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Histopathologic Study of X-linked Cone-rod Dystrophy (CORDX1) Caused by a Mutation in the *RPGR* Exon ORF15

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PURPOSE: To evaluate the donor retina of a patient with X-linked cone-rod dystrophy caused by an *RPGR* exon ORF15 mutation.

DESIGN: Histopathologic study of the retina.

METHODS: The eye of a 69-year-old man was fixed at 1.6 hours *postmortem* and processed for histopathology and immunocytochemistry.

RESULTS: Grossly, the macula was atrophic with a bull's-eye appearance. The remaining retina showed *postmortem* edema but no intraretinal pigment. Microscopically,

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the macular retinal pigment epithelium was absent focally and had pigmentary changes elsewhere. Cones and rods were absent from the perifovea and reduced with shortened outer segments elsewhere in the macula. In the remainder of the retina, cones but not rods were reduced and all photoreceptor outer segments were shortened.

CONCLUSIONS: The abnormalities in both cone and rod photoreceptors confirm the importance of *RPGR* in both cell types but leaves unresolved how various exon ORF15 mutations lead to different clinical phenotypes. (*Am J Ophthalmol* 2005;139:386–388. © 2005 by Elsevier Inc. All rights reserved.)

X-LINKED (XL) CONE-ROD DYSTROPHY (CRD) IS A RARE disease primarily affecting the cone photoreceptors with variable degrees of rod involvement. Affected males experience decreased visual acuities (VA), photophobia, abnormal color vision, full peripheral visual fields, decreased or absent photopic electroretinographic responses and macular retinal pigment epithelium disturbances and atrophy. We previously demonstrated that mutations in exon ORF15 of *RPGR* (retinitis pigmentosa GTPase regulator) are responsible for CORDX1 (formerly COD1) type XL CRD.¹ *RPGR* mutations also cause XL retinitis pigmentosa (RP3) and XL atrophic macular degeneration.^{2,3}

One of our XL CRD families demonstrated 1-nucleotide insertion mutation in exon ORF15 (1564_1565insA; seems to be the most 3' end point mutation published to date).¹ We evaluated the retinal histopathology of an affected 69-year-old family member who had been diagnosed in his 40s based on the following findings in both eyes: decreased VA (20/25), macular depigmentation and granular fine pigment deposits with absent foveal reflex, relative constriction of central VF with full peripheral fields, color vision abnormalities, slightly above normal dark adaptation thresholds, and reduction of cone and rod ERG responses (cone > rod). His younger brother was diagnosed with "heredomacular degeneration" at age 10. Our patient had decreased color discrimination, prolonged dark adaptation, reduced ERG responses, and VA deterioration 3 years before our evaluation at age 67. His fundi (Figure 1) showed bilateral peripapillary atrophy, perifoveal rings of depigmentation, patches of irregular macular retinal pigment epithelium, and fine hard extramacular drusen (best-corrected VA: 20/60 OU).

Two years later, the patient died, and his eyes were obtained through the Foundation Fighting Blindness (FFB #482) and the Eye Bank of Western Pennsylvania. One eye was fixed at 1.6 hours *postmortem* in 4% paraformaldehyde/0.5% glutaraldehyde in phosphate buffer, pH 7.4, and processed for histopathology and immunocytochemistry.⁴ Grossly (Figure 1), the macula was atrophic with a bull's-eye appearance. The remaining retina showed *postmortem* edema but no intraretinal pigment. Microscopically (Figure 2), the retinal pigment epithelium was absent focally in the macula and retained retinal pigment epithelium cells were hypo- or hyperpigmented. Cones and rods were absent in the perifovea



FIGURE 1. (Top) Fundus photographs of the male donor at age 67 show peripapillary atrophy and central ring of depigmentation around the fovea in both eyes. (Bottom) Gross pathology: The optic nerve head is pale with peripapillary atrophy. The macula is atrophic with a bull's-eye appearance. The remaining retina shows *postmortem* edema but no intraretinal pigment.

and reduced with shortened outer segments elsewhere in the macula. Neurons in the macular inner nuclear and ganglion cell layers were also decreased. The remaining retina showed some cone loss but near normal numbers of rods. All photoreceptors had shortened outer segments.

The histopathologic abnormalities in both cones and rods confirm the importance of *RPGR* in both cell types but leaves unresolved how various exon ORF15 mutations lead to different phenotypes. All *CORDX1*-related mutations that we identified¹ are in the 3' end coding region of exon ORF15, a finding also supported by subsequent studies.^{5,6} Recently, a late-onset CRD similar to this donor's phenotype was reported in a South African family with an exon ORF15 mutation at a similar position (1563_1566delAAGT).⁶ The only other histopathologic report of an exon ORF15 mutation (631delA) described a female RP3 carrier with patches of rod and cone pathology.⁴ Further studies will be necessary to determine the role of exon ORF15 in functions and survival of cone and rod photoreceptors.

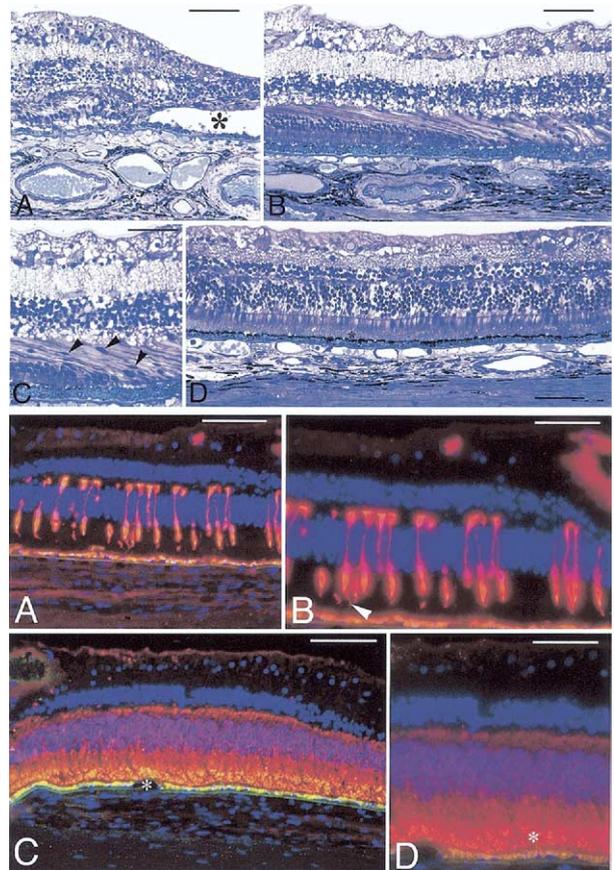


FIGURE 2. (Top Panel) Histopathology (bars = 100 μm in A, B, and D; 50 μm in C): Samples of the macula and peripheral retina were processed in JB4 plastic, sectioned at 2 μm thickness, and stained with Richardson's mixture of methylene blue and azure II. (A) Perifoveal cones are missing, and the foveal pit contains a large cyst (*). (B) Cones in the extrafoveal macula are reduced in number and have short outer segments. (C) At higher magnification, some degenerate macular cones have dense cytoplasm (arrowheads). (D) In the periphery, the rod and cone outer segments (*) are short and ganglion cells are sparse. (Bottom panel) Immunocytochemistry (bars = 100 μm in A and C; 50 μm in B and D): Samples of the central and peripheral retina were processed as 10- μm cryosections for immunocytochemistry. The primary antibodies were cone-specific mAb 7G6 anti-arrestin (from Dr. P. MacLeish) and anti-rod opsin mAb 4D2 (from Dr. R. Molday). Secondary antibodies were labeled with Cy3 (red) and cell nuclei were stained blue with DAPI. (A) The retinal pigment epithelium across the bottom of the panels contains autofluorescent (yellow-gold) lipofuscin granules. Labeling of the retina with mAb 7G6 reveals loss of regular cone spacing attributable to cell death. (B) A higher magnification of mAb 7G6-labeled cones reveals that the remaining cones have short outer segments (arrowhead). (C) Labeling with mAb 4D2 reveals that the visual pigment is abnormally delocalized to the rod somata and synapses. The number of rods is near normal. Note small druse (*). (D) A higher magnification of mAb 4D2-labeled rods reveals shortening of their outer segments.

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