Human Genetics Center, School of Public Health, The Univ. of Texas Health Science Center, Houston, TX; ¹Dept. Ophthalmology, Univ. of Texas Southwestern Medical Center, Dallas, TX; ²Ruiz Dept. of Ophthalmology and Visual Science, The Univ. of Texas Health Science Center, Houston, TX.

**Purpose:** Mutations in the pre-mRNA splicing factor gene PRPF31 are one of the most common causes of autosomal dominant retinitis pigmentosa (adRP), accounting for 5.5-8.7% of cases (Sullivan 2006; Daiger 2014). Here we investigate the relationships between visual acuity (VA), kinetic perimetry and the ellipsoid zone (EZ) width in adRP patients with mutations in PRPF31.

**Methods:** Spectral domain optical coherence tomography (SD-OCT) horizontal line scans through the fovea were obtained for both eyes of eighteen RP patients (range: 10-72 yrs; mean: 43 ± 20 yrs) from 10 families with mutations in PRPF31. The EZ band was delineated and its horizontal width was determined (Hood 2011). Visual acuity (VA) was measured with a computerized version of the electronic Early Treatment Diabetic Retinopathy Study (e-ETDRS). Octopus (isopter III) kinetic perimetry was used to measure visual field diameter. Correlations were examined by Pearson’s correlation tests.

**Results:** The mean EZ width was not significantly different between eyes (mean ± 95% CI: 12.0° ± 5.04 OD; 13.1° ± 4.9 OS). Mean VA was also comparable between eyes 0.38 ± 0.25 logMAR OD; 0.33 ± 0.18 logMAR OS), therefore OD was selected for correlation analysis. EZ width was significantly correlated with VA (r=-0.724, p=0.001) and visual field diameter (r=-0.885, p=0.002). EZ width was also significantly correlated with age (r=-0.458, p=0.001).

**Conclusions:** Previous studies have shown EZ width to be a useful tool to monitor disease progression in adRP, X-linked RP and Usher syndrome IB patients (Birch 2013; Cai, 2014; Sumaroka 2016). Here, we found that EZ width reflects disease severity in that it correlates with age, VA, and visual field diameter. These finding suggest that EZ width or area can be used as a measurement of disease progression in patients with mutations in PRPF31.

**Commercial Relationships:** Kaylie Webb-Jones, None; Martin Klein, None; Sara J. Bowne, None; Lori S. Sullivan, None; Stephen P. Daiger, None; David G. Birch, None

*Support:* Foundation Fighting Blindness, NEI EY09076, NIH EY007142, William Stamps Farish Fund

**Program Number:** 3217 Poster Board Number: B0350

**Program Number:** 3217 Poster Board Number: B0349

**Reversal of Cystoid Macular Edema in Gyrate Atrophy Patients**

Dan Heller¹, Chen Weiner², Iris Nasie¹, Yair Anikster¹, Yuvat Landau¹, Tal Koren¹, Russell Pokroy¹, Adi Abulafia¹, Eran Pras².

¹Department of ophthalmology, Assaf Haroof Medical Center, Rehovot, Israel; ²Matlow’s Ophthalmogenetic laboratory, Assaf Haroof Medical Center, Zerifin, Israel; ³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ⁴Metabolic Diseases Unit, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Tel-Hashomer, Israel.

**Purpose:** Gyrate atrophy (GA) of the choroid and the retina is an autosomal recessive disorder related to mutations in the ornithine-aminotransferase gene (OAT). This study reports the presentation of two families with GA. The aim of this study was to show the effect of low protein diet and pyridoxine treatment on accompanying macular edema.

**Methods:** Two unrelated patients with GA were studied for the effect of low protein diet (≤ 0.8 g/kg/d), and oral administration of pyridoxine (500mg/day) on serum ornithine levels, best corrected visual acuity (BCVA), slit-lamp, OCT, and auto-fluorescence findings. Blood samples for DNA, mRNA and exons of the OAT gene were screened for mutations, and splicing effect when relevant.

**Results:** At presentation both patients manifested typical ophthalmic features of GA including cystoids macular edema (CME). One patient also exhibited optic nerve head astrocytic hamartomas. Following treatment, in patient A, ornithine levels have lessened by 178 μmol/l, BCVA improved from 6/120 in both eyes to 6/30 OD and 6/21 OS. Central macular thickness (CMT) decreased by 270 μm OD and 161 μm OS.

Patient B showed improvement in BCVA from 6/15 to 6/12 OD and from 6/12 to 6/8.5 OS. CMT decreased by 80 μm OD and 47 μm OS. Ornithine levels decreased by 140 μmol/l. In both patients the effect remained for 14 months.

**OAT sequencing identified two known mutations:** OAT c.159delC; p.H53Qfs7*, c.386C>T pThr129ile (patient A, patient B respectively) and a novel splice site mutation, c.900+1 G>A (patient B).

**Conclusions:** We have identified a novel mutation and two formerly described mutations in patients with GA. Of them, one patient comprised an unusual phenotype including bilateral astrocytic hamartomas. We have recognized for the first time, improvement in CME following treatment with low protein intake and pyridoxine supplement. This finding may have significance in the understanding of treatment options for macular edema regardless of underlying etiology.

**Commercial Relationships:** Dan Heller, None; Chen Weiner, None; Iris Nasie, None; Yair Anikster, None; Yuval Landau, None; Tal Koren, None; Russell Pokroy, None; Adi Abulafia, None; Eran Pras, None

*Support:* This study was supported by the Clair and Amedee Maratier Institute for the Study of Blindness and Visual Disorders, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. This work was also supported in part by the Consortium for Mappin Retinal Degeneration Disorders in Israel; funded by the Foundation for Fighting Blindness (FFB) Grant number BR-GE-0214-0639-TECH, and the ‘Lirot’ Association – The Israeli research association for eye health and blindness prevention (http://lirot.org).

**Program Number:** 3218 Poster Board Number: B0351

**Presentation Time:** 11:00 AM–12:45 PM

**Course of visual field changes in retinitis pigmentosa patients followed by Humphrey Field Analyzer 10-2 program**


**Purpose:** Retinitis pigmentosa (RP) is a hereditary retinal disease characterized by a progressive constriction of the visual field due to photoreceptor degeneration. The purpose of this study was to determine the course of visual field constriction in 31 RP patients.

**Methods:** We reviewed the medical records of 263 RP patients who were examined at the Nagoya University Hospital. Of these, 31 eyes of 31 patients (18 men, 13 women; mean age, 44.1±14.8) were...
selected because they had had at least 3 determinations of the visual fields by Humphrey Field Analyzer 10-2 program (HFA 10-2) during the follow-up period. Eyes whose baseline mean deviation (MD) was less than -30.0 dB or more than -5.0 dB were excluded, and eyes with other ocular disorders were excluded. Eyes with fixation loss of more than 20% or false-positive or false-negative errors more than 33% were also excluded. The eye with the better MD at the baseline of each patient was chosen for the statistical analyses. Of the 31 patients, 7 had autosomal dominant RP, 8 had autosomal recessive RP, 1 had X-linked RP, and 15 were diagnosed as simplex RP. A linear mixed model was used to follow the changes in the MD measurements. We determined whether the age, sex, and mode of inheritance affected the rate of progression of the MD.

**Results:** The average follow-up time was 4.3±2.3 years, and the average frequency of the visual field tests was 4.84±3.47. The mean progression rate of the MD was -0.460 dB/year (SEM=0.115, P=0.0005). The age and sex did not affect the progression rate. The progression of visual field loss was not affected by the pattern of inheritance.

**Conclusions:** HFA 10-2 demonstrated the progressive nature of RP, and the mean MD progression rate was calculated with the use of mixed linear regression. Our findings and methods can be useful in counseling RP patients.

**Commercial Relationships:** Akira Sayo, None; Shinji Ueno, None; Ayami Nakanishi, None; Taro Kominami, None; Masashi Okado, None; Hiroko Terasaki, None

**Program Number:** 3219, Poster Board Number: B0352
**Presentation Time:** 11:00 AM–12:45 PM
**Clinical Characteristics of a Large Cohort of Patients with Retinitis Pigmentosa due to Biallelic FAM161A Mutations**


**Purpose:** FAM161A mutations are currently the most common cause of autosomal recessive RP in the Israeli population, while they seem to be rare elsewhere. In the present study we explored the clinical phenotype of patients harboring FAM161A mutations in order to provide information on the spectrum of disease associated with this gene.

**Methods:** Data was collected retrospectively from the medical records of 85 patients harboring biallelic FAM161A mutation/s, the majority being two founder mutations common in the Jewish population. Clinical information included best-corrected visual acuity (BCVA), refractive error, clinical ocular exam by slit lamp biomicroscopy, full-field electroretinography (FFERG), Goldmann visual fields, ocular coherence tomography (OCT), color, infrared and fundus autofluorescence (FAF) imaging.

**Results:** The most frequent initial symptom was night blindness. BCVA was largely preserved in most patients through the first three decades of life, and often severely deteriorated by the 6th decade. Ophthalmoscopy revealed classic signs of RP: waxy pallor of the optic discs, attenuated retinal vessels, and bone spicule-like pigmentation accompanied by retinal atrophy in the mid periphery. Interestingly, pigmentary changes were relatively late to appear, and in older patients (ages 50+), nummular pigmentation was also observed. ERG recordings revealed non-detectable rod responses at time of first testing (mean age 36) in 40 of 43 patients, while cone flicker was below detection in 33. FAF images showed a hyper-autofluorescent ring around the fovea in all patients already at young ages (third decade of life). Macular OCT showed thinning of the ONL around the fovea, with relative preservation of the fovea. In 42 of 46 patients, an epiretinal membrane (ERM) was observed, but frank cystoid macular edema (CME) was rare, appearing in only 4 patients.

**Conclusions:** Mutations in FAM161A cause ARRP with symptoms usually manifesting in the 3rd or 4th decade of life. The clinical phenotype falls within the spectrum of RP caused by other genes. Interestingly, pigmentedary changes seem to appear relatively late in the course of disease, ERM are relatively common, but CME is quite rare. The data collected can assist in evaluation of FAM161A patients, provides information on the course of disease and may be relevant for future application of novel therapies.

**Commercial Relationships:** Avigail Beryozkin, None; Samer Khateb, None; Carlos Idrobo, None; Mor Hanany, None; Alexey Obolensky, None; Dror Sharon, None; Eyal Banin, None
**Support:** Sinergia #CRSI13_141814, FFB BR-GE-0214-0639 and Yedidut research grant

**Program Number:** 3220, Poster Board Number: B0353
**Presentation Time:** 11:00 AM–12:45 PM
**Optical Coherence Tomography Angiography Assessment of Retinal Degeneration in Patients with Retinitis Pigmentosa**

Ramiro Maldonado, Wadih M. Zein, Robert B. Hufnagel, Brian P. Brooks, Laryssa Huryn. Ophthalmic Genetics, National Eye Institute, Bethesda, MD.

**Purpose:** Optical Coherence Tomography Angiography (OCTA) is a new imaging tool that provides structural information of retinal vasculature. The current study aims to evaluate vascular, photoreceptor and retina pigment epithelium (RPE) characteristics in the macula of patients with retinitis pigmentosa utilizing OCTA.

**Methods:** OCTA scans were obtained using a commercially available system (AngioPlex, Carl Zeiss Meditec) in twelve patients with a clinical diagnosis of retinitis pigmentosa. Scans with artifacts related to media opacity or segmentation errors that compromised study assessment were excluded. One eye from each patient was selected for analysis. Retinal vascular supply was evaluated at the following levels: superficial and deep retinal vasculature, choriocapillaris and chorioid. Photoreceptor outer segment and RPE integrity were estimated using en-face color-intensity maps by segmenting the ellipsoid-zone band and RPE respectively. Subjects were divided into three disease-severity groups depending on the maximal horizontal meridian on isopter I4e as follows: group-1 (<60 degrees, n=3); group-2 (21-60 degrees, n=4) and group-3 (<20 degrees, n=5).

**Results:** Twelve patients were included in the analysis; 7 were females (58%) and the median age was 26 years (range 15-83). Seven (58%) were Caucasians, two African-American, two Asian and one Hispanic. The superficial retinal vascular layer was the least frequently affected (n=5, 42%) followed by deep vasculature and RPE (n=10, 83%), choriocapillaris (n=11, 92%) and E-ZBand and chorioid (100%). Sub-group analysis showed that superficial vasculature was abnormal in 25%, 75% and 80% of groups 1, 2 and 3 respectively and the deep vasculature was abnormal in 50%, 75% and 100% of groups 1, 2 and 3 respectively. There was no difference in the distribution of abnormalities in other layers when comparing across severity groups.

**Conclusions:** OCTA may be a useful imaging tool to evaluate vascular and structural retinal changes in patients with retinitis pigmentosa. This novel technology could provide more insights in the sequence of events specific to retinal degenerations.

**Commercial Relationships:** Ramiro Maldonado, None; Wadih M. Zein, None; Robert B. Hufnagel, None; Brian P. Brooks, None; Laryssa Huryn, None
**Support:** NIH Intramural Research Support

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.
Intravitreal dexamethasone 0.7mg implants for the treatment of Retinitis Pigmentosa-associated cystoid macular edema

Margaret Reynolds, Jackson Abou Chehade, Raymond Iezzi
Ophthalmology, Mayo Clinic, Rochester, MN.

**Purpose:** Retinitis pigmentosa (RP) is an inherited retinal degenerative disorder that leads to photoreceptor cell loss associated with apoptosis, oxidative cell damage, and neuroinflammation. Cystoid macular edema (CME) has been demonstrated to be a negative prognostic factor. Our purpose is to report long-term outcomes in a retrospective consecutive case series of patients with RP-associated CME, refractory to systemic acetazolamide who received intravitreal dexamethasone implant 0.7mg (IVDI) therapy.

**Methods:** Patients underwent IVDI treatment according to a treat and extend protocol. After IVDI, patients were monitored for CME recurrence via spectral domain optical coherence tomography (SDOCT) and retreated with IVDI as needed. Outcome measures included best-corrected visual acuity (BCVA) and SDOCT macular thickness. Patients were monitored for cataract and ocular hypertension. One sample t-test was used to determine statistical significance between groups when samples were normally distributed; otherwise, one sample signed rank test was used.

**Results:** Four patients (8 eyes) underwent IVDI. Baseline macular volume was 7.74±1.19 mm³ (range 6.45-9.54mm³), BCVA was logMAR 0.357±0.271 (range logMAR 0.05-0.8), and intraocular pressure (IOP) measured 14.5±5.93 mmHg (range 8-27). All eyes had recurrent macular edema and fluctuations in BCVA requiring IVDI retreatment. Eyes were treated with an average of 11.6 ±4.60 implants (range 6-18) over a span of 40.8±3.52 months (range 38.0-46.0). Average time between implants was 106.3±55.5 days. Six of 8 eyes demonstrated significantly improved visual acuity (p<0.01). Mean BCVA at date of last follow-up was logMAR 0.78±0.92 (range logMAR 0.1-3.0). Three of 8 patients demonstrated significantly improved macular volume (p<0.001). Mean macular volume at date of last follow-up was 7.69±0.98 mm³ (range 6.47-9.29mm³). Four of 8 eyes required between 1-3 IOP lowering medications. Clinically significant elevation of IOP occurred in 5 of 8 eyes (mean post-tx IOP:15.38±7.85 mmHg [range 5-28]). One patient required selective laser trabeculoplasty bilaterally. Seven of 8 eyes underwent cataract surgery during the study.

**Conclusions:** Repeat IVDI improves VA in a majority of eyes with RP and CME. A majority of eyes experienced increased IOP and required cataract extraction. In conclusion, IVDI deserves consideration for refractory CME in patients with RP.

**Commercial Relationships:** Margaret Reynolds, None; Jackson Abou Chehade, None; Raymond Iezzi, None

---

**Hearing Loss as a Prognostic Indicator of Visual Function in Ush2A-associated Retinal Degeneration**

Derek S. Sengillo, Thiao Cabral, Kaspar Schuerch, Jimmy K. Duong, Winston Lee, Katherine Boudreault, Sally Justus, Yu Xu, Janet R. Sparrow, Vinh B. Mahajan, Stephen H. Tsang
Ophthalmology, Mayo Clinic, Rochester, MN; College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY; Ophthalmology, Federal University of Espirito Santo, Vitória, Brazil; Ophthalmology, Federal University of São Paulo, São Paulo, Brazil; Biostatistics, Columbia University, New York, NY; Ophthalmology, University of Montreal, Montreal, QC, Canada; Ophthalmology, Xiu Hua Hospital, affiliate of Shanghai Jiao Tong University School of Medicine, Shanghai, China; Ophthalmology & Visual Sciences, University of Iowa, Iowa City, IA; Omics Laboratory, University of Iowa, Iowa City, IA; Pathology & Cell Biology, Institute of Human Nutrition, Columbia University, New York, NY.

**Purpose:** Mutations in Usherin 2A (USH2A) cause Usher syndrome (USH), which manifests as retinitis pigmentosa (RP) with neurosensory hearing loss, or autosomal recessive non-syndromic RP (NSRP). However, few studies have characterized natural disease phenotype for patients with USH2A-associated retinal degenerations. Thus, we performed a cross-sectional analysis comparing electroretinography (ERG) data, retinal structure, and distribution visual fields. Full-field ERGs were performed in all the patients using the ISCEV standard stimuli. Retinal cross-sections were obtained with SD-optical coherence tomography. A 9-mm line scan along the horizontal meridian crossing the fovea was used for all the patients. Quantitation of ONL thickness and eccentricity of ellipsoid zone were measured. SW-AF (488 nm) was performed in the “high-speed” mode. Quantitative analyses of hypofluorescent central areas were manually measured.

**Results:** The patients ranged in age from 9 to 32 years (average, 24; SD, 8.0 years) when first diagnosed. Best-corrected visual acuities ranged from 20/200 to 4/200 in the eye with best vision at first examination. A common fundoscopic finding in 6 affected individuals from 4 different families was well demarcated pigmented lesions in the mid and far peripheral retina. The most common pattern of visual field abnormality was the presence of an absolute scotoma involving the central 5 degrees of vision with normal extent of peripheral visual field. The majority of the patients (9/10) showed more preservation of peripheral rod function in comparison with peripheral cone function by ERG. In vivo microstructure by SD-OCT showed central retinal thinning and loss of photoreceptors with variable degrees of extension. Abnormal autofluorescence was characterized by a localized central area of decreased autofluorescence surrounded by a heterogeneous background of high or low autofluorescence areas extending anterior to the vascular arcades.

**Conclusions:** We describe the retinal phenotype associated with a founder mutation in ABCA4 in a subgroup of STGD patients from Mexico. Population genetic studies for known mutations to determine allele frequencies and their regional distributions could lead to more precise recommendations for genetic testing and could also help to define a better genotype-phenotype correlation in the group of ABCA4-linked retinal dystrophies.

**Commercial Relationships:** Rodrigo Matsui, None; Salvador Lopez-Rubio, None; Oscar Chacon, None; Juan Carlos Zeneto Ruiz, None

**Support:** Foundation Fighting Blindness CD-GE-0816-0711-OICV

---

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to [http:// iovs.arvojournals.org/](http://iovs.arvojournals.org/) to access the versions of record.
of severe mutations between NSRP and Ush patients harboring compound heterozygous or homozygous mutations in USH2A.

**Methods:** A total of 15 RP patients with two pathogenic mutations in USH2A were included, specifically eight Ush patients and seven age-matched NSRP patients. Patients were diagnosed with Ush if subjective hearing loss was present or NSRP if hearing loss was denied. To evaluate visual function prognosis, 30 Hz-flicker ERG was compared between groups. Ellipsoid zone (EZ) line length on SD-OCT and autofluorescent (AF) ring diameters on fundus AF imaging were compared. To determine the distribution of alleles containing severe mutations between each group, logistic regression models were utilized.

**Results:** NSRP patients had higher mean 30 Hz-flicker amplitudes of 21.1 ± 8.0 μV (mean ± SE) compared to Ush patients, who had a mean of 2.1 ± 0.5 μV (p = 0.02). Of Ush patients, 75% (6/8) had at least one severe mutation, defined as a frameshift or nonsense mutation, compared to 29% (2/7) of NSRP patients (p = 0.13). The proportion of total alleles containing a severe mutation was 50% in the Ush group compared to 14% of NSRP patients, with an odds ratio of 6.0 (confidence intervals: 1.1, 32) (p = 0.04). There was no statistically significant difference in EZ-line length or AF ring diameters between groups.

**Conclusions:** NSRP patients had superior visual function prognoses as predicted by 30 Hz-flicker ERG and a higher proportion of alleles with severe mutations in this cohort. Our data suggests Ush manifests as a more severe phenotype compared to NSRP patients with mutations in the same Usherin gene. A genetic threshold in which mutation burden relates to visual and auditory phenotype may exist. Larger cohort studies that compare visual function and audiometry of Ush2A patients with their genotype are necessary to address this hypothesis. The presence or absence of hearing loss in Ush2A patients may allow specialists to provide a more accurate prognosis.

**Commercial Relationships:** Jesse D. Sengillo, None; Thiago Cabral, None; Kaspar Schuerch, None; Jimmy K. Duong, None; Winston Lee, None; Katherine Boudreault, None; Sally Justus, None; Yu Xu, None; Janet R. Sparrow, None; Vinícius B. Mahajan, None; Stephen H. Tsang, None

**Support:** Jonas Children’s Vision Care, and Bernard & Shirlee Brown Glaucoma Laboratory are supported by the National Institute of Health [5P30EY019007, R01EY018213, R01EY024698, R01EY026682, R21AG050437], National Cancer Institute Core [5P30CA013696], the Research to Prevent Blindness (RPB) Physician-Scientist Award, unrestricted funds from RPB, New York, NY, USA. J.D.S is supported by the RPB medical student research fellowship. T.C. is supported by the International Council of Ophthalmology - Retina Research Foundation Helmerich Fellowship, honoring Mr. W. H. Helmerich III. V.B.M is supported by NIH grants [R01EY026682, R01EY024665, R01EY025225, R01EY024698 and R21AG050437]. S.H.T. is a member of the RD-CURE Consortium and is supported by the Tistou and Charlotte Kerstan Foundation, the Schneeweiss Stem Cell Fund, New York State [C029572], the Foundation Fighting Blindness New York Regional Research Center Grant [C-NY05-0705-0312], the Crowley Family Fund, and the Gebroe Family Foundation.

**Program Number:** 3224 **Poster Board Number:** B0357

**Dysplasia and degeneration in NR2E3 retinopathy: an imaging study**

**Authors:** Rola Ba-Abbad1, 2, Ajoy Vincent1, Adam M. Dubis2, 3, Katelyn MacNeil1, Elise Heon1. 1Department of Ophthalmology and Vision Sciences, Hospital for Sick Children, Toronto, ON, Canada; 2Institute of Ophthalmology, University College London, London, United Kingdom; 3National Institute for Health Research & Biomedical Research Centre, Moorfields Eye Hospital, London, United Kingdom.

**Purpose:** Mutations in the nuclear receptor transcription factor NR2E3 manifest as autosomal recessive enhanced S-cone syndrome (ESCS), autosomal recessive retinitis pigmentosa (ARRP), or autosomal dominant retinitis pigmentosa (ADRPP). ESCS is characterized by retinal dysplasia, degeneration, and the absence of rod photoreceptors. This retrospective, observational case series examines the retinal structure and lamination, within and outside the macula, in NR2E3 retinopathy.

**Methods:** Clinical examination, electroretinography (ERG), fundus color and autofluorescence (AF) images, and optical coherence tomography (OCT) scans at the macula, nasal to the disc, and anterior to the vascular arcades were examined in ten patients (age range 13–57 years) with molecularly ascertained NR2E3 retinopathy. OCT scans at the same locations were obtained from seven healthy controls.

**Results:** Seven patients had ESCS, one had ARRP, and two had ADRP (best corrected visual acuity 20/25–20/500). Five patients had ERG features in keeping with ESCS, and five patients had undetectable ERG. Fundus photographs showed a featureless retina in one patient with ESCS; and perimacular outer retinal atrophy with intra-retinal pigment migration in six patients with ESCS; and diffuse bone-spicule pigmentation in ARRP. Both patients with ADRP showed outer retinal atrophy with mild intra-retinal bone-spicule pigmentation. OCT scans anterior to the vascular arcades and nasal to the optic nerve head showed retinal thickening, abnormal lamination, and intra-retinal hyperreflective lesions in ESCS and ARRP. The OCT in ADRP showed relatively preserved retinal lamination with loss of the inner segment-ellipsoid zone outside of the central macula, and attenuation of the outer nuclear layer.

**Conclusions:** This study demonstrates the value of OCT imaging of the extramacular retina in differentiating recessive and dominant NR2E3 retinopathies. The laminar disorganization associated with recessive NR2E3 retinopathy manifests in the regions that would have normally had high rod density; whereas the relatively preserved lamination in ADRP suggests normal retinal development. The mechanistic-structural differences between the two phenotypes give an insight into the pathophysiology of these disorders, and aid in selecting candidates for novel therapies.

**Commercial Relationships:** Rola Ba-Abbad, None; Ajoy Vincent, None; Adam M. Dubis, None; Katelyn MacNeil, None; Elise Heon, None
Clinical and Genetic Evaluation in a Cohort of Pediatric Patients with Inherited Retinal Dystrophies

Raffaella Brunetti-Pierri, Mariaelena Filippelli, Francesco Testa, Valentina Di Iorio, Giuseppina Di Frusci, Vincento Nigro, Mariateresa Pizzo, Nicola Brunetti-Pierri, Sandro Banfi, Francesca Simonelli.

Purpose: There are no reports, to the best of our knowledge, that describe genotype phenotype correlations in patients with inherited retinal dystrophies (IRD) with infantile/juvenile onset. The aim of our study is to focus attention on a cohort of Italian IRD patients, performing an extensive clinical evaluation and Next Generation Sequencing (NGS) analysis, in order to select IRD patients with the highest potential of successful outcome of gene therapy-based approaches.

Methods: Thirty-nine Italian patients (representative of 37 different families), aged between 2-18 years, with severe isolated non-syndromic IRD were recruited. Inclusion criteria were: disease onset ≤10 years of age, age ≤18 years, best corrected visual acuity ≤20/70, standard electroretinogram (sERG) abnormalities and macular thickness (MT) ≥100 μm (when sERG and Optical Coherence Tomography were performable). All patients underwent full ophthalmological examinations and targeted NGS-based analysis on a panel, termed RETplex.

Results: Based on ophthalmological assessment, 19 patients were affected by Leber Congenital Amaurosis (LCA) (48.7%), 15 by Early Onset Retinitis Pigmentosa (EORP) (38.5%) and 5 by Achromatopsia (ACHM) (12.8%). The most frequently mutated gene was CEP290. Ellipsoid band (EB) was explorable and carefully analyzed in 28/39 patients (71.8%). The most preserved EB was found in patients with mutations in CEP290, CNGB3, CNGA3, PDE6C genes. We identified causative mutations in 26/39 patients analyzed (66.6%). Causative mutations were found in 11/19 LCA, 10/15 EORP, and in all 5 ACHM patients. Clinical and molecular diagnosis did not always overlap. We found two notable cases of discordance: CEP290 causative of EORP instead of LCA and CNGB3 underlying LCA instead of ACHM. Fourteen patients (35.9%) displayed mutated genes involved in syndromic forms, but their young age masked them.

Conclusions: Our study provides the first detailed clinical/genetic assessment of severe IRDs with infantile/juvenile onset and lays the basis for a standardized protocol to identify the most suitable patients for successful gene replacement therapy. We highlight that the NGS results are very important for a critical re-evaluation of clinical cases in order to better understand and discriminate between diseases.

Genotype-phenotype correlations in patients with Usher syndrome type 2 harboring mutations in USH2A and ADGRV1

Marko Hawlinà, Ana Fakinè, Crystel Bonnetè, Anne Kurtenbach2, Saddek Mohand-Saidè, 3, Ditta Zobor2, Martina Jarc-Vidmar4, Katarina Stingl3, Francesco Testa1, Francesca Simonelli2, José-Alain Sahel1, 3, Isabelle S. Audo1, 3, Eberhart Zrenner2, Christine Petit4, 6. 1Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; 2Centre for Ophthalmology, Institute for Ophthalmic Research, University of Tuebingen, Tuebingen, Germany; 3Centre d’Investigation Clinique, Direction de l’Hospitalisation et de l’Organisation des Soins, Centre Hospitalier National d’Ophthalmologie des Quinze-Vingts, Paris, France; 4Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences Second University of Naples, Naples, Italy; 5Institut de la Vision, UMR 1120 INSERM/UPMC, Paris, France; 6Institut Pasteur, Collège de France, Paris, France.

Purpose: Mutations in USH2A are the most common cause of syndromic and non-syndromic retinitis pigmentosa (RP). Mutations in ADGRV1 (GPR98) are an infrequent cause of syndromic RP and the clinical presentation is less well known. The purpose of the study was to compare disease severity in a cohort of patients harboring mutations in USH2A and ADGRV1.

Methods: Study included patients with Usher syndrome type 2 and biallelic mutations in USH2A (N=188, median age 45 years) or ADGRV1 (N=17, median age 54 years). The onset of nystagmia was determined from the hospital records. The degree of macular involvement was evaluated in 109 patients using fundus autofluorescence (FAF) and optical coherence tomography (OCT). The right eye was studied except where poor image quality precluded measurements. The diameter of the hyperautofluorescent ring was measured on FAF if present, or considered zero if there was central hyperautofluorescent patch or atrophy. The central retinal thickness (CRT) of 1 mm radius was measured on the OCT scan.

Results: The median age of onset of USH2A and ADGRV1 patients was 18 vs. 30 years (p<0.05, Mann Whitney U test). FAF patterns were qualitatively similar among the two groups. When adjusted for age, there was no significant difference in ring diameter, while ADGRV1 patients had significantly higher CRT (Multiple regression analysis, p<0.001). Those USH2A patients with at least one missense variant (84/188) had significantly later median onset than those without (20 vs. 15 years, respectively; Mann Whitney U test, p<0.005). There was no significant difference in ring diameter or CRT among the two subgroups, when adjusted for age (Multiple regression analysis, p>0.05).

Conclusions: Results indicate milder retinal disease in Usher type 2 patients harboring ADGRV1 mutations although significance was reached only for CRT. Syndromic USH2A patients with missense variants were more likely to have a later onset than those with other variants however the degree of macular involvement determined objectively did not differ significantly.

Commercial Relationships: Marko Hawlinà, None; Ana Fakinè, None; Crystel Bonnetè, None; Anne Kurtenbach2, None; Saddek Mohand-Saidè, 3; Ditta Zobor2, Martina Jarc-Vidmar4, Katarina Stingl3, None; Francesca Simonelli2, None; José-Alain Sahel1, 3, Isabelle S. Audo1, 3, Eberhart Zrenner2, ReNeuron Group Plc/Ora Inc. (C), Retina Implant AG (I), Acucela Inc. (F), Retina Implant AG (F), QLT, Inc. (F), NightstarX Ltd. (F), Retina Implant AG (R), Retina Implant AG (S), Retina Implant AG (P), Retina Implant AG (C), Shire (C); Christine Petit4, None

Support: TREATRUSH (HEALTH-F2-2010-242013)
Optical coherence tomography examination of the retinal pigment epithelium and vitelliform lesions in Best vitelliform macular dystrophy

Cynthia X. Qian¹, ², Dionisio Charran¹, Cameron R. Strong³, Timothy J. Steffens⁴, Thiran Jayasundera⁵, John Heckenlively⁴.

¹Ophthalmology, Kellogg Eye Center, Ann Arbor, MI; ²University of Montreal, Montreal, QC, Canada; ³Instituto de Patologia Ocular en Santo Domingo, Santo Domingo, Dominican Republic.

Purpose: To describe the anatomical changes and natural history of vitelliform lesions and the status of the retinal pigment epithelium (RPE) in Best vitelliform macular dystrophy (BVMD) using spectral-domain optical coherence tomography (SD-OCT).

Methods: Twenty patients with molecular confirmation of mutation in the BEST1 gene and twenty age-matched controls were included in this prospective comparative case series. Color fundus photographs, fundus autofluorescence and SD-OCT were obtained in both eyes in all subjects and these findings were compared between the two groups. Fifteen of the twenty patients with Best disease had more than one visit and imaging study from each visit was analyzed comparatively for change and progression over time as well.

Results: BVMD patients demonstrated progressive disorganization and thinning of the submacular RPE on OCT as their disease progressed when compared to normal controls. Concurrent with the appearance of “egg yolk lesions”, the OCT showed a cleft in the outer retina, creating an apical and basal separation of retinal layers.

Conclusions: Our study suggests that in BVMD, subretinal vitelliform material accumulation leads to a clear separation of the outer retinal layers. The basal surface of the RPE manifests degeneration that slows or disrupts the water pump function.

Purpose: To identify the genetic defect of a non-consanguineous Japanese family with mild cone-rod dystrophy and sensorineural hearing loss in Japanese family.

Shuhei Kameya¹, Daiki Kubota¹, Sachiko Kituchi¹, Kiyoko Gocho¹, Keichiro Akeo¹, Kunihiko Yamaki¹, Hiroshi Takahashi¹.

¹Ophthalmology, Chiba Hokusoh Hosp Nippon Med Sch, Inba, Japan; ²Ophthalmology, Nippon Medical School, Sendagi, Japan.

Purpose: To identify the genetic defect of a non-consanguineous Japanese family with mild cone-rod dystrophy and sensorineural hearing loss using whole exome sequencing (WES).

Methods: Detailed ophthalmic and auditory examinations including high-resolution adaptive optics (AO) fundus imaging were performed on the proband and her family member. Whole exome sequencing (WES) was applied to the DNA obtained from the proband. Filtering with available genomic databases and in silico analyses were used to identify the disease causing variants. Sanger sequencing and co-segregation analysis of the proband and her family members were performed to identify the most likely pathogenic variant.

Results: Using WES on the DNA sample of the proband, we identified a compound heterozygous variants c.321C>A, p.Asp107Glu and c.668G>A, p.Arg223His in the DFNB31, a gene associated with Usher syndrome. Both of the mutation were predicted as damaging at SIFT prediction program. Minor allele frequency (MAF) of these mutation in ExAC database were 0.003% and 0.67% in worldwide and 0.04% and 2.3% in East Asian respectively. MAF of these mutation in HGVD database were 1.1% and 2.2% in Japanese population. The variants were verified by Sanger sequencing and were co-segregated with the disease in five members of the family. The affected sister of the proband also harbor a compound heterozygous variants. Fundus appearance of both patients were normal, however electrophysiological analysis revealed a mild cone-rod dystrophy phenotype in the proband and her sister. SD-OCT images of both patients showed blurred EZ and IQ. AO imaging revealed reduced cone density around fovea compared to peripheral region in both patients. Auditory examinations of both patients revealed slight sensorineural hearing loss mainly at high frequency.

Conclusions: Our data indicate that mutations of DFNB31 can cause mild cone-rod dystrophy and sensorineural hearing loss in Japanese patients. Although there are several Japanese patients reported to have only hearing loss with DFNB31 mutation, this is the first case to show DFNB31 mutation in Japanese family harboring both hearing loss and cone-rod dystrophy. Ophthalmological and auditory phenotype of these patients were very mild. Comparatively high MAF of these mutations in Japanese population may related to the findability of retinal and hearing abnormality.

Program Number: 3231 Poster Board Number: B0364
Presentation Time: 11:00 AM–12:45 PM

Necrotic Enlargement of Cone Photoreceptor Cells and the Release of High-mobility Group Box-1 in Retinitis Pigmentosa


Department of Ophthalmology, Kyushu University, Fukuoka, Japan.

Purpose: In retinitis pigmentos (RP), rod cell death due to genetic mutations has been shown to occur mainly through apoptosis, whereas the mechanisms and features of the secondary cone cell death have not been fully elucidated. Our previous study showed that, in a mouse model of RP, cone cell death involves necrotic features and is partly mediated by receptor-interacting protein kinases. In the present study, we further investigate the possible involvement of necrotic cone photoreceptor cell death in RP.

Methods: The morphological changes of cone cells in a mouse model of RP (rd10 mice) were evaluated by immunostaining and transmission electron microscopy. In 10 RP patients and 7 control subjects, the cone mosaic images were obtained by adaptive optics scanning laser ophthalmoscopy (AO-SLO), and the cone cell diameters were measured using automated cone labeling program and scale selection method. The vitreous samples were collected from 10 RP patients and 10 controls, and the amounts of high-mobility group box-1 (HMGB1), which is released from necrotic cells, were measured by ELISA.

Results: In rd10 mice, dying cone cells exhibited cellular enlargement, along with necrotic changes such as cellular swelling and mitochondrial rupture. In human eyes, AO-SLO analysis revealed significantly increased percentages of enlarged cone cells to more than 6 μm in the RP patients (5.3 ± 2.5%) compared with the controls (0.6 ± 0.6%, P<0.0004). The vitreous of the RP patients contained...
Intrafamilial and Interfamilial Variation

Artur V. Cideciyan\(^1\), Jason Chang\(^2\), Samuel G. Jacobson\(^1\), Alexander Sumaroka\(^1\), Sharon B. Schwartz\(^3\), Malgorzata Swider\(^4\), Alejandro J. Roman\(^1\), Rebecca Sheplock\(^1\), Manisha Anand\(^1\), Marc C. Peden\(^1\), Hemant Khanna\(^1\), Elise Heon\(^1\), Alan F. Wright\(^1\), Anand Swaroop\(^1\), Department of Ophthalmology, Scheie Eye Institute, Univ of Pennsylvania, Philadelphia, PA; Department of Ophthalmology, University of Massachusetts Medical School, Worcester, MA; Retina Associates of Florida, Tampa, FL; Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, ON, Canada; MRC Human Genetics Unit, Edinburgh, United Kingdom; Neurobiology-Neurodegeneration & Repair Laboratory, National Eye Institute, Bethesda, MD.

**Purpose:** An important aim for the treatment of inherited retinal degenerations (IRDs) is to arrest the progressive loss of photoreceptors. One of the common IRDs is X-linked retinitis pigmentosa (XLRP) caused by mutations in the ORF15 exon of RPRG. Preclinical gene therapy studies in RPRG-mutant dogs and mice have shown success in arresting progressive degeneration with intervention initiated at clinically-relevant disease stages already with substantial loss of photoreceptors. Clinical trials in patients will require not only knowledge of retinotopic distribution of remaining rods and cones to treat but also methods for the efficient evaluation of modifications to the natural history of disease.

**Methods:** There were 70 patients (ages 8–71 years) from 45 families with mutations in the ORF15 exon of the RPRG gene. Static threshold perimetry was used to quantify rod and cone function across the 168 deg width of visual field. Overall disease severity was defined as sum of sensitivity losses across the retina. At each retinal locus, relative involvement of photoreceptors was estimated from the difference of rod and cone sensitivity losses. Interocular symmetry was evaluated by limits of agreement analysis for repeated measures with linked replications.

**Results:** Severity of disease showed substantial intra- and interfamilial variation that did not correlate with genotype after controlling for age. There were major intrafamilial differences of disease, and retinotopic distribution of rod and cone dysfunction showed variegated patterns that could be different between individuals. When considering the inferior hemi-field likely to be targeted by potential treatments, more than 50% of the patients had detectable rod as well as cone function within a large swath of infero-temporal field spanning 50 to 100 deg eccentric. There was interocular symmetry with retina-wide limits of agreement of ~8 dB. Point-by-point measures of interocular variation in the infero-temporal field averaged 6.6 dB for rod function and 4.7 dB for cone function.

**Conclusions:** Many patients with ORF15-RPRG-XLRP retain rod and cone function within the infero-temporal field. Perimetry-based outcome measures can and should take advantage of high interocular symmetry of function in this region to determine safety and efficacy of uniouscicular interventions such as early phases of gene therapy.

**Commercial Relationships:** Artur V. Cideciyan, AGTC (F); AAV-mediated gene therapy for RPRG X-linked retinal degeneration (P); Jason Chang, AGTC (F); Samuel G. Jacobson, AGTC (F), AAV-mediated gene therapy for RPRG X-linked retinal degeneration (P); Alexander Sumaroka, AGTC (F); Sharon B. Schwartz, None; Malgorzata Swider, AGTC (F); Alejandro J. Roman, AGTC (F); Rebecca Sheplock, AGTC (F); Manisha Anand, None; Marc C. Peden, None; Hemant Khanna, None; Elise Heon, None; Alan F. Wright, None; Anand Swaroop, Application related to gene therapy of RPRG (P)

**Support:** AGTC, NEI, FFB, MVRF, and Chatlos Foundation.

---

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to [http://iovs.arvojournals.org/](http://iovs.arvojournals.org/) to access the versions of record.
Efficacy of Additional Topical Betamethasone in Persistent Cystoid Macular Edema after Carbonic Anhydrase Inhibitor Treatments in Retinitis Pigmentosa

Shohei Kitahata1, 2, Yasuhiko Hirami1, Seiji Takagi3, Masashi Fujiwara1, Yasuo Kuriyama1, Masayo Takahashi1. 1Retinal Regeneration Center for Developmental Biology, RIKEN FOR DEVELOPMENTAL BIOLOGY, Kobe, Japan; 2Graduate School of Medicine, Graduate School of Medicine and Faculty of Medicine Kyoto University, Kyoto, Japan; 3Ophthalmology, Kobe City Medical Center General Hospital, Kobe, Japan.

Purpose: Cystoid macular edema (CME), a vision-threatening condition, is one of the most frequent complications in retinitis pigmentosa (RP). Although various treatment approaches using carbonic anhydrase inhibitors (CAI) or steroids have been reported, and intravitreal or sub-Tenon’s corticosteroids have shown efficacy in managing CME, topical steroid therapy, which is less invasive, has not been reported yet. The present study hence retrospectively investigated the efficacy of additional topical 0.1% betamethasone (BM) in persistent CME after CAI therapy in RP.

Methods: This study included patients who started topical application of BM for persistent CME after previous CAI treatments from 2009 to 2016. Patients were excluded if they had complications that may contribute to CME. All patients received additional topical BM with the CAI treatment. BM therapy was stopped if the patients showed increasing intraocular pressure (IOP): >20 mmHg twice consecutively or >25 mm Hg once. CME was diagnosed using spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Central foveal thickness (CFT) was regarded as the average of vertical and horizontal foveal thickness. We defined response to treatment as reduction of ≥11% in CFT compared to the baseline. Best-corrected visual acuity (BCVA) and IOP were obtained from the medical records. We compared the CFT and BCVA between baseline and 1–3, 5–7, 10–14, and 16–20 months. Repeated measures ANOVA with Bonferroni’s correction was used for data analysis.

Results: Sixteen eyes of 10 patients with RP (39.4±13.8y; 5 men) were included. Previous treatments were brinzolamide in 14 eyes, dorzolamide in 5, bromfenac in 2, and systemic acetazolamide in 1 patient. CFT effectively decreased in 13 of 16 eyes (81.3%). CFT decreased significantly in 1–3 months (326±102 μm; N = 16; p = 0.03) and 5–7 months (297±102 μm; N = 12; p = 0.03) compared to baseline but not in 10–14 months (271±96 μm; N = 9; p = 0.485) and 16–20 months (281±134 μm; N = 9; p = 0.289). There were no significant intergroup differences in BCVA throughout the study. BM treatment was stopped in 4 patients because of IOP elevation.

Conclusions: We demonstrated the efficacy of BM administration with CAI treatment for persistent CME. Topical steroid could be an alternative option for managing CME in RP.

Commercial Relationships: Shohei Kitahata, None; Yasuhiko Hirami, None; Seiji Takagi, None; Masashi Fujiwara, None; Yasuo Kuriyama, None; Masayo Takahashi, None.

1

Support: NIH Grant EY007142, Foundation Fighting Blindness, William Stamps Farish Fund; Hermann Eye Fund

Program Number: 3235
Poster Board Number: B0368
Presentation Time: 11:00 AM–12:45 PM

ARVO 2017 Annual Meeting Abstracts

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.
**Retinopathy of Childhood**

James Tee

Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Rambam Health Care Campus, Haifa, Israel; Assaf Harofeh Medical Center, Tzrifin, Israel; Hadassah Medical Center, Jerusalem, Israel.

**Purpose:** Cystoid macular edema (CME) is reported in 10-15% of patients with retinitis pigmentosa (RP). The pathogenesis of CME in RP is not entirely understood, and both inflammatory and tractional mechanisms have been suggested. The purpose of this study was to evaluate intraretinal/intracytic fluid optical density (OD) of eyes with RP-associated CME in order to determine the more likely pathogenesis.

**Methods:** A retrospective multicenter study was conducted. Spectralis SD-OCT (Heidelberg, Germany) was used to evaluate intraretinal-intracytic OD in 12 treatment-naive eyes with RP as the sole ophthalmic pathology. OD in the vitreous and the CME cystic spaces was measured using ImageJ software (NIH) from exported raw scan data. OD ratios (ODR) were calculated by dividing the mean pixel intensity of the CME by the mean pixel intensity of the vitreous. An ODR cutoff value (1.0489, p=0.0001) was used to differentiate between an inflammatory (>1.0489) versus a tractional etiology (<1.0489), as determined in an earlier study by our group (93.6% sensitivity and 62.5% specificity). Level P < 0.05 was assumed to denote significance in all tests.

**Results:** The mean ODR value of the RP patients was 1.32, suggestive of a dominant inflammatory process (i.e., >1.0489). No significant difference was found between the RP eyes and the inflammatory ODR values (p=0.5), whereas RP ODR values differed significantly from the tractional ODR values (p=0.02), revealing a dominant inflammatory process in the pathogenesis of CME secondary to RP.

**Conclusions:** Our findings indicate a dominance of inflammatory processes in the CME of RP eyes. The higher reflectivity of the intraretinal fluid might reflect the presence of inflammatory proteins and acute-phase serum reactants. Understanding the pathogenesis of CME in RP may support a potential anti-inflammatory therapeutic approach for this ailment.

**Commercial Relationships:** Tomer Batash, None; Hadas Newman, None; Adiel Barak, None; Shiri Zayit-Soudry, None; Eran Pras, None; Eyal Banin, None; Michael Politis, None; Anat Loewenstein, None; Meira Neudorfer, None

**Program Number:** 3236 Poster Board Number: B0369 Presentation Time: 11:00 AM–12:45 PM

**Assessment of Interocular Disease Progression in Retinitis Pigmentosa-Associated Cystoid Macular Edema**

**Purpose:** Retinal pathologies in retinitis pigmentosa (RP) are a common and often disabling complication. Both inflammatory and tractional processes may contribute to cystoid macular edema (CME). In this study, we aimed to determine whether CME in RP is inflammatory or tractional.

**Methods:** Retina Specialist Dr. Anat Loewenstein reviewed all OCT and FAF images from patients with RP-associated CME in order to determine the more likely pathogenesis. The mean OD ratio (ODR) of the RP patients was 1.32, suggestive of a dominant inflammatory process (i.e., >1.0489). No significant difference was found between the RP eyes and the inflammatory ODR values (p=0.5), whereas RP ODR values differed significantly from the tractional ODR values (p=0.02), revealing a dominant inflammatory process in the pathogenesis of CME secondary to RP.

**Conclusions:** Our findings indicate a dominance of inflammatory processes in the CME of RP eyes. The higher reflectivity of the intraretinal fluid might reflect the presence of inflammatory proteins and acute-phase serum reactants. Understanding the pathogenesis of CME in RP may support a potential anti-inflammatory therapeutic approach for this ailment.

**Commercial Relationships:** James Tee, None; Michel Michaelides, MeiraGTx (C); Astellas (C)

**Support:** Supported by grants from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology (UK), Fight For Sight (UK), Moorfields Eye Hospital Special Trustees (UK), Moorfields Eye Charity (UK), the Foundation Fighting Blindness (USA), Retinitis Pigmentosa Fighting Blindness (UK), and NIH (RO1 EY017607) (USA). Michel Michaelides is supported by an FFB Career Development Award.

**Program Number:** 3238 Poster Board Number: B0371 Presentation Time: 11:00 AM–12:45 PM

**Analysis of RP2 and RPGR Mutations in Five X-Linked Chinese Families With Retinitis Pigmentosa**

Ningdong Li. Ophthalmology, Beijing Children Hospital, Beijing, China.

**Purpose:** To identify the gene mutations in Five Chinese families with X-linked retinitis pigmentosa.

**Methods:** Families were ascertained and patients underwent complete ophthalmological examinations. Blood samples were collected and DNA was extracted. An X chromosome wide linkage scan was performed for two families. Candidate genes were sequenced by direct PCR and Sanger sequencing, and mutations analyzed. Self-ligation of restriction endonuclease-digested DNA fragments with long-distance inverse PCR was performed for detecting the large gene deletion.

**Results:** A large deletion of approximately 16.529kb in length, including exons 4 and 5 of RP2 was detected in one family with X-linked RP. Four frameshift mutations were detected in the RPGR gene in four families, including a novel splicing mutation of c.1059+1G>T in intron 9, a novel insertion mutation (c.2002dupC), a novel small deletion (c.2236_2237del CT), and a previously reported mutation c.2899delG in exon ORF 15.
Conclusions: We identified three novel and two known mutations in RP2 and RPGR in five Han Chinese families with X-linked retinitis pigmentosa. These mutations expand the mutation spectrum of RP2 and RPGR, and will be helpful for further study molecular pathogenesis of RP.

Commercial Relationships: Ningdong Li

Support: National Natural Science Foundation of China, (NO. 81170884).

Program Number: 3239 Poster Board Number: B0372
Presentation Time: 11:00 AM–12:45 PM

Novel RPGRIP1 mutation in Leber congenital amaurosis patients

Imen Habibi1, 2, Yousra Falfo1, Ahmed Chebil1, Leila El Matri2, Daniel F. Schorderet1, 1Institute for Research in Ophthalmology, Sion, Switzerland; 2Department B of Ophthalmology, Research Laboratory of Oculogenetic (LR14SP01), Hedi Rais Institute of Ophthalmology, Tunis, Tunisia.

Purpose: To localize and identify the gene and mutations causing a Leber congenital amaurosis (LCA) in a Tunisian family

Methods: We performed a clinical and molecular genetic study of a consanguineous Tunisian family with two individuals affected with LCA. DNA sample from the index patient was subjected to whole exome sequencing (WES). Variants localized in homozygous regions were validated by Sanger sequencing. Familial segregation was performed.

Results: The index patient was 30 years old and reported congenital nystagmus. Night blindness and visual loss appeared during first years of life. Visual acuity was limited to hand motion. Fundus examination revealed bone spicule-shaped pigment deposits in the mid-periphery along with atrophy of the retina, narrowing of the vessels and waxy optic discs. Electoretinogram was unrecordable in both scotopic and photopic conditions. Homozygosity mapping and WES identified a homozygous genomic region harboring RPGRIP1. Sequencing analysis revealed a homozygous c.3113_3114delCT mutation of RPGRIP1 in both patients. The deletion results in a frameshift change p.(T1038Rfs*8).

Conclusions: We identified a novel mutation p.(T1038Rfs*8), in a Tunisian family with LCA. This mutation expands the mutation spectrum of RPGRIP1 and helps to further study molecular pathogenesis of LCA.

Commercial Relationships: Imen Habibi, None; Yousra Falfo, None; Ahmed Chebil, None; Leila El Matri, None; Daniel F. Schorderet, None

Program Number: 3240 Poster Board Number: B0373
Presentation Time: 11:00 AM–12:45 PM

Mevalonate Kinase Deficiency Associated With Ataxia And Retinitis Pigmentosa In 2 Brothers With MVK Gene Mutations (c.59A>C, c.1000G>A)

Ulrich Kellner1, Heidi Stoehr2, Silke Weinitz1, Ghazaleh Farmand1, Weber H. Bernhard1.

1RetinaScience, Bonn, Germany; 2Institut für Humangenetik, Universität Regensburg, Regensburg, Germany; 3MVZ ADTC Siegburg GmbH, Rare Retinal Disease Center, AugenZentrum Siegburg, Siegburg, Germany.

Purpose: To report the clinical and molecular genetic findings in two brothers with retinitis pigmentosa (RP) and mevalonate kinase deficiency (MKD).

Methods: Two brothers were examined clinically and with multimodal retinal imaging including MultiColor spectral reflectance, fundus autofluorescence (FAF), near-infrared autofluorescence (NIA) and spectral domain optical coherence tomography (SD-OCT).

Targeted resequencing was done with a custom designed gene panel containing 78 genes associated with RP. Mutations were confirmed by direct Sanger sequencing.

Results: Both brothers aged 46 and 47 years were found to carry compound heterozygous mutations in the MVK gene (c.59A>C, c.1000G>A) encoding mevalonate kinase. They presented with severe ataxia since childhood, pseudohypakia due to early onset cataract, and progressed retinitis pigmentosa. One brother presented with bilateral cystoid macular edema, treatment with dorzolamide was beneficial. Serum IgD levels were markedly increased in both brothers and mevalonic acid blood and urine levels were markedly increased in the one brother who could be examined. One brother had more severe ataxia and less severe visual deficiency compared to the other, indicating variable disease expression.

Conclusions: MKD can be associated with retinitis pigmentosa and early onset cataract. Most MKD patients developing retinitis pigmentosa reported so far carry the (p.Ala334Thr) mutation. Macular edema can be successfully treated using local dorzolamide.

Commercial Relationships: Ulrich Kellner; Heidi Stoehr, None; Silke Weinitz, None; Ghazaleh Farmand, None; Weber H. Bernhard, None

Support: Deutsche Forschungsgemeinschaft (DFG) We 1259 /16-2 and We 1259 /20-1

Program Number: 3241 Poster Board Number: B0374
Presentation Time: 11:00 AM–12:45 PM

Choroidal Morphology and Circulation in Early Retinitis Pigmentosa in the Young, based on Evaluation of Enhanced Depth Imaging Optical Coherence Tomography and Optical Coherence Tomography Angiography

Naohiro Motozawa, Kobe City Medical Center General Hospital, Kobe, Japan.

Purpose: The role of the choroid circulation in retinitis pigmentosa (RP) progression is not currently clear. Advances in optical coherence tomography (OCT) technology made in vivo assessment of choroidal structure of a level similar to histological evaluation possible.

We investigated correlations between changes in choroidal morphology and disease progression using enhanced depth imaging OCT (EDI-OCT) and OCT angiography (OCTA) in young patients with early RP, in a cross-sectional observational study.

Methods: We included 24 eyes from 12 patients (45.5 ± 9.0 y, 4 male) with relatively preserved visual acuity (20/25–30/20).

We evaluated the subfoveal vertical EDI-OCT images using two methods. First, we measured total choroid thickness (CT) and the large choroidal vessel thickness (LCVT) at the fovea. Next, the luminal and interstitial areas within 750 μm of the fovea were measured on binary images using ImageJ® software. The length of the remaining ellipsoid zone (ISe) through the fovea was also measured. The vascular density of the choriocapillaris (CC) at the fovea (250-μm diameter; 10-μm thickness) (CCVD) was obtained by OCTA. The correlations among total CT, LCVT, luminal area, interstitial areas, CCVD, age, refractive error, visual acuity, and ISe were evaluated.

Results: The total CT was 467 ± 194 μm, LCVT was 357 ± 166 μm, luminal area was 0.531 ± 0.268 mm2, and interstitial area was 0.176 ± 0.064 mm2. The CCVD was 0.612 ± 0.061. LCVT was significantly correlated with luminal area (r = 0.947, p < 0.01). ISe was significantly negatively correlated with total CT (r = -0.473, p = 0.02), LCVT (r = -0.496, p = 0.01), and luminal area (r = -0.542, p = 0.006), and significantly positively correlated with the CCVD (r = 0.479, p = 0.02).

Conclusions: The foveal choroidal thickness of young eyes with early RP was thicker than that previously reported; in particular, the large vessel layer was thicker in eyes with shorter ISe, which are considered to reflect comparatively advanced RP. In contrast, the
CCVD was decreased in the comparatively advanced RP eyes. In the early stage of RP in the young, the enlargement of large choroidal vessel could be a compensatory mechanism for atrophy of the CC prior to the stage of atrophy of all layers of the choroid.

Commercial Relationships: Naohiro Motozawa

Program Number: 3242 Poster Board Number: B0375
Presentation Time: 11:00 AM–12:45 PM
The relationship between the retinal structure and visual field measured with the microperimetry: MP-3, in patients with retinitis pigmentosa
Yuichi Asahina, Hiroshi Murata, Ryo Obata, Tatsuya Inoue, Ryo Asaoka. Ophthalmology, University of Tokyo, Tokyo, Japan.

Purpose: To investigate the structure-function relationship between the area of remaining ellipsoid zone (EZ) and visual field (VF) measured with the microperimetry: MP-3, in patients with type 2 retinitis pigmentosa (RP).

Methods: This retrospective study included 22 eyes of 11 patients with a clinical diagnosis of RP and with different diameters of hyperautofluorescent rings on fundus autofluorescence. VF measurements were carried out with these patients, using MP-3 and Humphrey Field Analyzer (HFA, Carl-Zeiss, CA). These VF measurements were carried out using the 10-2 test grid pattern for both perimetrics. In addition, optical coherence tomography (OCT, Spectralis, Heidelberg, Germany) measurement was carried out. The remaining EZ was identified using the OCT image and the boundary of the area with EZ was defined as ‘EZ edge’. Then the mean retinal sensitivities inside and outside the EZ edge were calculated. Finally, difference between the mean of retinal sensitivities inside and outside the EZ edge was evaluated and the magnitude of the difference was compared between MP-3 and HFA.

Results: 11.6±5.9 test points were located within the EZ edge. The mean retinal sensitivity inside the EZ edge was 23.4±4.0 and 30.4±3.5 dB, with MP-3 and HFA, respectively, whereas the mean retinal sensitivity outside the EZ edge was 8.7±3.7 and 19.1±4.2 dB with MP-3 and HFA, respectively. The difference between the retinal sensitivity inside and outside the EZ edge was significantly larger with MP-3 than that with HFA (p <0.001, linear mixed model).

Conclusions: Our findings reflect that MP-3 shows the difference of the retinal sensitivity between inside and outside the EZ edge more clearly than HFA.

Commercial Relationships: Yuichi Asahina, None; Hiroshi Murata, None; Ryo Obata, None; Tatsuya Inoue, None; Ryo Asaoka, None

Program Number: 3243 Poster Board Number: B0376
Presentation Time: 11:00 AM–12:45 PM
Risk factors for Posterior Subcapsular Cataract in Retinitis Pigmentosa

Purpose: Posterior subcapsular cataract (PSC) is a frequent complication in patients with retinitis pigmentosa (RP). The risk factor for PSC formation in RP is largely unknown. The purpose of this study was to investigate the risk factor for PSC.

Methods: We retrospectively studied a total of 322 eyes of 174 patients who were diagnosed with typical RP. Aqueous flare values were measured consecutively in 2012 and 2013 using a laser flare cell meter. The lens including PSC was examined at the slit lamp after dilation with tropicamide 1% and phenylephrine 2.5%.

Results: The geometric mean values of aqueous flare and mean values of visual acuity were significantly higher for the RP patients with PSC compared to those without PSC (P=0.0003, P=0.0004, respectively). When the aqueous flare values were assessed continuously, each 1-log-transformed increase in flare levels was associated with an elevation of the likelihood of having PSC after multivariable adjustment (OR, 1.80; 95% CI, 1.13–2.86). In other possible risk factors, there are no significant associations with PSC.

Conclusions: Our analysis demonstrated that elevated aqueous flare is a significant risk factor for PSC formation, suggesting that inflammation may be implicated in the pathogenesis of PSC formation in RP.

Commercial Relationships: Jun Funatsu, None; Kohta Fujiwara, None; Yasuhiro Ikeda, None; Yusuke Murakami, None; Shunji Nakatake, None; Takashi Tachibana, None; Noriko Yoshida, None; Shintaro Nakao, None; Toshio Hisatomi, None; Shigeo Yoshida, None; Tatsuro Ishibashi, None; Koh-hei Sonoda

Program Number: 3244 Poster Board Number: B0377
Presentation Time: 11:00 AM–12:45 PM
Central visual function over two-year follow-up of patients with RBP1 retinitis pigmentosa enrolled in a prospective Natural History Study
Kalliopi Stasi1, Michael Wald2, Marie Burstedt1, Jane Green1, James Whelan1, Michael Rossol1, Xiao Ni1, Zhenghong Su1, Jean-Yves Deslandes1, Cynthia L. Grosskreutz2, Karen Holopigian1, NIBR, Cambridge, MA; 2Umeå University, Umeå, Sweden; 3Memorial University of Newfoundland, St. John’s, NL, Canada.

Purpose: Central visual function is typically affected in moderate to advanced stages of retinitis pigmentosa. A subset of patients with retinitis pigmentosa due to mutations in both alleles of the RBP1 gene (RBP1P) shows early foveal involvement. A prospective Natural History Study was initiated to evaluate functional and structural endpoints in RBP1P RP patients. Here, we report preliminary 2-year results on test-retest variability and progression of central visual function measurements, namely best-corrected visual acuity, contrast sensitivity and color vision (results from other endpoints are presented in additional abstracts).

Methods: This non-interventional, two-center (Sweden and Canada), prospective study included evaluations of 45 RBP1P RP patients every 6 months. Central visual function was evaluated as best-corrected visual acuity (BCVA) in logMAR (ETDRS letter scores and low vision down to no light perception were converted to logMAR); contrast sensitivity (CS) in logCS using Pelli-Robson charts; and color vision (CV) as Bowman’s Total Color Difference Score (TCDS) assessed with Farnsworth D15 under illuminant C equivalent conditions. Annual progression was estimated as the slope of a random effect linear growth model and test-retest variability was assessed using the intra-class correlation coefficient (ICC). Between-eye correlations were made for each measurement at each visit.

Results: BCVA, CS and CV preliminary results (mean values) as well as annual progression slope and test-retest variability (ICC) for right (OD) and left (OS) eyes are displayed in the table. Statistically significant Pearson’s correlations between the two eyes at baseline and at each follow-up visit were observed for BCVA ranging from 0.92 to 0.96 (p <0.001), CS ranging from 0.91 to 0.94 (p <0.001), and CV ranging from 0.79 to 0.92 (p <0.001). No noticeable differences in mean and standard deviation for any assessments were observed between the two clinical sites.

Conclusions: For BCVA, CS and CV, there was no statistically significant progression over the 2-year follow-up. Patients with
RLBP1 RP showed similar severity of the disease in both eyes on all measurements of central vision.

Table: BCVA, CS and CV preliminary results (mean values) as well as annual progression slope and test-retest variability (ICC) for right (OD) and left (OS) eyes of RLBP1 RP patients.

<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.94</td>
<td>0.97</td>
<td>0.86</td>
<td>0.88</td>
<td>0.85</td>
<td>0.87</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.95</td>
<td>0.96</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.94</td>
<td>0.97</td>
<td>0.86</td>
<td>0.88</td>
<td>0.85</td>
<td>0.87</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.95</td>
<td>0.96</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>Month 24</td>
<td>0.94</td>
<td>0.97</td>
<td>0.86</td>
<td>0.88</td>
<td>0.85</td>
<td>0.87</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.95</td>
<td>0.96</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>Annual progression</td>
<td>0.94</td>
<td>0.97</td>
<td>0.86</td>
<td>0.88</td>
<td>0.85</td>
<td>0.87</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.95</td>
<td>0.96</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>ICC</td>
<td>0.97</td>
<td>0.97</td>
<td>0.86</td>
<td>0.88</td>
<td>0.85</td>
<td>0.87</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.95</td>
<td>0.96</td>
<td>0.06</td>
<td>-0.007</td>
<td>0.94</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Commercial Relations: Kalliopi Stasi, Novartis (E); Michael Wald, Novartis (E); Marie Burstedt, Novartis (C); Jane Green, Novartis (C); James Whelan, Novartis (C); Michael Rosol, Novartis (E); Xiao Ni, Novartis (E); Zhenzhong Su, Novartis (E); Jean-Yves Deslandes, Novartis (E); Cynthia L. Grosskreutz, Novartis (E); Karen Holopigian, Novartis (E)

Program Number: 3245 Poster Board Number: B0378
Presentation Time: 11:00 AM–12:45 PM

Dark Adaptation Testing in Retinitis Pigmentosa Patients using the AdaptDx
Tracey Topacio1, Ava K. Bittner2, 1College of Osteopathic Medicine, Nova Southeastern University, Davie, FL; 2Nova Southeastern University, Davie, FL.

Purpose: We report our experience with testing RP patients who have a wide range of vision loss using an instrument that has received FDA 510(k) clearance for measurement of dark-adaptation function, the AdaptDx (Maculogix).

Methods: The AdaptDx was used for dark adaptation testing at 5 degrees from fixation using a 76% initial bleach to assess the most sensitive location (i.e., temporal, nasal, inferior or superior) determined by photopic Humphrey 10-2 static perimetry in 23 RP subjects. Testing was stopped after 5-6 minutes if there was no evidence of dark adaptation (i.e., consistent cone-mediated sensitivity only). Testing was completed twice at two visits within a month for 16 of the subjects. At the same visits, subjects completed the following central visual function tests with and without a NoIR U23 4% transmission filter to simulate low luminance: ETDRS visual acuity (VA), Pelli-Robson contrast sensitivity (CS), and quick contrast sensitivity function (qCSF).

Results: Mean VA across subjects was 0.45 logMAR (SD 0.46; range -0.07 to 1.56). About a quarter to a fifth of the subjects (n=5; 22%) had a measurable rod intercept at 3 log units. Two subjects had a cone plateau at 2 log units and the majority (n=16; 70%) had only a minimal cone response <1 log unit. The test-retest 95% confidence of repeatability was 0.5 log units for mean sensitivity across subjects with cone-only AdaptDx responses (i.e., no measurable rod intercept).

A Bland-Altman graph analysis revealed there was no tendency across subjects with cone-only AdaptDx responses to perform better at either the first or second visit. Reduced mean sensitivity for cone-only AdaptDx responses was significantly associated with reduced central vision with the 4% transmission filter: VA (-0.76; 95%CI: -1.29, -0.23; p=0.005), CS (0.74; 95%CI:0.35,1.12; p<0.001) and qCSF (0.97; 95%CI: 0.51,1.42; p<0.001). Subjects who had >0.2 logMAR reduction in VA with the 4% filter compared to without the filter had significantly reduced AdaptDx cone sensitivity on average (-0.65; 95%CI: -1.12, -0.18; p=0.007).

Conclusions: The AdaptDx may be helpful to characterize RP patients who have rod versus cone-mediated dark adaptation at perifoveal locations and monitor for longitudinal changes.

Commercial Relations: Tracey Topacio, None; Ava K. Bittner, Adaptive Sensory Technology (F)
Support: NIH Grant EY023720 to AKB
Clinical Trial: NCT02086890

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.

Program Number: 3246 Poster Board Number: B0379
Presentation Time: 11:00 AM–12:45 PM

Humphrey visual field and flicker electroretinogram changes over two-year follow-up in patients with RLBP1 retinitis pigmentosa enrolled in a prospective Natural History Study
Karen Holopigian1, Jane Green1, James Whelan1, Marie Burstedt1, Zhenzhong Su1, Jean-Yves Deslandes2, Xiao Ni3, Michael Wald3, Cynthia L. Grosskreutz4, Kalliopi Stasi5, NIBR, East Hanover, NJ; 1Memorial University of Newfoundland, St. John’s, NL, Canada; 2Memorial University of Newfoundland, St. John’s, NL, Canada; 4Umea University, Umea, Sweden.

Purpose: Visual field defects and abnormal full-field electroretinograms (ERGs) occur early in retinitis pigmentosa due to RLBP1 mutations (RLBP1 RP) and can be used to follow disease progression. Visual fields and ERGs together with other functional and structural endpoints were monitored in a prospective Natural History Study in RLBP1 RP patients. Here, we report preliminary 2-year results on test-retest variability and progression of Humphrey visual fields and flicker ERGs (results from other endpoints are presented in additional abstracts).

Methods: This non-interventional, two-center (Sweden and Canada), prospective study included evaluations of 45 RLBP1 RP patients every 6 months. All participants had Humphrey visual fields (HVF) using the STIA standard 30-2 program. A subset of patients (n=15) had full-field light-adapted 30 Hz flicker ERGs with Ganzfeld stimulation (after pupil dilation). Annual progression was estimated as the slope of a random effect linear growth model and test-retest variability was assessed using the intra-class correlation coefficient (ICC). Between-eye correlations were performed for each measurement and at each visit.

Results: HVF mean deviation (MD) and ERG amplitude and implicit time preliminary results (mean values), as well as annual progression slope and test-retest variability (ICCs) for right (OD) and left (OS) eyes are displayed in the table. Statistically significant Pearson’s correlations between the two eyes at baseline and at each follow-up visit were noted for HVF MD ranging from 0.908 to 0.984 (p <0.001) for ERG amplitude ranging from 0.941 to 0.983 (p<0.001) and for ERG implicit time ranging from 0.923 to 0.964 (p<0.001).

Conclusions: RLBP1 RP patients showed HVF and flicker ERG deficits consistent with photoreceptor degeneration. Both eyes were similarly affected with respect to HVF and ERG measurements. There was no statistically significant progression over the 2-year follow-up.

Table: Mean of HVF mean deviation, ERG amplitude and implicit time, and annual progression slope and test-retest variability (ICCs) for right (OD) and left (OS) eyes of RLBP1 RP patients.

<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVF mean deviation (dB)</td>
<td>-22.3</td>
<td>-22.4</td>
<td>-23.0</td>
<td>-22.9</td>
<td>-23.0</td>
<td>-22.1</td>
<td>-0.45</td>
<td>-0.18</td>
<td>0.94</td>
<td>0.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERG amplitude (µV)</td>
<td>9.6</td>
<td>8.8</td>
<td>12.0</td>
<td>12.6</td>
<td>14.2</td>
<td>14.9</td>
<td>-0.68</td>
<td>-0.28</td>
<td>0.47</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERG implicit time (ms)</td>
<td>38.9</td>
<td>39.2</td>
<td>38.3</td>
<td>38.5</td>
<td>40.2</td>
<td>40.6</td>
<td>0.04</td>
<td>-0.09</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Commercial Relations: Karen Holopigian, Jane Green, Novartis Pharmaceuticals (C); James Whelan, Novartis Pharmaceuticals (C); Marie Burstedt, Novartis Pharmaceuticals (C); Zhenzhong Su, Novartis Pharmaceuticals (E); Jean-Yves Deslandes, Novartis Pharmaceuticals (E); Xiao Ni, Novartis Pharmaceuticals (E); Michael Wald, Novartis Pharmaceuticals (E); Cynthia L. Grosskreutz, Novartis Pharmaceuticals (E); Kalliopi Stasi, Novartis Pharmaceuticals (E)
TLR4 deficiency delays photoreceptor cell loss and visual function decline in the rd10 mouse model of retinitis pigmentosa

Catalina Hernandez-Sanchez, Alonso Sanchez-Cruz, Pedro de la Villa, Lizasoain Ignacio, Enrique J. De La Rosa.

1 Molecular and Cellular Medicine, Centro De Investigaciones Biologicas (CSIC), Madrid, Spain; 2 Universidad Complutense de Madrid, Madrid, Spain; 3 Universidad de Alcalã­ de Henares, Alcalã­ de Henares, Spain.

**Purpose:** Retinitis pigmentosa (RP) is a group of inherited retinal dystrophies that leads to blindness. Mutations in over 60 genes/loci have been associated to RP. Despite of the heterogeneous mutational etiology, RP courses, in most of the cases, with dysfunction and degeneration of photoreceptors. Reactive micro and macrogliosis and an inflammatory response are common traits that contribute to the pathogenesis of the disease. The aim of our study is to characterize the contribution of the innate immunity response to the RP physiopathology. In particular, in the current study we evaluated the implication of the Toll Like Receptor 4 (TLR4).

**Methods:** We compared the retinal degeneration time-course of the rd10 mouse null for the Tlr4 gene with the rd10 control. Retinal function was evaluated by ERG-recordings and the cytoarchitecture of the retina was analyzed by immunostaining of cryosections. Gene expression was assessed by RT-PCR.

**Results:** Tlr4 expression in rd10 mouse model showed up to six fold increase starting at P18, an early stage of degeneration. Visual function in the interval P26-47 declined significantly slower in TLR4+/− rd10 mice than in rd10 controls. Moreover ONL thickness was partially preserved in TLR4+/− rd10 mouse retinas, whereas the expression of proinflammatory cytokines showed a trend to decrease in TLR4 deficient animals.

**Conclusions:** TLR4 deficiency attenuates molecular, cellular and functional signs of retinal degeneration in the rd10 mouse model of RP.

**Commercial Relationships:** Catalina Hernandez-Sanchez, None; Alonso Sanchez-Cruz, None; Pedro de la Villa, None; Lizasoain Ignacio, None; Enrique J. De La Rosa, None.

Support: SAF2013-41059-R

---

Retinal structure evaluation using spectral domain optical coherence tomography in patients with Syndromic and Non-Syndromic forms of Retinitis Pigmentosa due to USH2A gene mutations


1 Université Libre de Bruxelles, Brussels, Belgium; 2 Università di Milano, Milan, Italy; 3 ASST Santi Paolo e Carlo - Ospedale San Paolo, Milan, Italy.

**Purpose:** To evaluate morphological macular changes using spectral domain optical coherence tomography (S- OCT) and their relationships with visual function, comparing patients affected by syndromic and non-syndromic forms of RP due to USH2A gene mutations.

**Methods:** 27 patients (54 eyes) with clinical signs and genetic diagnosis of Usher syndrome type IIa and 27 (54 eyes) with nonsyndromic RP with USH2A mutations were recruited. Data on clinical characteristics and best corrected visual acuity (BCVA) were extracted from medical charts, while morphological macular changes were evaluated on S-OCT scans by the analysis of the following structures: extension of ellipsoid zone (EZ), extension of external limiting membrane (ELM), central macular thickness (CMT), presence or absence of epiretinal membrane (ERM), presence or absence of cystoid macular edema (CME).

**Results:** All analyses were age corrected using multivariate mixed models. Usher patients were significantly younger compared to non syndromic patients (44.4±13.21 vs 55.7±12, p<0.01). Only male non syndromic patients had higher BCVA with respect to Usher subjects (0.77±0.07 vs 0.3±0.08, decimals). We found a significant difference in the extension of the EZ between non syndromic RP and Usher patients in both male and female (estimated difference 1648±380 μm, p=0.0001), while the difference in the extension of the ELM was significant for male subjects only (2584±55 μm, p=0.0001). Non syndromic patients had a higher CMT (estimated difference 53.61±19.4 μm, p 0.008). CMT was significantly affected by CME in males only (p<0.0001). Male Usher patients had a higher incidence on ERM compared to female Usher (OR 2.5, p=0.04).

**Conclusions:** Despite the younger age, Usher patients showed generally a more advanced stage of retinal degeneration, both in functional and in morphological aspects, with male subjects usually more impaired than females. The significant difference in CMT related to CME in male patients but not in females suggests a more important edema in male subjects. OCT data should be considered as markers of disease progression for future clinical trials evaluating RP therapies.

**Commercial Relationships:** Giulia Torregrossa, None; Leonardo Colombo; Giovanni Montesano, None; Fabio Patelli, None; Luca M. Rossetti, None.
six hours. Additionally, patients had abnormal FST thresholds which correlated (Pearson’s correlations) with age and BCVA at baseline as shown in Table 2.

**Conclusions:** RLPB1 RP patients showed severely delayed dark adaptation. There was no significant disease progression in FST thresholds over 2 years. There were good correlations of FST thresholds with age and BCVA.

Table 1: FST kinetics (mean values), as well as mean progression slope and test-retest variability (ICC) in RLPB1 RP patients.

<table>
<thead>
<tr>
<th>FST Min</th>
<th>Pre-Bleach</th>
<th>0 minutes</th>
<th>10 minutes</th>
<th>15 minutes</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>1 hour</th>
<th>6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-5.79</td>
<td>-3.22</td>
<td>-4.00</td>
<td>-4.13</td>
<td>-5.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 24 (log min)</td>
<td>-0.06</td>
<td>-3.33</td>
<td>-3.66</td>
<td>-4.04</td>
<td>-5.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.107</td>
<td>-0.047</td>
<td>-0.094</td>
<td>-0.084</td>
<td>-0.182</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICC</td>
<td>0.83</td>
<td>0.72</td>
<td>0.68</td>
<td>0.71</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Commercial Relationships:** Xiaon, Novartis (E); Michael Wald, Novartis (E); Marie Burstedt, Novartis (C); Jane Green, Novartis (C); James Whelan, Novartis (C); Zhenzhong Su, Novartis (E); Jean-Yves Deslandes, Novartis (E); Cynthia L. Grosskreutz, Novartis (E); Kalliopi Stasi, Novartis (E); Karen Holopigian, Novartis (E)

**Program Number:** 3250 Poster Board Number: B0383

**Presentation Time:** 11:00 AM–12:45 PM

**Volumetric assessment of scotopic visual field sensitivity in retinitis pigmentosa**

*Lea D. Bennett, Richard G. Weleber, Travis B. Smith, Martin Klein, David G. Birch* 1 Retina Foundation of the Southwest, Dallas, TX; 2 Oregon Health and Science University, Portland, OR.

**Purpose:** Static perimetry evaluates local luminance sensitivity and provides global indices, (mean sensitivity, mean deviation) as simplified metrics of a patient’s field of vision. Recently, Weleber et al., 2015, applied topographic hill of vision modeling and volumetric indices to quantify magnitude and extent of photopic visual field sensitivity in patients with retinitis pigmentosa (RP). We retrospectively applied this method to scotopic full-field sensitivities to determine if volumetric indices enhanced interpretation of rod function in patients with RP.

**Methods:** Normal controls (n=7) and 63 consecutive patients diagnosed with RP with visual acuity >20/400 and kinetic visual field >10°, had one eye dilated and dark-adapted for 45 minutes. Sensitivity to a 505nm size V stimulus was tested with a 144°, 120-loci grid (solid angle 2.797 steradian, sr) with a dark-adapted chromatic perimeter (Medmont International Pty Ltd; Victoria, Australia). Field volumes were calculated with Visual Field Modeling and Analysis software (Weleber et al. 2015). Responses to scotopic ISCEV standard FERG flashes were analyzed. Relationships were evaluated with Pearson’s correlation coefficient (r) and least squares regression.

**Results:** The mean total scotopic visual field volume, VTOT, in dB-sr, for normal controls and patients with RP was 146.7±9 SD (range 135.159) and 44±34 SD (range 0-122), respectively. Of the 63 patients, 54(86%) had rod-mediated sensitivity in at least 3 field locations. FERG responses to 0.01 and 3.0cd/s·m² flashes were measurable from 32(51%) and 50(79%) of patients, respectively. The FERG response to 0.01cd/s·m² increased 1 log unit for every 42dB-sr increase in total field volume (r=0.6574, p<0.0001). Responses to the 3.0cd.s/m² flash increased 1 log unit for every 49dB-sr increase in total field volume in patients with RP (r=0.7558, p<0.0001).

**Conclusions:** Rod-mediated vision was detected with scotopic perimetry in a higher percentage of patients than with fFERG. Volumetric indices broadened interpretation of rod function in patients with RP by providing a topographic model of the scotopic field of vision and by extracting the depth and magnitude of both rod-mediated function and scotomatous regions in the peripheral visual field. Scotopic perimetry will be beneficial for targeted treatment and as an index for the scope of rod impairment in patients with retinal diseases affecting rod photoreceptors.

**Commercial Relationships:** Lea D. Bennett, None; Richard G. Weleber, SAB member AGTC (travel reimbursement, no honorarium) (R), OHSU Sanofi, AGTC and FFB (F), The Foundation Fighting Blindness (FFB) Serves on Scientific Advisory Boards (with honorarium) (S), US patent 8,657,446, Method and apparatus for visual field monitoring, also known as Visual Field Modeling and Analysis, or VFMA, not licensed, no royalty accrued (P), AGTC (C); Travis B. Smith, None; Martin Klein, None; David G. Birch, None

**Support:** NIH EY09076 and FFB

**Program Number:** 3251 Poster Board Number: B0384

**Presentation Time:** 11:00 AM–12:45 PM

**Cross-sectional evaluation of patient-reported outcomes (PROs) in patients with RLPB1 retinitis pigmentosa enrolled in a Natural History Study**

*Annol Mullins, Marie Burstedt, Jane Green, James Whelan, Brigitte Sloesen, Xiaon, Zhenzhong Su, Michael Wald, Cynthia L. Grosskreutz, Kalliopi Stasi, Karen Holopigian, Jean-Yves Deslandes, NIBR, Novartis, Cambridge, MA; 1 Umeå University, Umeå, Sweden; Memorial University of Newfoundland, St John’s, NL, Canada*

**Purpose:** Evaluation of patient reported outcomes (PROs) enables an understanding of the relationship between patient quality of life (QoL) and disease severity as assessed by various functional and structural measures. The National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) has been associated with visual function outcomes in retinitis pigmentosa (RP) due to mutations in the RLPB1 gene (RLPB1 RP) (Burstedt et al., 2005 and 2010). However, there is a limited understanding of the Low Luminance Questionnaire (LLQ) in RLPB1 RP patients. The VFQ-25 and the LLQ, together with functional and anatomic endpoints, were assessed as part of a prospective Natural History Study in RLPB1 RP patients. Here, we report preliminary cross-sectional results of the PRO evaluations and their relationship to functional endpoints (results of other endpoints from this study are presented in additional abstracts).

**Methods:** In a non-interventional, two-center, prospective study of 45 RLPB1 RP patients, annual PRO evaluations (VFQ-25 and the LLQ) were added beginning with the Month 24 follow-up visit. Weighted averages of visual function [logMAR visual acuity (VA), contrast sensitivity (CS) and Humphrey visual field mean deviation (MD)] were calculated (wVA, wCS and wMD) for the visits at which the PRO questionnaires were administered. To account for binocular vision, single weighted averages (wV A, wCS and wMD) of binocular vision, single weighted averages (wV A, wCS and wMD) for the visits at which the PRO questionnaires were administered. To account for binocular vision, single weighted averages (wV A, wCS and wMD) of individual eye scores were calculated as 0.75 of the value for the eye with better VA and 0.25 of the value for the fellow eye.

**Results:** Forty-one patients of the 45 patients enrolled in two sites (26 patients in Umeå, Sweden and 15 in St John’s, Canada) completed both questionnaires. The mean (min, max) total scores of VFQ-25 and LLQ were 55.1 (25.1, 100) and 38.5 (8.7, 80.6), respectively. The mean and standard deviation (SD) age, wVA, wCS and wMD were 48.6 (14.8) years, 0.95 (0.82) logMAR, 0.88 (0.59) respectively.

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to [http://iovs.arvojournals.org/](http://iovs.arvojournals.org/) to access the versions of record.
Commercial Relationships: Anmol Mullins, Novartis (E); Marie Burststedt, Novartis (C); Jane Green, Novartis (C); James Whelan, Novartis (C); Brigitte Sloesen, Novartis (E); Xiao Ni, Novartis (E); Zhenzhong Su, Novartis (E); Michael Wald, Novartis (E); Cynthia L. Grosskreutz, Novartis (E); Kalliopi Stasi, Novartis (E); Karen Holopigian, Novartis (E); Jean-Yves Deslandes, Novartis (E)

Program Number: 3252 Poster Board Number: B0385
Presentation Time: 11:00 AM–12:45 PM

Hyper reflective foci represent decreased fundus auto fluorescence in eyes with retinitis pigmentosa

Yosuke Nagasaka, Yasuki Ito, Shinji Ueno, Hiroko Terasaki. Ophthalmology, Nagoya University Graduate school of Medicine, Nagoya, Japan.

Purpose: Recently, hyper reflective small dots in optical coherence tomography (OCT) scan, called hyper reflective foci (HRFs), as an abnormal retinal finding and those relation to disease activity have been reported in various retinal diseases including retinitis pigmentosa (RP). To investigate the behavior of HRFs in the eyes with RP, we compared OCT scans, fundus scanning laser ophthalmoscope (SLO) images, fundus auto fluorescence (AF) and fundus photograph in this study.

Methods: Clinical charts of a total of 48 RP patients (age of 43.1±16.0 years, range 10 to 85) were retrospectively reviewed. The spectral domain (SD)-OCT macular volume scans of 48 patients (92 eyes) were reviewed and compared with fundus AF images of corresponding area, to investigate the distribution of outer retinal HRFs in the macular area and the relation with area of photoreceptor inner and outer segment junction (IS/OS) preservation and AF defect. Representative 10 eyes were used for statistical analysis.

Results: The areas with HRF were corresponded to decreased AF area in the fundus AF in all eyes. The areas with HRFs were not overlapped with the areas with IS/OS. The manually measurements of area with HRF were significantly correlated with those of area with decreased AF in 10 eyes (p<0.001, r=0.99).

Conclusions: HRFs distribute in the area with IS/OS disruption and specifically correspond to decreased AF area. HRFs appear in the area that outer retinal degeneration and relate to AF defect.

logCS and -22.2 (10.3) dB, respectively. The table below provides pairwise Spearman’s correlation coefficients.

Conclusions: The VFQ-25 total score in this study was in agreement with prior studies in 49 RLBP1 RP patients (Burststedt et al., 2005). The VFQ-25 was strongly correlated with wVA, wCS and wMD while the LLQ was strongly correlated with wVA and wMD. VFQ-25 and LLQ scores were strongly correlated.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>wVA</th>
<th>wCS</th>
<th>wMD</th>
<th>VFQ-25raw</th>
<th>VFQ-25cont</th>
</tr>
</thead>
<tbody>
<tr>
<td>wVA</td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wCS</td>
<td>-0.29</td>
<td>-0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wMD</td>
<td>-0.44</td>
<td>-0.70</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VFQ-25raw</td>
<td>-0.39</td>
<td>-0.73</td>
<td>0.72</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLQcont</td>
<td>-0.63</td>
<td>0.65</td>
<td>0.49</td>
<td>0.53</td>
<td>0.50</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Representative images of 10 RP patients (A-J), comparing fundus photograph, distribution map, fundus auto fluorescence. The areas with HRF (yellow), IS/OS (blue) are shown.

Commercial Relationships: Yosuke Nagasaka, None; Yasuki Ito, None; Shinji Ueno, None; Hiroko Terasaki, None

Program Number: 3253 Poster Board Number: B0386
Presentation Time: 11:00 AM–12:45 PM

Vitreo-macular interface alterations in retinitis pigmentosa patients determined by spectral domain optical coherence tomography

Carmela Carnevale, Serena Fragiotta, Erika Rigoni, Enzo Maria Vingolo. Ophthalmology, Sapienza University of Rome, Fondi, Italy.

Purpose: To determine the prevalence and to analyze structural characteristics of vitreo-macular interface (VMI) alterations in Retinitis Pigmentosa (RP) patients using spectral domain optical coherence tomography (SD-OCT). We categorized the presence of different macular abnormalities such as epiretinal membrane (ERM), vitreo-macular traction (VMT) syndrome, macular hole (MH) and cystoid macular edema (CME).

Methods: A retrospective cross-sectional study was performed in 167 RP patients. They underwent a complete ocular examination including assessment of best-corrected visual acuity (BCVA), slit-lamp and fundus examination. All SD-OCT images were acquired by only examiner using the Heidelberg SD-OCT (software version 5.4.7.0) in a pattern of 20-x15-degree (5.8x4.3 mm) rectangle centered on the fovea. The scanning protocol comprised 25 line scans each composed of 50 averaged frame. Continuous variables were expressed as mean±SD. Categorical variables were compared using Chi-squared test. P values <0.05 were considered statistically significant and P<0.001 was considered highly statistically significant.

Results: Out of the 167 RP patients included, 76 of them (121 eyes, 41 ♂ and 35♀, mean age 49.70±13.91 years) showed VMI alterations on OCT. The average BCVA for all patients was 0.42 logMAR units. VMI alterations were found as isolated (eg, ERM) in 63,78% of cases and in association (eg, ERM+VMT) in 36,22% of cases. ERM was observed in 75 eyes (59.05%) of 76 patients. The discontinuity of ERM was found in 73 eyes and it was continuous in 38 eyes (31.4%) (P<0.001). The cleavage’s area was detectable in only 34 eyes (28.1%), VMT was detected in 13 eyes; it was broad in 11 eyes and focal in 2 eyes (P<0.02). MH are full thickness in 2 of
14 cases (14.3%) and lamellar hole in 6 of 14 cases (42.8%). CME was observed in association only with ERM in 25 eyes (19.68%) and combined with ERM and MH in 2 eyes (1.57%).

**Conclusions:** SD-OCT is a powerful tool to detect VMI alterations in RP patients. It allows to monitor the clinical course of these abnormalities and the effectiveness of therapy for patients by providing reproducible measurements. VM complications in RP patients are well noted but we reported for the first time the structural characterization of those abnormalities in order to establish which patients could benefit from current or innovative therapeutic strategies.

**Commercial Relationships:** Carmela Carnevale, None; Serena Fragiotta, None; Erika Rigoni, None; Enzo Maria Vincolo, None

**Program Number:** 3254 Poster Board Number: B0387
**Presentation Time:** 11:00 AM–12:45 PM

**Baseline characteristics of patients with RLB1P1 retinitis pigmentosa enrolled in a prospective Natural History Study**

Jane Green↑, Marie Burstedt↑, James H. Whelan↑, Yunsheng He↑, Zhenzhong Su↑, Xiao Ni↑, Michael Wald↑, Guillaume Normand↑, Jean-Yves Deslandes↑, Cynthia L. Grosskreutz↑, Karen Holopigian↑, Kalliopi Stasi↑.

**1.** Medical Genetics, Memorial University, Memorial Univ of Newfoundland, Middle Cove, NL, Canada; 2. Umea University, Umea, Sweden; 3. Surgery (Ophthalmology), Memorial University, Memorial University of Newfoundland, St. John’s, NL, Canada; 4. Novartis, Cambridge, MA.

**Purpose:** Purpose: Retinitis pigmentosa (RP) due to biallelic mutations in the RLB1P1 gene (RLBP1 RP) is an autosomal recessive form of RP, characterized by prolonged dark adaptation and progressive loss of peripheral and then central vision. No prospective natural history study has been conducted on these patients. 159 to 165 patients with identified mutation(s) in RLBP1 have been reported in the peer-reviewed literature. The purpose of this study is to evaluate variability and progression of functional and structural endpoints in RLBP1 RP patients. Here, we report the study design and preliminary baseline data (results of 2-year follow-up are presented in additional abstracts).

**Methods:** Methods: This is a non-interventional, two-center, prospective study evaluating RLBP1 RP patients every 6 months. The study assessments were: 1) basic eye exam (slit-lamp exam, dilated fundus exam, tonometry), 2) functional assessments including best corrected visual acuity (BCVA) in logMAR (ETDRS letter scores down to no light perception converted to logMAR); contrast sensitivity (CS); color vision (CV); full-field flicker electroretinograms (ERGs); full-field stimulus threshold (FST) dark-adaptation kinetics up to 6 hours for 2 wavelengths (450 and 632 nm); Humphrey visual fields (HVF); and 3) structural assessments by optical coherence tomography and fundus photography. All assessments were performed in both eyes, except the FST.

**Results:** Results: Forty-five patients (15 men and 30 women) aged 18-70 with RLBP1 mutations were enrolled between Sept 2013 and Jan 2015 (30 patients in Umeå, Sweden and 15 in St John’s, Canada). Key baseline measurements and the correlation between right (OD) and left (OS) eyes are shown in the table below. The recovery of FST to prebleach retinal sensitivity was severely prolonged (between 3-6 hours for both wavelengths). No noticeable differences were observed in any assessments between the two clinical sites. Pearson’s correlations between age and BCVA, central retinal thickness (CRT), HVF mean deviation were 0.60 (p = 0.0001), -0.15 (p = 0.035) and -0.50 (p = 0.0005), respectively (for FST-tested eye).

**Conclusions:** Conclusions: All endpoints collected for both eyes showed high correlations between eyes confirming bilateral symmetry of the disease. All patients showed severe dark adaptation prolongation. BCVA and HVF mean deviation were correlated with age.

<table>
<thead>
<tr>
<th>Table: Baseline measurements and correlation between right (OD) and left (OS) eyes in RLBP1 RP patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ap (years)</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>41.1</td>
</tr>
<tr>
<td>Pearson’s correlation coefficient</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Commercial Relationships:** Jane Green, Novartis (C); Marie Burstedt, Novartis (C); James H. Whelan, Novartis (C); Yunsheng He, Novartis (E); Zhenzhong Su, Novartis (E); Xiao Ni, Novartis (E); Michael Wald, Novartis (E); Guillaume Normand, Novartis (E); Jean-Yves Deslandes, Novartis (E); Cynthia L. Grosskreutz, Novartis (E); Karen Holopigian, Novartis (E); Kalliopi Stasi, Novartis (E)

**Program Number:** 3255 Poster Board Number: B0388
**Presentation Time:** 11:00 AM–12:45 PM

**Longitudinal evaluation of optical coherence tomography and color fundus photography over 2 year follow up in patients with RLBP1 retinitis pigmentosa**

James H. Whelan↑, Guillaume Normand↑, Michael Maker↑, Marie Burstedt↑, Jane Green↑, Michael Wald↑, Zhenzhong Su↑, Xiao Ni↑, Karen Holopigian↑, Cynthia L. Grosskreutz↑, Kalliopi Stasi↑.

1. Surgery/Ophthalmology, Memorial University, St. John’s, NL, Canada; 2. Novartis Institute of BioMedical Research, Cambridge, MA; 3. Umea University, Umea, Sweden.

**Purpose:** Purpose: Retinal thinning is a common feature of retinitis pigmentosa including patients with RLBP1 mutations (RLBP1 RP). Some RLBP1 RP patients also have white dots in the retina. A Natural History Study was initiated to evaluate functional and structural endpoints in RLBP1 RP patients. Here, we report preliminary 2-year results of optical coherence tomography (OCT) and color fundus photography (CFP) including OCT sublayer analysis (other endpoints in additional abstracts).

**Methods:** In a non-interventional, two-center, prospective study, 45 patients with RLBP1 RP were followed every 6 months, with OCT (3D-OCT 2000, Topcon & Cirrus, Zeiss) and CFP (3D-OCT 2000, Topcon). Total retinal thickness was reported for each of the nine ETDRS subfields. All scans were processed using single retinal layer analysis (OCTExplorer, IDx) for the following layers of interest: Ellipsoid Zone (EZ), Outer Nuclear Layer (ONL), total photoreceptors (PR) and Inner Retina (IR). Two trained graders evaluated OCT and CFP for retinal abnormalities. Annual progression and test-retest variability were calculated as change from baseline and intra-class correlation coefficients (ICC), respectively.

**Results:** OCT data were obtained from 43 RLBP1 RP patients over 2 years. The baseline central retinal thickness (CRT) was 173 and 163 μm, with test-retest variability measured by ICC of 0.83 and 0.98 and annual progression slope of -0.002 and -0.004 for the right (OD) and left eye (OS), respectively. The retinal thickness in the other eight ETDRS subfields did not show significant changes. Preliminary results of OCT sublayer thickness analysis are displayed in the table. Epiretinal membrane (mostly peripheral) was observed in 86.7% and 80.0% at baseline, and 86.7% and 86.7% at 2 years in OD and OS eyes, respectively. Cystoid macular edema was observed in 4.4% and 6.7% at baseline, and 2.2% and 4.4% at 2 years in OD and OS eyes, respectively. Macular traction, macular holes and retinal cysts were also observed in some patients. Common features in CFP were: slight
optic disc pallor, white dots or dark pigment, mild macular atrophy and slight narrowing of blood vessels.

**Conclusions:** RLPB1 RP patients showed reduced central and sublayer retinal thickness. There were no significant changes in retinal thickness over 2 years. CFP showed consistent features with the disease phenotype.

<table>
<thead>
<tr>
<th>Table: OCT sublayer thickness (mean values) and test-retest variability (ICC) in RLPB1 RP patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZ</td>
</tr>
<tr>
<td>20.4</td>
</tr>
<tr>
<td>58.3</td>
</tr>
<tr>
<td>127.2</td>
</tr>
<tr>
<td>72.9</td>
</tr>
</tbody>
</table>

**Commercial Relationships:** James H. Whelan, Novartis (C); Guillaume Normand, Novartis (E); Michael Maker, Novartis (E); Marie Burstedt, Novartis (C); Jane Green, Novartis (C); Michael Wald, Novartis (E); Zhenzhong Su, Novartis (E); Xiao Ni, Novartis (E); Karen Holopigian, Novartis (E); Cynthia L. Grosskreutz, Novartis (E); Kalliopi Stasi, Novartis (E)

**Program Number:** 3256 Poster Board Number: B0389
**Presentation Time:** 11:00 AM–12:45 PM
**OCT Angiography and Correlation with Macular Structure and Function in Retinitis Pigmentosa**

Sandeep Grover, Kumar Sambhav. Ophthalmology, University of Florida College of Medicine, Jacksonville, FL.

**Purpose:** To correlate the optical coherence tomography angiography (OCTA) findings with macular structure - central macular thickness (CMT) and ellipsoid zone (EZ) width on OCT, and macular function - best-corrected visual acuity (BCVA) in patients with retinitis pigmentosa (RP).

**Methods:** Retrospective study evaluated 30 eyes of 16 subjects (age range, 12 to 59 years) with RP. The BCVA was measured in all subjects and they underwent SD-OCT scans (Heidelberg, Germany) and OCTA scans (RTVue XR 100Avanti, Optovue, CA, USA). The CMT and EZ width were calculated from the SD-OCT scans and the ‘vessel density (VD)’ was calculated for various retinal en-face zones and choriocapillaris layer from the OCTA scans.

**Results:** The mean visual acuity was 0.40±0.3 (range, 0-1.2; median, 0.3) and the CMT was 268.23±61.15μm (range, 133-387μm; median, 282μm). The mean EZ width was 1204.23±907.24μm (n=26). OCTA of the foveal area showed a VD of 30.07±6.01 in the superficial zone, 28.84±5.77 in the deep zone, 47.67±5.69 in the photoreceptor zone and 62.37±5.41 in the choriocapillaris zone. GraphPad InStat v.3 (San Diego, California, USA) was used for statistical analysis. Spearman’s correlation coefficient was tested to evaluate the linear correlation among variables in RP patients. P value of <0.05 for multiple correlation coefficients was considered significant.

The EZ width correlated significantly only with the superficial zone VD. The CMT correlated significantly with the VD of all 3 retinal zones – more so with superficial and photoreceptor zones. The visual acuity correlated significantly with the VD of the superficial and photoreceptor zones. None of the macular structural tests or functional tests correlated significantly with choriocapillaris VD.

**Conclusions:** Macular structure (CMT and EZ width) and function (visual acuity) correlate most with the superficial foveal VD and photoreceptor VD. The significance of photoreceptor VD is unknown as there are no vessels in that area. These findings may provide a clue to the pathophysiology of RP and the vascular attenuation. Future studies in RP patients may shed further light on the role of the developing novel technology of OCTA in this condition. OCTA may become a new useful additional tool to monitor disease activity and efficacy of new therapeutic approaches.

**Commercial Relationships:** Sandeep Grover, None; Kumar Sambhav, None

**Program Number:** 3257 Poster Board Number: B0390
**Presentation Time:** 11:00 AM–12:45 PM
**Intrafamilial Phenotype Variation Associated with BBS1 Met390Arg**

Conor P. Malone1, Matthew Carrigan2, Karen Collins2, Hilary Dempsey1, Adrian Dockery3, G. J. Farrar2, Paul F. Kenna1, 2. 1Research Foundation, Royal Victoria Eye and Ear Hospital, Dublin 2, Ireland; 2Ocular Genetics Unit, School of Genetics and Microbiology, Trinity College Dublin, Dublin, Ireland.

**Purpose:** To report wide phenotype variation in 3 siblings, homozygous for BBS1 Met390Arg, identified by Next Generation Sequencing (NGS)

**Methods:** Over 700 retinopathy patients, including 3 siblings reported here, have been recruited to our ongoing Target 5000 NGS initiative at the Research Foundation, Royal Victoria Eye and Ear Hospital, Dublin. Patients are assessed using best-corrected visual acuity (BCVA), perimetry, colour vision testing, slit-lamp biomicroscopy, electroretinography, fundus photography, and optical coherence tomography. With informed consent, DNA samples undergo exon sequencing of 218 retinopathy-associated genes using target-capture oligo panels.

**Results:** The proband had nyctalopia at 12 and marked concentric field-loss symptoms at 25. Fundoscopy showed extensive bone-spicule retinal deposits. She was diagnosed with Retinitis Pigmentosa (RP) at 25. BCVA at 45 was Hand Movements in each eye. A sister had reduced day vision and moderate concentric field loss at 18. Fundoscopy showed macular changes. Peripheral pigment deposits have never been observed. She had good night vision until 32. BCVA at 36 was 6/15 in each eye. A brother had nyctalopia and poor day vision at 25. BCVA at 48 was 6/24 in each eye. Peripheral pigment and macular changes supported a diagnosis of RP. Another sibling and both parents were phenotypically normal. NGS revealed all 3 were homozygous for a T > G transition at nucleotide 1169 in BBS1 resulting in Methionine to Arginine substitution at codon 390. Following clinical diagnosis of RP, but prior to the elucidation of the BBS1 Met390Arg mutation, the proband was diagnosed with renal dysfunction responsive to diet restriction. Her sister with predominantly macular changes was diagnosed with diet-controlled non-insulin dependent diabetes. None of the 3 is significantly obese and none has any evidence of compromised mentation. Following genotyping it emerged that 2 of the 3 had supernumerary toes removed in childhood.

**Conclusions:** Pleiotropism in Bardet Biedl syndrome (BBS) is well documented. Approximately 17 genes are implicated; BBS1 mutations account for almost 25% of cases. Met390Arg accounts for 80% of BBS due to mutations in BBS1. Our study shows that even among siblings BBS may present differently. Identification of a well-known BBS1 mutation in patients in whom clinical findings did not initially point to BBS emphasises the utility of genotyping in refining clinical diagnosis.

**Commercial Relationships:** Conor P. Malone, None; Matthew Carrigan, None; Karen Collins, None; Hilary Dempsey, None; Adrian Dockery, None; G. J. Farrar, None; Paul F. Kenna, None

**Support:** Fighting Blindness (Ireland), Health Research Board (Ireland)
Progressive Loss of Rod Sensitivity in Patients with Autosomal Dominant Retinitis Pigmentosa (adRP) due to RHO Pro23His Mutation

Kirsten G. Locke1, Sarah Duwel2, Artur V. Cideciyan3, David B. McGugan4, Alessandro Iannaccone5, John Heckenlively6, Samuel G. Jacobson1, Michael McCaleb3, David G. Birch3

1Retina Foundation of the Southwest, Dallas, TX; 2Emmes Corporation, Rockville, MD; 3Schie Eye Institute, Univ of Pennsylvania, Philadelphia, PA; 4Ophthalmology, Duke University, Durham, NC; 5Ophthalmology, Univ of Michigan, Ann Arbor, MI; 6Ionis Pharmaceuticals, Carlsbad, CA.

Purpose: Although longitudinal clinical characterization of patients having RHO mutations has been reported, there has been insufficient quantitative characterization of rod photoreceptor loss to enable the design of therapeutic clinical trials for this form of adRP. As part of an ongoing multi-center 2-year natural history study, patients with a confirmed RHO Pro23His mutation were evaluated for clinical and retinal endpoints every 6 months at 4 sites in the US. Testing included measures of visual acuity, visual fields, dark-adapted fundus perimetry, ERG and spectral domain optical coherence tomography. Here we report preliminary rod sensitivity data obtained from a subset of study participants over one year follow-up.

Methods: A total of 27 adRP patients (8-66 yr age; BCVA of -0.1 to +0.5 logMAR) having a confirmed P23H RHO mutation were enrolled. Following pupil dilation and at least 30 minutes of dark adaptation, sensitivity was measured with an MP-1S (Nidek USA) at 64 locations within the vessel arcades but excluding the fovea. Blue stimuli (spot-size V) were used to obtain sensitivity values, and red stimuli in the same locations were used to identify locations where sensitivity was mediated by rods. Subjects with no detectable rod sensitivity were excluded. For those retaining rod-mediated sensitivity, average change was calculated for each patient over 6 and 12 months at locations that were rod mediated at baseline.

Results: Preliminary data were available from 16 patients followed through one year. In the right eye, mean (+1 s.e.) sensitivity at rod-mediated locations was 28.8 (+1.6) dB at baseline, 27.3 (+1.8) dB at 6 months, and 24.2 (+2.2) dB at 12 months. In the left eye, mean (+1 s.e.) sensitivity at rod-mediated locations was 29.5 (+1.7) dB at baseline, 26.1 (+1.8) dB at 6 months, and 23.8 (+1.8) dB at 12 months. Repeated measures analyses of variance indicated significant progression over 1 year for OD (F=8.9; p=0.0009) and for OS (F=15.4; p<0.0001).

Conclusions: Preliminary results suggest that rod sensitivity loss can be detected with scotopic fundus perimetry over 1 year in adRP patients with RHO Pro23His mutation.

Commercial Relationships: Kirsten G. Locke, None; Sarah Duwel, None; Artur V. Cideciyan, None; David B. McGugan, None; Alessandro Iannaccone, Ionis Pharmaceuticals (C); John Heckenlively, None; Samuel G. Jacobson, None, Michael McCaleb, Ionis Pharmaceuticals (E); David G. Birch, Ionis Pharmaceuticals (C)

Support: Ionis Pharmaceuticals

Program Number: 3259
Poster Board Number: B0392
Presentation Time: 11:00 AM–12:45 PM

Fundus Findings Associated with Complications in X-Linked Retinoschisis

Abigail Fahim1, Naser Ali1, Taylor Blachley1, Michel Michaelides1

1University of Michigan, Ann Arbor, MI; 2Moorfields Eye Hospital, London, United Kingdom.
**Purpose:** Complications of vitreous hemorrhage and retinal detachment cause a precipitous decline in vision in a subset of patients with X-linked retinoschisis (XLRS), an otherwise a slowly progressive condition. We compared the frequency of specific fundus findings in XLRS patients with and without vitreous hemorrhage and retinal detachment to determine whether any fundus findings are associated with these complications.

**Methods:** A retrospective observational chart review was performed for patients with XLRS, confirmed by detection of a disease-causing variant in RS1. The presence of macular and peripheral retinal findings (including macular schisis, macular atrophy, peripheral retinoschisis, metallic sheen, vascular sheathing, pigimentary changes, white spiculations, and vitreous veils) and the presence of complications of vitreous hemorrhage and retinal detachment were determined by review of examination notes, fundus photographs, and optical coherence tomography (OCT). Fisher exact tests and univariable logistic regression analysis were used to determine the association between peripheral retinal findings and complications.

**Results:** The presence of peripheral retinoschisis was significantly associated with both vitreous hemorrhage and retinal detachment. Out of 10 eyes with complications, 9 (90%) had peripheral retinoschisis, compared with only 33 out of 116 eyes (28%) without complications (p=0.0014). In addition, each additional peripheral finding increased the odds of RD by a factor of 4.06 (95% CI 1.58-10.39, p=0.028). There were no complications in the 28 eyes with a normal periphery (p=0.84) or in the 35 eyes with metallic sheen (p=0.42). Seven eyes (8%) showed normal macular structure on OCT.

**Conclusions:** The data suggest that patients with peripheral retinoschisis are at increased risk for complications of vitreous hemorrhage and retinal detachment. Furthermore, patients with additional peripheral retinal findings together with peripheral schisis may carry additional risk for retinal detachment.

**Commercial Relationships:** Abigail Fahim, None; Naser Ali, None; Taylor Blachley, None; Michel Michaelides, None

---

**Purpose:** Stargardt disease (STGD) is caused by pathogenic variants in the ABCA4 gene and has characteristic fundus findings such as macular atrophy and flecks at the posterior pole, which tend to extend peripherally. Fundus autofluorescence (FAF) has proven to be a valuable tool in the diagnosis and surveillance of this condition. Standard 30° field imaging is generally utilized with these patients, however limiting evaluation to the posterior pole. Using wide-field fundus photography (WF-P) and wide-field fundus autofluorescence (WF-FAF), we studied peripheral retinal changes in patients with mutation-proven Stargardt disease.

**Methods:** A retrospective chart review was performed for patients with a clinical diagnosis of STGD and with two or more variants in the ABCA4 gene that were classified by the genetic testing lab as either pathogenic or likely pathogenic. We excluded patients without WF-P, defined as either Optos 200° retinal imaging (Optos 200 Tx, Optos PLC, Dunfermline, United Kingdom) or composites of 50° fundus photographs. Age of symptoms, disease duration, full-field electroretinogram (fERG) and WF-FAF were examined.

**Results:** Of 145 patients with a molecular diagnosis of SGDT, 97 had WF imaging. Among those, 12 (12.37%) presented with peripheral pigmented retinal lesions. All patients presented with early-onset disease (mean age 9.33 years, range 7-13), with mean disease duration of 16 years (range 6-29), 53.8% were female. Rod-cone loss on ERG was observed in 91.3%. On WF-P, all peripheral lesions were pigmented, and on WF-FAF, most lesions were hyperautofluorescent, except for a newly formed one that was hypoautofluorescent with some mottled hypoautofluorescence in the center. In 6 patients with follow-up images, 4 showed growth of those lesions including one patient who developed new lesions.
Conclusions: Pigmented peripheral lesions may occur in patients with early-onset STGD, seem to be acquired and may progress. These lesions mostly present as hypoautofluorescent lesions on FAF, although in early stages might be hyperautofluorescent. These lesions can be mistaken for congenital hypertrophy of retinal pigment epithelium.

Program Number: 3263 Poster Board Number: B0396
Presentation Time: 11:00 AM–12:45 PM
Survival and functionality of iPSC-RPE cultured as a polarized monolayer on ultrathin parylene assessed in a new immunodeficient RCS rat model
Biju Thomas1, 2, Yousuf Shad1, Juan C. Martinez1, 4, Niharika Singh1, Young Chang Kim1, Seth Freeman1, Sean A. Mu1, Vishweshwer Shastri1, Kapil Bharti1, Mark S. Humayun1, 4, David R. Hinton1, Danhong Zhu1. 1Ophthalmology, USC Eye Institute, Chino Hills, CA; 2National Eye Institute, Bethesda, MD; 3Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA; 4USC Institute for Biomedical Therapeutics, Los Angeles, CA; 5McMaster University, Hamilton, ON, Canada.

Purpose: RPE replacement therapy is now evolved as a feasible approach to treat human retinal degeneration diseases like Age-related Macular Degeneration (AMD). This study is aimed to evaluate the survival and functionality of induced pluripotent stem cell derived retinal pigment epithelium (iPSC-RPE) cultured as a polarized monolayer on parylene substrate and transplanted into the subretinal space of a new immunodeficient Royal College of Surgeon (RCS) rat disease model.

Methods: Polarized iPSC-RPE (passage two cells generated from healthy adult human fibroblast cells) was cultured for 2 weeks on rectangular pieces of ultrathin parylene (0.4mm x 0.9mm). After the cells developed into a confluent monolayer, the implants were surgically placed into the subretinal (SR) space of postnatal day (P) 28 RCS rat pups (n=10). Histological assessments were performed using H&E and immunostaining techniques. Visual function was tested using an optokinetic (OKN) head-tracking apparatus and by electrophysiological mapping of the superior colliculus (SC).

Results: iPSC-RPE cultured on ultrathin parylene substrate appeared as a confluent monolayer and expressed RPE 65 and ZO1. In vitro characterization data demonstrated that this iPSC-RPE shows good similarity to fetal RPE (compared to hESC-RPE). Based on histological evaluation at 1 month and 2 month post-implantation, the iPSC-RPE survived and maintained its monolayer structure in all implanted rats. The transplanted RPE expressed RPE 65, iRBP and performed phagocytosis of shed photoreceptor outer segments. Visual functional improvement in immunodeficient dystrophic RCS rats following iPSC-RPE transplantation was demonstrated by SC luminance threshold mapping data (iPSC-RPE implanted rats -3.1±1.7 log cd/m² vs non-transplanted rats -0.6±0.3 log cd/m²). Based on OKN visual behavioral test, good preservation of visual activity was observed in the iPSC-RPE implanted eyes whereas no such responses were observed in the non-implanted eyes.

Conclusions: iPSC-RPE cells implanted as a polarized monolayer into the SR space of immunodeficient RCS rats can survive as a monolayer and contribute to visual functional benefits. The results support the use of such implants for therapeutic approaches aimed at slowing the progression of outer retinal degeneration diseases.

Commercial Relationships: Biju Thomas, None; Yousuf Shad, None; Juan C. Martinez, None; Niharika Singh, None; Young Chang Kim, None; Seth Freeman, None; Sean A. Mu, None; Vishweshwer Shastri, None; Kapil Bharti, None; Mark S. Humayun, None; David R. Hinton, None; Danhong Zhu, None

Support: Research to Prevent Blindness (RPB), Bright Focus Foundation

Upper: baseline WF-P showing peripheral retinal pigmented lesions in the left eye. Lower: follow-up showing newly developed lesions in both eyed and growth of pre-existent lesion.

WF-FAF showing both hypo and hyperautofluorescent lesions compatible with the lesions seem on WF-P.

Commercial Relationships: Maria Fernanda Abalem, None; Peter Yu Cheng Zhao, None; Daniel Nadelman, None; Cynthia X. Qian, None; Kari E. Branham, None; Dana Schiegel, None; Naheed W. Khan, None; John R. Heckenlively, None; Thiran Jayasundera, None

Support: Research to Prevent Blindness (RPB), Bright Focus Foundation

These abstracts are licensed under a Creative Commons Attribution-NonCommercial-No Derivatives 4.0 International License. Go to http://iovs.arvojournals.org/ to access the versions of record.