<tr>
<th>Family Member/ Sex/Age, y</th>
<th>BCVA</th>
<th>Refraction, Diopters</th>
<th>Fundus Examination Results</th>
<th>ERG Results</th>
<th>Goldmann Perimetry Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:3/M/66</td>
<td>Right eye</td>
<td>0.03</td>
<td>(Aphakia) +5.00/-2.00 × 70</td>
<td>Bilateral extensive chorioretinal atrophy and midperipheral pigmentation</td>
<td>Extinguished</td>
</tr>
<tr>
<td>Left eye</td>
<td>0.01</td>
<td>(Aphakia) +4.00/-1.00 × 100</td>
<td></td>
<td>Extinguished</td>
<td>ND</td>
</tr>
<tr>
<td>II:2/M/45</td>
<td>Right eye</td>
<td>2.0</td>
<td>+0.50/-0.50 × 160</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Left eye</td>
<td>2.0</td>
<td>+0.25/-0.25 × 145</td>
<td>Normal</td>
<td>Normal</td>
<td>Full</td>
</tr>
<tr>
<td>II:3/F/17</td>
<td>Right eye</td>
<td>0.8</td>
<td>-15.0/-2.0 × 125</td>
<td>Bilateral myopic fundi; few peripheral pigmentations</td>
<td>Reduced</td>
</tr>
<tr>
<td>Left eye</td>
<td>0.8</td>
<td>-14.5/-2.25 × 180</td>
<td></td>
<td>Reduced</td>
<td>NA</td>
</tr>
<tr>
<td>III:1/M/19</td>
<td>Right eye</td>
<td>0.7</td>
<td>-1.0/-1.25 × 170</td>
<td>Bilateral midperipheral pigmentation</td>
<td>Extinguished</td>
</tr>
<tr>
<td>Left eye</td>
<td>0.5</td>
<td>-2.0/-1.25 × 10</td>
<td></td>
<td>Extinguished</td>
<td>PS, II-4e, 15°</td>
</tr>
<tr>
<td>III:2/F/17</td>
<td>Right eye</td>
<td>0.7</td>
<td>-18.25/0.75 × 50</td>
<td>Bilateral chorioretinal atrophy</td>
<td>Reduced</td>
</tr>
<tr>
<td>Left eye</td>
<td>0.7</td>
<td>-17.25/-1.00 × 160</td>
<td></td>
<td>Reduced</td>
<td>Slightly reduced</td>
</tr>
</tbody>
</table>

Table 1. Summary of Clinical Findings for the Family With X-linked Retinitis Pigmentosa

Abbreviations: BCVA, best-corrected visual acuity; ERG, electroretinography; NA, not available; ND, not determined; PS, paracentral scotoma.

*Best-corrected visual acuity was obtained using a projected Landolt chart.

*With proven mutation.
by silver stain and manual inspection. The pedigree and haplotypes were constructed by Cyrillic software version 2.1 (Cyrillic Software, Oxfordshire, England).

The coding fragments and intron-exon boundaries of RPGR, including exons 1 to 19, exon 15a, and ORF15, were amplified by polymerase chain reactions and sequenced according to the protocols described previously.\textsuperscript{12,15} Nucleotide positions were based on GenBank sequence AF286472. The DNA for 118 normal subjects was screened as described previously.\textsuperscript{14}

Figure 2. Representative fundus photographs and electroretinography (ERG) results of individuals with X-linked retinitis pigmentosa, including the propositus (II:1) (A), the carrier II:3 (B), the patient I:3 (C), and the carrier III:2 (D).
peripheral fundi (thalmologic examinations revealed pigmentation in mid-
hospital for examination when he was aged 18 years. Oph-
did not go to the hospital then. He visited our university
noticed night blindness and blurred vision at age 13 years but
rized in
2 affected males and 2 obligate carriers in the 3-gen-
family were assessed. The clinical data are summa-
Two affected males and 2 obligate carriers in the 3-gen-
tions in exon ORF15 have been reported.17 However, the
macular degeneration. To date, at least 97 different muta-
sponsible for nonsystematic or systematic XLRP, XLCORD,
findings, 4 of the ORF15 mutations identified in families
slight-to-moderate loss of rod function. Consistent with their
implicate the early preferential loss of cone function with
there are
of codon 365) of the highly repetitive region may cause
OF15 mutations identified in families
fected individuals identified a 2-bp deletion at positions 1232
and 1233 (Figure 3) in exon ORF15, which was pre-
duced higher retention of rod function and hence milder RP
phenotypes. Sharon et al10 also proposed a hypothesis that
findings, 4 of the ORF15 mutations identified in families
with ORF15 and with subse-
sequent shorter abnormal amino acid sequences produce higher retention of rod function and hence milder RP
phenotypes. Sharon et al10 also proposed a hypothesis that
mutations downstream of codon 445 in ORF15 strongly
implicate the early preferential loss of cone function with
sight-to-moderate loss of rod function. Consistent with their
findings, 4 of the ORF15 mutations identified in families
with XLCORD or X-linked cone dystrophy were located
end of the ORF15 highly repetitive stretch, Zhang et al18
referred to a frameshift mutation in which Gly411 is the first amino acid
altered and the termination of the ORF is at residue 492. The mutation was cosegregated with affected individuals
in the family and was not observed in any of the unaf-
fected family members or the group of normal controls.

**GENOTYPING AND MUTATIONAL ANALYSIS**

Haplotyping analysis showed that the affected individuals in the
family shared a common haplotype with 5 markers (Figure 1). Direct polymerase chain reaction sequencing of af-
fected individuals identified a 2-bp deletion at positions 1232
and 1233 (Figure 3) in exon ORF15, which was pre-
dicted to create an early termination at position 492
(Gly411fsTer492). The ORF15Gly411fsTer492 refers to a
frameshift mutation in which Gly411 is the first amino acid
altered and the termination of the ORF is at residue 492. The mutation was cosegregated with affected individuals
in the family and was not observed in any of the unaf-
fected family members or the group of normal controls.

**RESULTS**

**CLINICAL EVALUATIONS**

Two affected males and 2 obligate carriers in the 3-gen-
eration family were assessed. The clinical data are summa-
rized in **Table 1**.

The propositus’s (III:1) was an 18-year-old man. He no-
ticed night blindness and blurred vision at age 13 years but
did not go to the hospital then. He visited our university
hospital for examination when he was aged 18 years. Oph-
thalmologic examinations revealed pigmentation in mid-
peripheral fundi (Figure 2A). On his most recent visit
(when he was aged 19 years), Goldmann perimetry showed
peripheral scotoma (isopter II-4e and III-4e) and depres-
sion of threshold values (isopter II-4e, 15°; III-4e, 30°; and
V-4e, 45°). Both maximum-flash ERG and 30-Hz flicker
ERG showed extinguished responses (Figure 2A). The pro-
positus’s mother (II:3), a heterozygous woman aged 39
years, did not have night blindness. She had high myopia
with best-corrected visual acuity of 0.8 OU, and the fun-
dus examination showed chorioretinal thinning, myopic
optic discs, and peripapillary atrophy, which were consis-
tent with high myopia. Few spicule formations were ob-
served in the peripheral fundi (Figure 2B). The ERG showed
a reduced response (Figure 2B). The propositus’s grand-
father (I:3), aged 66 years, had night blindness and severe
myopia from childhood. Phacnectomy was performed on one
of his eyes at age 18 years and on the other eye at age 66
years because of high myopia. He had very poor visual acu-
ty and severe myopic fundi with extensive chorioretinal
atrophy as well as midperipheral pigmentation (Figure 2C).
The ERG showed a distinguished response (Figure 2C).
Goldmann perimetry results were unrecordable because of
the low vision. The propositus’s younger sister (III:2) no-
ticed night blindness at age 17 years. Fundus examination
showed bilateral chorioretinal atrophy that was consis-
tent with high myopia (Figure 2D). The ERG showed a
severely reduced response (Figure 2D) and the visual field
was slightly reduced. The propositus’s father and young-
est sister had no symptoms or signs of RP, and their ERG
and Goldmann perimetry results were normal.

**COMMENT**

**RPGR** accounts for up to 20% of all cases of RP,16 which is
higher than any other RP locus. Mutations of **RPGR** are
responsible for nonsystematic or systematic XLRP, XLCORD,
X-linked cone dystrophy, and X-linked recessive atrophic
macular degeneration. To date, at least 97 different muta-
tions in exon ORF15 have been reported.17 However, the
precise role of ORF15 is still unclear. Studying the genotype-
phenotype correlation can elucidate the expressivity and
penetration of the phenotype in the patient with a specific
mutation in **RPGR**. By evaluating 2 different dog strains with
mutations in different locations of ORF15, Zhang et al18
found that mutations toward the 3’ end of ORF15 and with
subsequent shorter abnormal amino acid sequences pro-
duce higher retention of rod function and hence milder RP
phenotypes. Sharon et al10 also proposed a hypothesis that
mutations downstream of codon 445 in ORF15 strongly
implicate the early preferential loss of cone function with
sight-to-moderate loss of rod function. Consistent with their
findings, 4 of the ORF15 mutations identified in families
with XLCORD or X-linked cone dystrophy were located
downstream of codon 445 of ORF15. Zhang et al18
found that mutations toward the 3’ end of ORF15 and with
subsequent shorter abnormal amino acid sequences pro-
duce higher retention of rod function and hence milder RP
phenotypes. Sharon et al10 also proposed a hypothesis that
mutations downstream of codon 445 in ORF15 strongly
implicate the early preferential loss of cone function with
sight-to-moderate loss of rod function. Consistent with their
findings, 4 of the ORF15 mutations identified in families
with XLCORD or X-linked cone dystrophy were located
downstream of codon 445 of ORF15.5,7,10 A recent study
reported 2 nonsense mutations (codons 365 and 392) lo-
dated in the 3’ end of the ORF15 highly repetitive stretch,
indicating that mutations toward the 3’ end (downstream
codon 365) of the highly repetitive region may cause
cone-predominant dysfunction.9 It is noted that there are
more XLRP mutations in the 3’ end of the highly repeti-

![Figure 3. Sequence chromatograms. The normal alleles (A) were compared with the hemizygous (B) and heterozygous (C) mutations identified in the study. The chromatograms are shown as the reverse sequence. The square indicates the deleted 2 nucleotides.](image-url)
tive stretch of ORF15 than XLCORD mutations, and the region downstream of codon 445 harbors more XLCORD mutations than XLRP mutations. Hypothetically setting codon 365 as a point of demarcation, there were at least 24 mutations downstream of codon 365 that were identified in patients diagnosed with XLRP. Even setting codon 445 as a point of demarcation, 10 different mutations downstream of codon 445 had been reported, and this most 3' end of ORF15 coding sequence was reported in a family with XLRP,22 but the investigators admitted that the patients had cone-rod dystrophy in their records. Most recently, Pelletier et al19 reported the mutation g.ORF15 + 1641_1642delAA closest to the 3' end of ORF15 in a family with XLCORD. Interestingly, the mutation of ORF15 + 1339-1340delAG was detected in 3 families with XLCORD20 as well as in 1 family with XLRP. The remaining 24 mutations, including the mutation identified in our study, were reported in 32 unrelated families with XLRP.5,7,10,11,14,19-22 It is worthwhile to note that, to our knowledge, few detailed phenotypes were documented in these families with XLRP with mutations at the 3' end of the coding sequence of exon ORF15.11

The detailed phenotypes of the family in our study are consistent with XLRP. The affected males had night blindness at early ages and experienced progressive deterioration in central vision with no apparent macular degeneration in their fundi. The 2 male patients had typical RP symptoms and extinguished ERG responses (on both max-

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Protein Change</th>
<th>Diagnosis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>g.ORF15 + 1094A-&gt;C/1095T-&gt;G</td>
<td>ORF15Glu364Asp/Glu365Ter</td>
<td>XLCORD</td>
<td>Ebenezer et al.6 (2005)</td>
</tr>
<tr>
<td>g.ORF15 + 1098_1101delGAGG</td>
<td>ORF15Glu366Ter/503</td>
<td>XLRP</td>
<td>Sharon et al.6 (2003)</td>
</tr>
<tr>
<td>g.ORF15 + 1113delG</td>
<td>ORF15Glu371Ter503</td>
<td>XLRP</td>
<td>Ayyagari et al.6 (2006)</td>
</tr>
<tr>
<td>g.ORF15 + 1114delG</td>
<td>ORF15Glu371Ter503</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1140delG</td>
<td>ORF15Glu380Ter503</td>
<td>XLRP</td>
<td>García-Hoyos et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1146 G&gt;T</td>
<td>ORF15Glu385Ter</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1171_1190dup20</td>
<td>ORF15Glu397Ter503</td>
<td>XLRP</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
<tr>
<td>g.ORF15 + 1176 G&gt;T</td>
<td>ORF15Glu392Ter</td>
<td>XLCORD</td>
<td>Ebenezer et al.6 (2005)</td>
</tr>
<tr>
<td>g.ORF15 + 1178_1179ins [AAAGG + 1155_1178dup24]</td>
<td>ORF15Glu393Ter503</td>
<td>XLRP</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
<tr>
<td>g.ORF15 + 1184_1187delGGG</td>
<td>ORF15Glu413Ter492</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1211_1212delGG</td>
<td>ORF15Glu411fsTer492</td>
<td>XLRP</td>
<td>Our study</td>
</tr>
<tr>
<td>g.ORF15 + 1231_1232delGG</td>
<td>ORF15Glu411fsTer492</td>
<td>XLRP</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
<tr>
<td>g.ORF15 + 1242_1245delGG</td>
<td>ORF15Glu414fsTer492</td>
<td>XLRP</td>
<td>Breuer et al.9 (2002)</td>
</tr>
<tr>
<td>g.ORF15 + 1254_1255delGG</td>
<td>ORF15Glu418fsTer492</td>
<td>XLRP</td>
<td>Bader et al.14 (2003)</td>
</tr>
<tr>
<td>g.ORF15 + 1254_1257delGGG</td>
<td>ORF15Glu418fsTer503</td>
<td>XLRP</td>
<td>Sharon et al.6 (2003)</td>
</tr>
<tr>
<td>g.ORF15 + 1258_1259delAG</td>
<td>ORF15Glu419fsTer503</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
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<tr>
<td>g.ORF15 + 1274_1275delGG</td>
<td>ORF15Glu425fsTer503</td>
<td>XLRP</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
<tr>
<td>g.ORF15 + 1279_1280delAG</td>
<td>ORF15Glu425fsTer503</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1339delA</td>
<td>ORF15Glu446fsTer503</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1339_1340delAG</td>
<td>ORF15Glu446fsTer503</td>
<td>XLRP</td>
<td>Breuer et al.9 (2002)</td>
</tr>
<tr>
<td>g.ORF15 + 1343_1344delGGG</td>
<td>ORF15Glu447fsTer493</td>
<td>XLCORD</td>
<td>Demirci et al.9 (2002)</td>
</tr>
<tr>
<td>g.ORF15 + 1344delG</td>
<td>ORF15Glu448fsTer503</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1422_1423delAG</td>
<td>ORF15Glu475fsTer492</td>
<td>XLRP</td>
<td>García-Hoyos et al.10 (2006)</td>
</tr>
<tr>
<td>g.ORF15 + 1458G&gt;T</td>
<td>ORF15Glu486Ter</td>
<td>XLRP</td>
<td>Sharon et al.6 (2003)</td>
</tr>
<tr>
<td>g.ORF15 + 1479G&gt;T</td>
<td>ORF15Glu493Ter</td>
<td>XLRP</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
<tr>
<td>g.ORF15 + 1564_1565delA</td>
<td>ORF15Glu521fsTer524</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1563_1566delAGG</td>
<td>ORF15Glu521fsTer545</td>
<td>XLRP</td>
<td>Vervoort et al.9 (2000)</td>
</tr>
<tr>
<td>g.ORF15 + 1641_1642delAA</td>
<td>ORF15Glu547Ter557</td>
<td>XLCORD</td>
<td>Pelletier et al.9 (2007)</td>
</tr>
</tbody>
</table>

Abbreviations: XLCORD, X-linked cone-rod dystrophy; XLRAMD, X-linked recessive atrophic macular degeneration; XLRP, X-linked retinitis pigmentosa.

a Indicates the newly identified mutation in our study.
b Indicates the only mutation that has been reported in families with XLRP and XLCORD.
c Indicates the family with suspected XLCORD, although the investigators claimed in their article that the family had XLRP.
Because the numbers of families with XLCORD or X-contrast to the previous hypothesis proposed by Sharon et al.10 tion have both rod and cone dysfunctions, which is in con- trast in individual III:2 (the data for II:3 were not available). It appears that the patients and carriers with this mutation have both rod and cone dysfunctions, which is in con- trast to the previous hypothesis proposed by Sharon et al.10 Because the numbers of families with XLCORD or X-contrast to the previous hypothesis proposed by Sharon et al.10 tion have both rod and cone dysfunctions, which is in con- trast in individual III:2 (the data for II:3 were not available). It appears that the patients and carriers with this mutation have both rod and cone dysfunctions, which is in con- trast to the previous hypothesis proposed by Sharon et al.10

Because some cases of cone-rod dystrophy may have only minor macular retinal pigment epithelium atrophy without typical bull’s-eye maculopathy and may show both cone and rod involvements in ERGs, which also appear in some RP cases (especially in XLRP with rapid deterioration and severe degeneration of both rods and cones), the similarity in symptoms leads to an indecisive diagnosis. More def- inite clinical diagnosis and classification are necessary for a differential diagnosis of XLCORD and for elucidating the role of ORF15 in cone and rod involvements. We have identified a novel mutation in a family with XLRP and have documented the clinical manifestations. The clinical findings are consistent with previous reports of XLRP phenotypes associated with mutations in RPGR, leading us to speculate that the mutation 3’ toward the highly repetitive stretch of ORF15 or in the 3’ end of the ORF15 coding sequence may be the cause of XLRP as well as XLCORD, and the mutation in the 3’ end of ORF15 can lead to a spectrum of phenotypes. Our findings are consis- tent with the previous studies listed in Table 2 that have suggested the tendency of XLRP mutations to cluster in the highly repetitive region and support the observation that RPGR exon ORF15 mutations (including those that are located at the 3’ end of the exon ORF15 coding se- quence) can cause different phenotypes. The summa- rized ORF15 mutations downstream from codon 365 (Table 2) also clearly suggest that the cone-predominant phenotype-related mutations can be located irregularly in the exon ORF15 coding sequence, and the number of fami- lies is not sufficient for a meaningful conclusion given the rare occurrence of this phenotype. The detailed pheno- types of patients with the mutation close to the 3’ end of the ORF15 coding sequence may be helpful in compar- ing the XLRP with the increasing XLCORD caused by ORF15 mutations and in establishing the significance of the mutation distribution and genotype-phenotype cor- relation. Further studies exploring the correspondence be- tween mutations and phenotypes are required to gain in- site into the pathogenesis of XLRP and XLCORD.

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5. Bader I, Brandau O, Achatz H, et al. X-linked retinitis pigmentosa: mutations in the XLRP with the increasing XLCORD caused by ORF15 mutations downstream from codon 365 (Table 2) also clearly suggest that the cone-predominant phenotype-related mutations can be located irregularly in the exon ORF15 coding sequence, and the number of fami- lies is not sufficient for a meaningful conclusion given the rare occurrence of this phenotype. The detailed pheno- types of patients with the mutation close to the 3’ end of the ORF15 coding sequence may be helpful in compar- ing the XLRP with the increasing XLCORD caused by ORF15 mutations and in establishing the significance of the mutation distribution and genotype-phenotype cor- relation. Further studies exploring the correspondence be- tween mutations and phenotypes are required to gain in- site into the pathogenesis of XLRP and XLCORD.

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5. Bader I, Brandau O, Achatz H, et al. X-linked retinitis pigmentosa: mutations in the XLRP with the increasing XLCORD caused by ORF15 mutations downstream from codon 365 (Table 2) also clearly suggest that the cone-predominant phenotype-related mutations can be located irregularly in the exon ORF15 coding sequence, and the number of fami- lies is not sufficient for a meaningful conclusion given the rare occurrence of this phenotype. The detailed pheno- types of patients with the mutation close to the 3’ end of the ORF15 coding sequence may be helpful in compar- ing the XLRP with the increasing XLCORD caused by ORF15 mutations and in establishing the significance of the mutation distribution and genotype-phenotype cor- relation. Further studies exploring the correspondence be- tween mutations and phenotypes are required to gain in- site into the pathogenesis of XLRP and XLCORD.

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