Retinal transplantation, stem cell therapy, gene editing, systemic medications, and vitamin supplements are all areas of active research. Understanding the full complement of pathways that can lead to the pathogenesis of RP is important to developing potential therapeutic strategies. Mutations in more than 60 genes have been linked to nonsyndromic RP, 35 of which cause recessive disease. Causative genetic mutations usually fall into a few categories of rod photoreceptor function, such as phototransduction, outer segment (ciliary) protein trafficking, disk formation and stabilization, ATP production, lipid metabolism, and the visual cycle. Because rod photoreceptors depend on RPE cells to regenerate photopigment as part of the visual cycle, as well as for rod outer segment phagocytosis, mutations inhibiting either of these two RPE functions account for some cases of RP.

In an effort to discover novel mutations causing eye disease, systematic ophthalmic screening was performed on every mouse line as part of the Knockout Mouse Production and Phenotyping (KOMP2) Project in the International Mouse Phenotyping Consortium conducted at the University of...
Californian (U.C.) Davis Mouse Biology Program. Mice deficient in Arap1 were generated using embryonic stem cells with a homozygous knockout of this gene from the European Conditional Mouse Mutagenesis Program. Retinal abnormalities were identified during comprehensive ophthalmic screening, and detailed investigation revealed that Arap1−/− mice undergo a progressive retinal degeneration similar to RP in humans. The fundus of these animals developed pigmented changes, retinal vascular attenuation, optic nerve pallor, and outer retinal thinning reminiscent of the analogous disease in humans. The retina developed all neuronal cell types with appropriate lamination and morphology, and began to degenerate in young adulthood, similar to the onset of disease in typical recessive human cases of RP. Most cell death is limited to the photoreceptor layer, and ERG amplitudes are correspondingly reduced.

The function of Arap1 in the retina is unclear. In general, small guanosine triphosphatase (GTPase) ADP-ribosylation factors (Arfs) regulate membrane traffic and actin reorganization under the control of GTPase-activating proteins (GAPs). Arap1 is an Arf-directed GAP that inhibits the progression of epidermal growth factor receptor (EGFR) to the early endosome, but the diversity of its functions is poorly understood. Arap1 has multiple pleckstrin homology (PH) domains that recognize phosphatidylinositol 3,4,5-trisphosphate. It can be located near the Golgi apparatus or at the plasma membrane in certain cell types, and has been shown to regulate members of the Arf and Rho small GTPase protein families in vitro. Whether Arap1 regulates cellular processes in the retina through one or more of the above mechanisms, and/or via other molecular partners remains to be determined.

Methods
This study was conducted according to a protocol that was approved by the Institutional Animal Care and Use Committee at U.C. Davis and was compliant with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Animals
Mice were generated by the U.C. Davis Mouse Biology Program using embryonic stem cells with a homozygous knockout of Arap1 obtained from the European Conditional Mouse Mutagenesis Program by the KOMP2 Project as part of the International Mouse Phenotyping Consortium. A targeting cassette with a LacZ insert was used to knock out exon 9 of the Arap1 gene. This causes a frameshift in every protein-coding transcript of the gene, making residual transcript subject to nonsense mediated decay. Heterozygous Arap1+/− mice were generated on a C57BL/6N background, and intercrossed to establish homozygous male and female cohorts for the retina degeneration, animals were euthanized by isoflurane inhalation followed by cervical dislocation.

Indirect Ophthalmoscopy
Mice were screened by a veterinary ophthalmologist (B.C.L.) at 16 weeks postnatal age with a handheld 60-diopter lens. Seven male and seven female homozygous Arap1 knockout mice and two male and two female wild-type littermates were evaluated in a blinded fashion. All animals that were part of the original screening process were on the C57BL/6N background.

Electroretinography
Mice were dark-adapted overnight and anesthetized with an intraperitoneal injection of a ketamine/dexametomidine (50–75/0.25–0.5 mg/kg) cocktail. Eyes were dilated with 1% tropicamide (Bausch + Lomb, Rochester, NY, USA) and 2.5% phenylephrine hydrochloride (Paragon, Portland, OR, USA). 2.5% hypromellose (OcuSOFT, Rosenberg, TX, USA) and GenTeal Gel (Novartis, Sacramento, CA, USA) were used as eye lubricant. Full-field ERG was used to test scotopic retinal function (white flashes of 0.001, 0.01, 0.1, 1.0, 2.5, and 10.0 cd/s/m²) and, after 10 minutes of light adaptation (30 cd/m²), photopic retinal function (white flashes of 0.1, 0.4, 1.0, 2.5, and 10.0 cd/s/m²). Stimuli were generated by a Ganzfeld stimulator (UTAS Visual Diagnostic System with BigShot LED; LKC Technologies, Gaithersburg, MD, USA). Responses were referenced and grounded to needle electrodes between the ears and the lower back, respectively. Dexmedetomidine was reversed with atipamezole (0.25–0.5 mg/kg). B-wave amplitudes were measured from the trough of the a-wave to the peak of the third oscillatory potential past the resting potential.

Fundus Photography and Optical Coherence Tomography
Mice were anesthetized with an intraperitoneal injection of a ketamine/midazolam (50–75/1–2 mg/kg) cocktail. Eyes were dilated with tropicamide 1% and phenylephrine 2.5% drops, and lubricated with methylcellulose. Fundus photographs were taken with the Micron III (Phoenix Research Laboratories, Pleasanton, CA, USA), and spectral-domain optical coherence tomography (OCT) images were taken with the Envisu R2200 (Bioptigen, Morrisville, NC, USA) at 14 to 18 weeks postnatal age.

Immunohistochemistry and X-Gal Staining
Eyes were enucleated and then fixed in 4% paraformaldehyde for 20 minutes at room temperature. Cornea and lens were removed; eyecups were then cryoprotected in a 10%–20%–30% sucrose gradient (4°C) for at least 1 hour at each concentration. Eyecups were embedded in optimum cutting temperature medium (Thermo Fisher Scientific, Waltham, MA, USA), frozen in dry ice and 2-methylbutane slurry, and sectioned at 10 μm onto Superfrost Plus (Thermo Fisher) slides with a cryostat (LEICA CM3050; Leica, Wetzlar, Hesse, Germany).

For immunohistochemistry, slides were washed with 1× PBS (10 mM phosphate, 137 mM NaCl, 2.7 mM KCl), sections were circled with a PAP pen (Ted Pella, Redding, CA, USA) and blocked with 1% to 3% BSA in 0.3% Triton X-100 in PBS for 3 hours at room temperature. Sections were incubated in primary antibody overnight (4°C), washed in PBS, and then, for immunohistochemistry, slides were washed with 1× PBS and secondary antibody.
incubated with the matching secondary antibody for 2 hours at room temperature, washed in PBS, and then coverslipped with FluorSave (Calbiochem, Temecula, CA, USA) and imaged.

For colabeling experiments, eyes were enucleated and rapidly frozen by immersion in dry ice-cooled liquid propane for 30 seconds, and transferred to glass vials containing 97% methanol and 3% acetic acid (M-AA) held at dry ice temperatures. The glass vial with the eyes was placed at −80°C for 48 hours. After 48 hours, the vial was warmed stepwise by 4-hour stops at −40°C and −20°C, and then at room temperature for 48 hours. After 48 hours at room temperature, the M-AA was replaced with three changes of 100% xylene, then three 45-minute changes of acetone, and then air-dried for a total of 18 to 48 hours. After a PBS wash, slides were coverslipped with Vectamount (Vector Laboratories, Burlingame, CA, USA) and imaged.

**Histology**

Eyes were enucleated and immediately oriented in optimum cutting temperature medium and frozen in liquid nitrogen. Cryosections were prepared as described above. Sections were all imaged using a Nikon (Melville, NY, USA) Eclipse E800 microscope with an X-Cite (Waltham, MA, USA) 120–light-emitting diode fluorescence source and Q Capture Pro 7 software (Surrey, BC, Canada).

**Statistical Analysis**

For all quantification, at least three animals (n = 5) were imaged for each genotype and each age. Images were obtained from at least three sections for each animal, and measurements for each animal were combined to determine the average measurement for each animal. These values were then averaged with the other animals in each group. Pairwise analyses were done using the Student’s t-test; P values of 0.05 or less were considered statistically significant.

**Imaging**

Immunohistochemistry, X-gal staining, and histology slides were all imaged using a Nikon (Melville, NY, USA) Eclipse E800 microscope with an X-Cite (Waltham, MA, USA) 120–light-emitting diode fluorescence source and Q Capture Pro 7 software (Surrey, BC, Canada).

**Results**

**Arap1**⁻⁻ Mice Undergo Degeneration of the Outer Nuclear Layer

Veterinary ophthalmology team members examined animals at 16 weeks postnatal age as part of the KOMP2 project conducted by the U.C. Davis Mouse Biology Program by indirect ophthalmoscopy with the aid of a handheld 60-diopter lens (Fig. 1A). The phenotyping examiner (BCL) was presented 18 animals at the same time in a blinded fashion. These
consistent of seven male and seven female homozygous knockout animals, and two male and two female wild-type littermates. The retinal degeneration phenotype identified by fundoscopy segregated with animal genotype. The original histology was performed by U.C. Davis veterinary pathologists. They reported thinning and dysplasia of the photoreceptor layer of the retina of Arap1-/- animals (Fig. 1) when compared with wild-type animals (Fig. 1C). The original knockout mice (Fig. 1) were generated on a C57BL/6N background bearing the rd8 mutation. To better study the role of Arap1 in the retina, Arap1-/- animals were crossed with wild-type C57BL/6 mice and then heterozygous intercrossed to establish a homozygous colony free from the confounding rd8 mutation common in the 6N strain. All subsequent figures show data independent of rd8.

The fundus appearance of adult Arap1-/- mice showed changes typical of mouse models of RP. By age 14 weeks, the fundus exhibited optic nerve pallor, attenuated retinal arteries, retinal pigmentary changes, and focal areas of RPE atrophy (Fig. 2A). These features were not present in wild-type littermates (Fig. 2B). Consistent with the histopathology, the OCT performed on these eyes showed profound thinning of the outer retina with relative preservation of the inner retina in Arap1-/- mice (Fig. 2C) in comparison with the OCT of wild-type littermates (Fig. 2D). Manual segmentation quantifying the retinal thickness of OCT layers (E) from animals 14 to 18 weeks postnatal age confirmed the thinning is in the ONL (n = 3 each group, *P < 0.05, error bars represent SE).

Arap1 Is Not Required for Retinal Histogenesis

To distinguish if Arap1-/- mice fail to generate appropriate numbers of photoreceptors, or if they have normal retinal histogenesis followed by photoreceptor degeneration, animals were killed just after retinal development ended, and eyes were taken for more detailed histologic analysis. Arap1-/- retinas at 2 weeks postnatal were sectioned and stained with hematoxylin and eosin, which demonstrated similar retinal lamination and thickness when compared with wild-type controls (Figs. 3A, 3E). However, when animals were examined at 4, 6, and 8 weeks postnatal, the outer nuclear layer of Arap1-/- mice had progressively degenerated (Figs. 3B–D), whereas control retinas had not (Figs. 3E–H). Quantification of the retinal lamination between Arap1-/- and wild-type controls demonstrated no significant difference between any of the layers of the retina at 2 weeks postnatal age (Supplementary Figs. S1A–G). However, at postnatal weeks 4, 6, and 8, we measured a progressive thinning of the outer nuclear layer in Arap1-/- mice (Supplementary Fig. S1E). By 8 weeks postnatal, we observed some thinning of the retinal ganglion cell layer, inner nuclear layer, and outer plexiform layer (Supplementary Figs. S1A, S1C, S1D, respectively), which may be secondary to the primary photoreceptor degeneration. The thickness of the photoreceptor inner/outer segments was consistently less in Arap1-/- mice at all ages examined (Supplementary Fig. S1F).

To test if various retinal cell types are generated appropriately in the Arap1-deficient retina, retinal sections from 2 weeks postnatal mice were stained for retinal ganglion cells and amacrine cells using antibodies against the transcription factor Pax6. Arap1-/- retinal sections marked for Pax6 (Fig. 4A) demonstrated that these cell types were generated in similar density and pattern as wild-type control retinas (Fig. 4B). The staining pattern of Pax6-positive cells remained similar between knockout and control mice at 8 weeks postnatal age.
suggesting no obvious loss of these inner retinal cell types. Bipolar neurons and photoreceptors were stained using the marker Otx2. At 2 weeks postnatal, the number and location of these cell types appeared grossly indistinguishable between Arap1+/C0/C0 (Fig. 4E) and wild-type mice (Fig. 4F). However, by 8 weeks postnatal age, the Otx2-positive photoreceptor layer had markedly thinned in Arap1+/C0/C0 mice (Fig. 4G) when compared with wild-type mice at the same age (Fig. 4H).

**Arap1 Is Expressed in the Retina and Is Required for Photoreceptor Survival**

Taking advantage of the LacZ cassette knocked into the Arap1 locus and under the control of its promoter, a histochemical reaction was performed to determine the expression pattern of Arap1 in the retina. Blue signal from the X-gal reagent was seen in the retinal ganglion cell layer, inner nuclear, and in the outer nuclear layer at 4 weeks postnatal age in Arap1+/C0/C0 (Fig. 5A) and Arap1+/C0/C0 mice (Fig. 5B). Surprisingly, few cells in the outer nuclear layer expressed LacZ. Similarly, only a few cells in the RPE layer showed a positive signal. The reagent did not give a signal in control retina at the same age (Fig. 5C).

Immunohistochemistry was performed using a primary antibody against β-galactosidase, and the pattern of reactivity was reminiscent of a Müller glial staining pattern. Colabeling experiments confirmed that β-galactosidase immunolabeling coincided with glutamine synthetase signal in Müller cells in Arap1+/C0/C0 (Figs. 5E, 5E', 5E'') and Arap1+/C0/C0 mice (Figs. 5F, 5F', 5F''), but not in wild-type controls (Figs. 5D, 5D', 5D'').

To determine if photoreceptor cells were being lost due to programmed cell death, immunohistochemistry was performed against activated Caspase-3. Retinal sections from mice at 4 weeks postnatal age showed the highest number of immunoreactive cells (Fig. 6A), all of which localized to the outer nuclear layer, and were in a distribution consistent with mainly rod photoreceptor death. Programmed cell death is limited to just the occasional cell in wild-type control retina (Fig. 6B). The vast majority of apoptosis was observed to take place between postnatal day 27 and 33 in Arap1+/C0/C0 mice, and was quantified at 4 weeks postnatal (Fig. 6C). Activated Caspase-3 immunoreactivity was not seen in Arap1+/C0/C0 retina at 2 weeks postnatal, and seemed to decrease to only an occasional cell by 8 weeks postnatal age (data not shown).

We performed ERG on Arap1+/C0/C0 mice to determine if they have decreased retinal activity. We found that Arap1+/C0/C0 mice had reduced amplitudes in scotopic and photopic ERG conditions. Flash-response functions are shown from Arap1+/C0/C0 mice at postnatal day 24 and age-matched controls (Fig. 7A). At this stage, the a-wave and b-wave in both groups are similar in amplitude. At later stages in the degeneration (15–18 weeks), both the a-wave and b-wave amplitudes are consistently reduced in Arap1+/C0/C0 mice (Fig. 7B). The photopic responses were reliable only at the highest stimulus level (10 cd/s/m²). The b-wave amplitude at this stimulus level was relatively
DISCUSSION

The findings in this study demonstrate that Arap1 is required for the survival of photoreceptors in the mouse. The retinal developmental program appears to proceed normally in producing various retinal neurons with appropriate lamination by 2 weeks postnatal age. By postnatal day 27, massive apoptosis is observed in the outer nuclear layer, which proceeds actively through postnatal day 33 before slowing down to a very low level thereafter. Surprisingly, before and after the fifth week of life, which represents the peak of cell death, much less apoptosis is seen. It is possible that the thinning of the outer nuclear layer, which takes place well after the apoptotic markers decline, is in part due to removal of already dead photoreceptors. It is difficult to determine definitively from the ERG data obtained which photoreceptors, rods or cones, are affected primarily. The relative preservation of the photopic b-wave suggests the cones may be less dependent on Arap1 than rods, but more detailed analysis of the apoptotic cells with colabeling experiments will be required to clarify this issue.

In 2002, the laboratory of Paul Randazzo discovered Arf GAP, Rho GAP, Ankyrin repeat, and Pleckstrin homology protein 1 (ARAP1), and it was initially proposed to function at a potential crossing point between Arf- and Rho-GTPase signaling. Arap1 Deficiency Causes Photoreceptor Degeneration. IOVS March 2017 Vol. 58 No. 3 1714
**Arap1** is expressed in Müller glia. LacZ histochemical reaction using X-gal reagent showed faint blue staining in the retinal GCL, INL, and in the ONL (arrows) in the **Arap1**+/− (A) and **Arap1**−/− (B) retina at 4 weeks postnatal age. There was sporadic staining in a few cells in the RPE. Control wild-type littermates showed no staining (C). Immunohistochemistry for β-galactosidase showed no staining in wild-type retina at 6 weeks (D). Glutamine synthetase labeling (D') highlighted Müller cells (red), and the merged image is shown (D''). In 6-week-old **Arap1**+/− (E) and **Arap1**−/− (F) mice, β-galactosidase labeling is seen (green) in a pattern reminiscent of Müller cell staining. Colabeling with glutamine synthetase (**Arap1**+/− in [E']; **Arap1**−/− in [F']) confirms colocalization with β-galactosidase in Müller glia. Merged images are shown for **Arap1**+/− (E'') and **Arap1**−/− (F''). Arrows show filamentous Müller glial processes. Arrowhead shows Müller glial end feet surrounding retinal ganglion cell bodies in the inner retina. Double arrowhead shows staining in the OPL.
reasonable to posit that Arap1 is required for photoreceptor survival by maintaining appropriate levels of EGFR signaling in the retina. Indeed, previous studies have shown that EGF and related ligands can stimulate proliferation of retinal progenitors in vitro.9–13 However, careful analysis of EGFR-deficient mice showed that this receptor is required for only a modest degree of proliferation in late retinal progenitor cells, and no defect in rod photoreceptor development or survival was detected at any stage.14 Given that rod cells develop and survive normally in EGFR−/− mice, we reason that it is unlikely that the in vivo photoreceptor degeneration in Arap1−/− animals is related to dysfunction in EGFR signaling.

We have not detected Arap1 in photoreceptors, although we cannot exclude that it may be expressed at low levels. Although there is no known function of Arap1 in photoreceptors, there is a known function for another Arf GAP of the AZAP family, Asap1, in rod photoreceptors.15 Asap1 acts on Arf4 as its substrate to target rhodopsin to the rod outer segment. Arf4 recognizes the VxPx outer segment localization sequence of rhodopsin, whereas Asap1 binds rhodopsin’s FR localization sequence. Many other small G-proteins (Rab11, Rab8, Rab6), GEFs (Rabin 8, RPGR), Arls, and Arl GAPs (RP2) present in the rod inner segment and participate in transport of rhodopsin to the outer segment through the connecting cilium (see Wang and Deretic16 for review). Asap1 functions as a scaffold for these soluble regulators of rhodopsin transport from the trans-Golgi network to the connecting cilium.17 The presence of two GEFs, Rabin 8 and RPGR, which both can act on Rab8, suggests the need for an exquisitely high level of regulation of rhodopsin trafficking to the outer segment. Therefore, it is plausible that Arap1 represents another Arf GAP, in addition to Asap1, that serves to regulate Arf4. Based on the function of Asap1 in rods, it is tempting to speculate that Arap1 also regulates rhodopsin trafficking. However, as there is no obvious expression in photoreceptors, this implies a cell nonautonomous mechanism for the requirement of Arap1 for photoreceptor homeostasis. Most retinal degenerations are due to mutations in genes expressed in the dying photoreceptors. However, mutations in neighboring cells, such as RPE-specific genes, can be required for photoreceptor survival.18–20 Although some expression by LacZ histochemistry is seen in the RPE, it is difficult to determine the degree of RPE expression in pigmented animals.

**FIGURE 6.** Arap1−/− photoreceptors undergo programmed cell death. Immunohistochemistry using anti-activated Caspase-3 on adult (4 weeks) retinal sections of Arap1−/− animals showed extensive staining in the ONL (A, arrows), indicative of widespread apoptosis in these photoreceptors. Control retinal sections from age-matched animals showed only the occasional apoptotic cell (B). Quantification of cell death at 4 weeks postnatal is shown in (C), with an average of 212.3 labeled cells per ×20 field in Arap1−/− retina, and 1.7 labeled cells in wild-type retina. Arap1−/− and wild-type retinal sections stained at 2 weeks and 8 weeks postnatal showed almost no apoptosis (data not shown) (n = 3 each group. *P < 0.05, error bars represent SE).

**FIGURE 7.** Arap1−/− mice have reduced electrophysiologic function in rod and cone mediated pathways. Electroretinography (A) under dark-adapted conditions in Arap1−/− animals at 24 days’ postnatal age (solid line) show a normal a- and somewhat reduced b-wave in comparison with age-matched wild-type animals (dashed line). At later stages (15–18 weeks postnatal age), the scotopic a- and b-waves are significantly decreased (B) in Arap1−/− animals compared with wild-type animals. The magnitude of the photopic b-wave (C) at the highest stimulus level (10 cd·s/m²) shows somewhat reduced, although not statistically significant, responses in Arap1−/− animals at both 24 days’ and 15 to 18 weeks postnatal age (n = 3 each group, error bars represent SE).
Arap1 is known to regulate the size of circular dorsal ruffles (CDR) in NIH 3T3 cells in vitro, which are believed to facilitate bulk internalization of membranes or macropinosytosis.\textsuperscript{22} Arap1 was found to control CDR size via its Arf GAP function, binding to and activating the GTPase function of Arf1 and Arf5.\textsuperscript{22,23} Arf1 regulates GTPase function of Arf1 and Arf5,\textsuperscript{23} and is essential for phagocytosis.\textsuperscript{24} It is possible that Arap1 expressed in RPE cells regulates the physiologic diurnal phagocytosis of photoreceptor outer segments. Mutations altering the phagocytic function of the RPE resulting in photoreceptor degeneration have been described.\textsuperscript{25} Further assays for the presence of ARAP1 protein and mRNA are necessary, likely on an albino background, to clarify its presence in the RPE.

We have detected β-galactosidase, a surrogate marker for Arap1 expression, in Müller cells. Immunohistochemistry for β-galactosidase shows expression of protein in the same compartment as glutamine synthetase, within the cytoplasm of Müller glia. The LacZ histochemistry with X-gal reagent also shows a pattern consistent with Müller cell cytoplasmic compartments, which are largest at the end feet at the internal limiting membrane, in the inner retina, and at the external limiting membrane at the boundary between the outer nuclear layer and photoreceptor inner and outer segments. Single-cell transcriptome studies of Müller glia support the expression of Arap1 (aka Centd2) in these cells.\textsuperscript{26} Furthermore, next-generation sequencing analysis from mouse and human brain tissues suggest a predominantly glial expression profile of Arap1 in the central nervous system.\textsuperscript{27} It is known that selective depletion of Müller glia leads to rod photoreceptor death,\textsuperscript{28,29} but the mechanism of the dependence of photoreceptors on these cellular neighbors is unknown. Müller glia are involved in glucose metabolism and secrete ATP,\textsuperscript{30} and photoreceptors are highly metabolic cells requiring constant supply of cellular energy.\textsuperscript{31} Müller glia secrete numerous factors that may be required for photoreceptor neuroprotection, including CNTF, bFGF, PEDF, IGF-1, GDNF, VEGF, LIF, NGF, and BDNF.\textsuperscript{32} The structural contribution of Müller glia to retinal architecture may be required for photoreceptor survival, as their processes form the external limiting membrane, a key boundary between photoreceptor nuclei and their inner and outer segments.\textsuperscript{33,34} The ionic environment of the retina is regulated by Müller glia,\textsuperscript{35} and they are involved in vitamin A metabolism. Visual cycle genes are expressed in Müller glia, and it is known they participate in the visual cycle,\textsuperscript{36} and perturbation of their role in regeneration of photopigment may lead to photoreceptor death. Further studies in Müller glia are necessary to determine the mechanisms by which they are required for photoreceptor survival.

The data presented here demonstrate that Arap1 knockout mice undergo photoreceptor degeneration strikingly similar to RP in humans; however, there is no recognized relationship between Arap1 or related genes to humans with rod-cone dystrophies. Disruption of Arap1, and the pathways in which it is related to photoreceptors, is a novel and previously unknown cause of rod-cone dystrophy in mice. ARAP1, and/or its family members, may represent a new genetic locus responsible for a segment of human patients with RP. Although ARAP1 mRNA is found in adult human retina at significant levels,\textsuperscript{37} whole-genome sequencing in RP patients who do not have common disease-causing mutations is required to determine if ARAP1 is clinically relevant in humans. We are not aware of any single gene mutation in Müller glia implicated in photoreceptor disease in humans or other vertebrates. Further studies are necessary to elucidate the role of Arap1 in photoreceptor homeostasis and its clinical relevance to retinal disease.

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