265 Inherited retinal diseases and mactel
Monday, May 08, 2017 3:45 PM–5:30 PM
Ballroom 3 Paper Session
Program #/Board # Range: 2010–2016
Organizing Section: Retina

Program Number: 2010
Presentation Time: 3:45 PM–4:00 PM
Natural History of Inherited Retinal Disease (IRD) in Patients with Mutations in the Retinal Pigment Epithelial 65 Protein (RPE65) or Lecithin:Retinol Acyltransferase (LRAT) Genes
Robert K. Koenekoop. McGill Ocular Genetics Laboratory, McGill University Health Centre, Montreal, QC, Canada.
Purpose: Studies over the past several decades have reported on the natural history of visual function in IRD subjects but were not always inclusive or limited to patients with particular genetic defects. This retrospective, multicenter, case history study was designed to expand this knowledge in subjects with LCA or RP due to *RPE65* or *LRAT* gene mutations, including treatment naïve patients and those previously treated with oral synthetic retinoid, Zuretinol acetate (QLT091001) therapy (ZA-treated) in order to assess the extent to which ZA treatment may improve or prolong visual function.
Methods: Study subjects with IRD were divided into two cohorts, treatment naïve and previously ZA-treated. Inclusion criteria for the treatment naïve cohort 1 included at least two documented kinetic visual fields (KVFs) of the same isopter(s) in at least one eye at least 2 years apart between ages of 6 and 65 years. Inclusion criteria for the treated cohort 2 included at least one documented KVF and/or visual acuity (VA) assessment prior to or following participation in the ZA trials. The natural history slopes of KVF and VA over time were generated using a random coefficient regression model.
Results: Data of 54 subjects at 9 study centers are reported, including 29 subjects in cohort 1 and 25 in cohort 2. Overall there were equal numbers of males and females with a mean age of first assessment of 11.1 years for cohort 1 and 15.2 years for cohort 2. Forty six subjects (85%) were diagnosed with LCA and 8 subjects (15%) with RP. The majority of cohort 1 subjects showed loss in KVF area over time. The rate of decline in KVF area appeared to be faster for the larger target sizes and slower for the smaller target sizes. VA also declined but showed periods of relative stability. For cohort 2, ZA-treatment resulted in improvement in visual function for a majority of subjects. Most subjects lost KVF area prior to ZA-treatment and continued to lose function after ZA-treatment effects ceased.
Conclusions: The study demonstrated a progressive deterioration over time in both VF area and VA in subjects with LCA or RP associated with *RPE65* or *LRAT* gene mutations. A majority of cohort 2 subjects demonstrated improvements in VF and/or VA with ZA-treatment, which cannot be explained by the natural history of the disease.
Commercial Relationships: Robert K. Koenekoop, Novelion Therapeutics (C)
Clinical Trial: NCT02575430

Program Number: 2011
Presentation Time: 4:00 PM–4:15 PM
The Effect Of Vitamin A On Progression Of Retinitis Pigmentosa Is Not Determined By The Underlying Genetic Cause Of Disease
Eric A. Pierce, Kinga M. Bujakowska, Emily Place, Daniel Navarro-Gomez, Matthew Maher, Carol Weigel-DFranco, Jason Comander. Ocular Genomics Institute, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA.
Purpose: Three clinical trials were performed between 1984 and 2008 to test the hypothesis that vitamin A supplementation alone or in combination with DHA or lutein can slow the rate of progression of retinal degeneration for patients with retinitis pigmentosa (RP). The results of these trials showed that on average, patients taking 15,000 IU of vitamin A per day experienced slower decline in 30 Hz electroretinogram (ERG) response amplitudes than controls (Berson et al Arch Ophthalmol 130: 707, 2012). The goal of this study was to ask if patients with different genetic forms of RP respond to vitamin A supplementation differently.
Methods: 330 subjects were identified who participated in one or more of the three vitamin A clinical trials, and who had sufficient 30Hz ERG amplitudes to avoid floor artifacts. We performed panel-based genetic testing for subjects who did not have genetic diagnoses from prior studies. Robust linear regression and mixed regression models were used to construct exponential rate of decay estimates for each subject, grouped by gene and vitamin A treatment status.
Results: 189 subjects with genetic diagnoses were available for analyses, including 126 in the vitamin A treated group, and 63 in the control group. 47 had mutations in *USH2A*, 35 in *RHO*, 28 in *RPGR*, 11 in *PRPF31*, and 8 in *PRPH2*. The rate of loss of retinal function of subjects with *USH2A* mutations was faster than that in other genotypes ($p<0.0001$), and slower with *PRPH2* mutations ($p=0.04$). Subjects with *RHO*-associated RP (N=35) who took vitamin A did not have a significantly slower rate of decline of 30Hz amplitude than controls (-8.3% vs -7.6%/year, $p>0.05$). Vitamin A supplementation appeared to reduce the rate of decline in retinal function for subjects with *PRPH2*-associated RP: -3.8%/yr in controls (N=5) versus +2.1%/yr in the vitamin A group (N=3), $p=0.007$.
Conclusions: The treatment effect of vitamin A did not appear to be concentrated in patients with specific genetic causes of disease. One small genetic subgroup of patients with *PRPH2*-associated RP showed a larger than average vitamin A treatment effect, but this finding was based on a small number of subjects. These data suggest that the previously observed benefit of vitamin A supplementation for adults with typical RP applies broadly for patients with different genetic forms of disease, within the limits of the sample sizes evaluated.
Commercial Relationships: Eric A. Pierce, None; **Kinga M. Bujakowska**, None; **Emily Place**, None; **Daniel Navarro-Gomez**, None; **Matthew Maher**, None; **Carol Weigel-DFranco**, None; **Jason Comander**, None
Support: Foundation Fighting Blindness, National Eye Institute [EY012910 and P30EY014104 (MEEI core support)], Research to Prevent Blindness.
Clinical Trial: NCT00000114

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Program Number: 2012
Presentation Time: 4:15 PM–4:30 PM
***RPGR*-associated retinal dystrophies: a longitudinal study**
Mays Talib[1], Mary J. van Schooneveld[2], Jan Wijnholds[1], Nicoline Schalij-Delfos[1], Ralph J. Florijn[3], Ingeborgh Van Den Born[9], Frans P. Cremers[8], Alberta A. Thiadens[7], Carel C. Hoyng[6], Caroline Klaver[5, 6], Arthur Bergen[3, 4], Camiel J. Boon[1, 2]. [1]Ophthalmology, Leiden University Medical Center, Leiden, Netherlands; [2]Ophthalmology, Academic Medical Center, Amsterdam, Netherlands; [3]Clinical Genetics, Academic Medical Center, Amsterdam, Netherlands; [4]The Netherlands Institute for Neuroscience (NIN-KNAW), Amsterdam, Netherlands; [5]Ophthalmology and Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands; [6]Ophthalmology, Radboud University Medical Center, Nijmegen, Netherlands; [7]Ophthalmology, Erasmus Medical Center, Rotterdam, Netherlands; [8]Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands; [9]The Rotterdam Eye Hospital, Rotterdam, Netherlands.
Purpose: Variants in the *RPGR* gene account for the majority of X-linked retinal dystrophies. As *RPGR* gene therapy is being developed, a thorough understanding of the phenotypic spectrum and natural history of *RPGR*-associated retinal dystrophies is important. We performed a retrospective, observational clinical study to describe the clinical course of these patients.
Methods: Medical records of 71 male patients with *RPGR*-associated retinal dystrophies, from 37 families, were reviewed for age at onset, best corrected visual acuity (BCVA), retinal imaging, full-field electroretinography, and Goldmann visual fields (GVF). GVF areas were digitized to seeing retinal areas (mm^2). The decline rate of the seeing retinal area was determined with mixed model analysis.
Results: Presence of a pathogenic *RPGR* variant was molecularly confirmed in 68 patients (96%), while 3 patients were first degree relatives of patients with a confirmed *RPGR* mutation. We found 31 distinct variants; 10 in exon 1-14 (21 patients, 30%) and 21 in exon ORF15 (50 patients, 70%). The median follow-up time was 11.3 years (range 0-57.1). Forty-nine patients had a retinitis pigmentosa (RP) phenotype (69%), and 15 (21%) and 7 (10%) patients had a cone-rod dystrophy or cone dystrophy, respectively. ORF15 mutations were found in higher proportions ($p<0.05$) in patients with predominantly cone disease (20/22, 91%) than in RP patients (30/49, 61%). The mean age at symptom onset was 4.9 years (±4.8; range 0-14) for RP patients and 25.9 years (±21.7; range 0-65) for patients with predominantly cone disease. The mean ages for reaching low vision (BCVA<0.3) and blindness (BCVA<0.05) were 46.7 (SE 3.6) and 67.5 (SE 4.7) years for RP patients, and 61.9 (SE 5.0) and 73.3 (SE 6.2) years for patients with predominantly cone disease, respectively. The survival distributions for BCVA did not differ between patients with ORF15 or exon 1-14 mutations. Symmetry in BCVA was found in 86% of patients. RP patients had a faster decline in seeing retinal area than patients with predominantly cone disease ($p<0.001$), with a yearly decline of 7%.
Conclusions: Based on the BCVA survival, the intervention window for future gene therapy is broader in patients with primary cone disease than in RP patients, but does not differ between patients with ORF15 or exon 1-14 mutations. Patients with primary cone involvement had a more favourable course of GVF decline than RP patients.
Commercial Relationships: Mays Talib, None; **Mary J. van Schooneveld**, None; **Jan Wijnholds**, None; **Nicoline Schalij-Delfos**, None; **Ralph J. Florijn**, None; **Ingeborgh Van Den Born**, None; **Frans P. Cremers**, None; **Alberta A. Thiadens**, None; **Carel C. Hoyng**, None; **Caroline Klaver**, None; **Arthur Bergen**, None; **Camiel J. Boon**, None
Support: Curing Retinal Blindness Foundation, Stichting Blindenhulp, Janivo Stichting

Program Number: 2013
Presentation Time: 4:30 PM–4:45 PM
Progression of Atrophic Lesions Determined by Fundus Autofluorescence: The Natural History of the Progression of Atrophy secondary to Stargardt Disease (ProgStar) Study
Rupert W. Strauss[1, 2], Xiangrong Kong[3], Alex Ho[4], Anamika Jha[4], Michel Michaelides[1], Artur V. Cideciyan[5], Jose A. Sahel[6, 7], David G. Birch[8], Amir H. Hariri[4], Srinivas R. Sadda[4, 9], Sheila West[3], Hendrik P. Scholl[10, 11]. [1]Moorfields Eye Hosp & Inst of Ophthal UCL, London, United Kingdom; [2]Ophthalmology, Johannes Kepler University & Medical University Graz, Linz, Austria; [3]DANA Center for preventive ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD; [4]Doheny Eye Institute, Los Angeles, CA; [5]Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA; [6]Institut de la Vision, Paris, France; [7]Ophthalmology, UPMC Medical Center, Pittsburgh, PA; [8]Retina Foundation of the Southwest, Dallas, TX; [9]UCLA David Geffen School of Medicine, Los Angeles, CA; [10]Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD; [11]Department of Ophthalmology, University of Basel, Basel, Switzerland.
Purpose: The multicenter ProgStar study aims to characterize the natural history of Stargardt disease type 1 (STGD1) and develop new outcome measures for trials. The yearly rate of growth of atrophic lesions measured by fundus autofluorescence (FAF) imaging is the primary endpoint.
Methods: Participants were enrolled from nine sites in the US and Europe, and were followed every 6 months. 18-month follow-up data were used in this analysis. FAF images were sent from the nine participating sites to a central reading center and areas of definitely decreased AF (DDAF), well-demarcated questionably decreased AF (WD-QDAF), and poorly demarcated questionably decreased AF (PD-QDAF) were outlined and quantified. Based on background uniformity, homogeneous versus heterogeneous background was defined. Linear mixed effects models were used to estimate the annual rate of change in lesion areas while accounting for between-eye and within-eye correlations.
Results: 489 study eyes of 259 patients (54 % female) were enrolled in the prospective study. Mean age at baseline was 33.3 (sd 15.1) years. At baseline, DDAF was present in 307 (63%) eyes, mean lesion size 3.94 (sd 4.36) mm2; WD-QDAF in 71 (15%) eyes, mean lesion size 1.54 (sd 1.38) mm2, and PD-QDAF in 300 (62%) eyes, mean lesion size 2.16 (sd 1.91) mm2. Over 18 months, 50 eyes out of the 151 eyes (33.1 %) without any DDAF at baseline and available at month 18, developed a lesion of DDAF. Among eyes with DDAF at baseline, progression rate of DDAF was 0.75 (95%CI 0.61-0.90) mm2 per year ($p<.001$), and the rate of DDAF growth was significantly different by baseline AF background ($p<.001$): it was 0.44 (0.23-0.65) and 1.02 (0.83-1.21) mm^2 per year in eyes with homogeneous versus heterogeneous background, respectively. Baseline DDAF size was also significantly associated with DDAF growth rate - the larger the baseline lesion, the faster the progression ($p<.001$). Combining all lesion types, the mean progression rate was 0.65 (CI 0.55-0.74) mm^2 per year.
Conclusions: FAF may serve as an outcome measure of treatment trials that aim to slow/halt the progression of STGD1.
Commercial Relationships: Rupert W. Strauss; **Xiangrong Kong**, None; **Alex Ho**, None; **Anamika Jha**, None; **Michel Michaelides**, None; **Artur V. Cideciyan**, None; **Jose A. Sahel**, ERC Synergy

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"HELMHOLTZ" (F), Foundation Fighting Blindness (F), Genesignal (C), Pixium Vision (I), Chronocam (I), Pixium Vision (C), GenSight (F), GenSight Biologics (I), GenSight Biologics (C), Chronolife (I), LabEx LIFESENSES (ANR-10-LABX-65) (F), Banque publique d'Investissement (F); **David G. Birch**, None; **Amir H. Hariri**, None; **Srinivas R. Sadda**, Novartis (C), Optos (C), Allergan (F), Carl Zeiss Meditec (F), Genentech (C), Thrombogenics (C), Optos (F), Genentech (F), Iconic (C), Allergan (C); **Sheila West**, None; **Hendrik P. Scholl**, Gerson Lehrman Group (C), Intellia Therapeutics (C), ReNeuron Group Plc/Ora Inc. (C), Vision Medicines, Inc. (C), Acucela Inc. (F), Gensight Biologics (C), Genzyme Corp./Sanofi (R), NightstaRx Ltd. (F), Guidepoint (C), QLT, Inc (F), Boehringer Ingelheim Pharma GmbH & Co. KG (C), Daiichi Sankyo (C), Genentech Inc./F. Hoffmann-La Roche Ltd. (R), Shire (C)
Support: Foundation Fighting Blindness Clinical Research Institute (FFB CRI) and a grant to FFB CRI by the U.S. Department of Defense USAMRMC TATRC, Fort Meade, Maryland (grant numbers W81-XWH-07-1-0720 and W81XWH-09-2-0189)
Clinical Trial: NCT01977846

Program Number: 2014
Presentation Time: 4:45 PM–5:00 PM
Insensitive short-term clinical trial endpoint in Stargardt disease: progression of best-corrected visual acuity
Sanne K. Verbakel[1], Stanley Lambertus[1], Nathalie Bax[1], Dyon Valkenburg[1], Ramon van Huet[1], Joannes Groenewoud[2], Carel C. Hoyng[1]. [1]Department of Ophthalmology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, Netherlands; [2]Department for Health Evidence, Radboud university medical center, Nijmegen, Netherlands.
Purpose: To evaluate the efficacy of future gene augmentation therapy trials for Stargardt disease, the endpoint needs to distinguish a treatment effect from the effect of time. Visual acuity demonstrates an extremely variable decline rate; yet, it may well be an appropriate endpoint in children progressing rapidly. We performed a retrospective, observational clinical study to determine if best-corrected visual acuity (BCVA) decline is an appropriate endpoint at different ages at presentation.
Methods: We selected 218 patients (422 eyes) with clinically confirmed Stargardt disease supported by at least one variant in the *ABCA4* gene. We collected BCVA over a maximum period of five years. Patients were grouped based on their age at presentation <18 years, 18–26 years, or >26 years. We estimated the BCVA decline using a linear mixed-effects model with time, subgroups, and an interaction term between time and subgroups as covariates. We performed sample size calculations for a theoretical intervention with 50% effect in slowing BCVA decline, using an unpaired t-test with a two-sided significance level of 0.05 and a power of 0.80.
Results: A total of 1446 eye-visits were included with a median follow-up of 3.3 years (interquartile range [IQR], 3.8), 1.1 years (IQR 3.9) and 0.71 years (IQR 3.2) in the <18, 18-26 and >26 group, respectively ($p<0.001$). The average baseline BCVA was 0.29 logMAR (95% CI, 0.26 – 0.33) for the age subgroup >26 years, and was 0.20 logMAR (0.15 – 0.25) and 0.20 logMAR (0.14 – 0.25) higher for age groups < 18 years, and 18 – 26 years, respectively. The average BCVA decline was 0.098 logMAR/year (0.07 – 0.13). The model failed to detect differences between age groups.
To detect a 50% treatment effect within 2 years of follow-up, 860 patients are needed.
Conclusions: Best-corrected visual acuity failed to identify differences in progression speed between children and adults, and thus does not support a preferred selection of children in therapeutic trials. However, failure in detecting differences in progression speed is likely because of the insensitivity of BCVA itself rather than the absence of such differences. As a large number is needed to identify a treatment effect, BCVA is unlikely to be a sensitive endpoint for short-term treatment efficacy.
Commercial Relationships: Sanne K. Verbakel, None; **Stanley Lambertus**, None; **Nathalie Bax**, None; **Dyon Valkenburg**, None; **Ramon van Huet**, None; **Joannes Groenewoud**, None; **Carel C. Hoyng**

Program Number: 2015
Presentation Time: 5:00 PM–5:15 PM
Sex steroids and macular telangiectasia type 2
Simone Mueller[1], Jean-Pierre Allam[2], Chris Bundzek[2], Traci E. Clemons[4], Frank G. Holz[1], Peter Charbel Issa[1, 3]. [1]Department of Ophthalmology, University of Bonn, Bonn, Germany; [2]Department of Dermatology/Andrology Unit, University of Bonn, Bonn, Germany; [3]Oxford Eye Hospital, University of Oxford, Oxford, United Kingdom; [4]The Emmes Corporation, Rockville, MD.
Purpose: To investigate the relationship between macular telangiectasia (MacTel) type 2 and systemic levels of sex steroids or their antagonization.
Methods: In 41 male MacTel patients as well as 115 age related healthy controls, free serum testosterone levels were measured. 49 female patients were evaluated for previous surgical (e.g. ovariectomy) and/or pharmacological (e.g. aromatase inhibitors, tamoxifen) therapies resulting in reduced systemic availability of sex steroids or suppression of their effects. Disease onset was determined by an interview about the patients' first disease-related visual disturbances.
Results: Female patients frequently (33%, 14/49) had a history of pharmacological suppression of sex steroids and/or ovariectomy, and this subgroup was significantly younger at disease-onset when compared to those without previous therapy affecting sex steroids (mean ± SD: 47.1±7.8 versus 60.1±7.6; $p<0.01$). The mean interval (±SD) between initiation of therapy/surgery and first symptoms was 3.4±5.0 years. Male MacTel patients showed significantly lower free serum testosterone levels compared to age related controls. Differences were highly significant in young patients, as opposed to non-significant differences in older patients. In men aged ≤60 years, a biochemical hypogonadism (defined as free serum testosterone <0.05 ng/ml) was present in 53% (8/15) and 4% (2/49) of patients and controls, respectively. Due to the age-related physiological decline in sex steroids, this difference was less pronounced in those >60 years-of-age (patients: 54%, 14/26; controls: 36%, 24/66).
Conclusions: The results indicate that steroidal sex hormones might be involved in the pathophysiology of MacTel type 2, a complex, multifactorial disease.
Commercial Relationships: Simone Mueller, ProRetina Deutschland (F), Lowy Medical Research Institute (F); **Jean-Pierre Allam**, Jenapharm (F); **Chris Bundzek**, Jenapharm (F); **Traci E. Clemons**, Lowy Medical Research Institute (F); **Frank G. Holz**, ProRetina Deutschland (F), Lowy Medical Research Institute (F); **Peter Charbel Issa**, Lowy Medical Research Institute (F), ProRetina Deutschland (F)

Program Number: 2016
Presentation Time: 5:15 PM–5:30 PM
Penetrance Estimation of Macular Telangiectasia Type 2 (MacTel) from Families in Utah and Idaho
Cecinio Ronquillo, Paul S. Bernstein. Department of Ophthalmology, John A. Moran Eye Center, University of Utah, Salt Lake City, UT.
Purpose: Macular telangiectasia (MacTel) is an adult-onset autosomal dominant disease with reduced penetrance. Here, we a)

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describe newly-identified families affected with MacTel; b) determine disease penetrance estimates by sibling and parent analysis; and c) highlight one of the probands who, at 21 years old, is one of the youngest reported to have MacTel.

Methods: From a total of more than 50 probands identified from clinical records in Utah and Idaho, 23 were clinically phenotyped, diagnosed with MacTel and confirmed by the London Reading Centre. Clinical phenotyping included a baseline eye exam, OCT of the macula, fluorescein angiography, fundus autofluorescence and measurement of macular pigment density. If p is the penetrance probability of a candidate gene causing MacTel and under the assumption that this disease is very rare, the probability that a sibling or parent is affected was calculated to be $p/2$.

Results: For 15 of the probands, there were a total of 51 siblings. Of the 44 siblings who were clinically phenotyped, 9 were diagnosed with MacTel. Four probands had both parents clinically phenotyped and only 1 out of the 4 probands did not have either of the parents affected. Analysis shows vertical transmission of MacTel from both male and female in 3 of our families suggesting an autosomal dominant disease. From our sibling data, we estimate the penetrance to be 0.41 (standard error: 0.12, 95% CI: 0.17, 0.65). From analysis of our parent data, an unbiased estimate of penetrance is 0.75. With such a small sample, formal analysis is not advised. Finally, one of our probands, a 21-year-old male shows the characteristic clinical appearance of MacTel with decreased macular pigment and telangiectatic parafoveal capillaries.

Conclusions: Our results show that the penetrance of MacTel is 41% by sibling analysis and 75% by parent analysis. Sibling penetrance may be a low estimate because some of the siblings may still be too young to exhibit symptoms. Also, the current teaching that MacTel is an age-related disease is now being challenged with diagnosis in younger individuals.

Commercial Relationships: Cecinio Ronquillo; **Paul S. Bernstein**, None

Support: Lowy Research Medical Research Institute and Research to Prevent Blindness

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