Drug treatment


Treatment of Neovascular Age-Related Macular Degeneration with Anti-VEGF Agents: Predictive Factors of Long-Term Visual Outcomes.

Pedrosa AC, Sousa T, Pinheiro-Costa J, Beato J, Falcão MS, Falcão-Reis F, Carneiro A.

PURPOSE: To evaluate the predictive factors of long-term visual outcomes in neovascular age-related macular degeneration (nAMD) treated with antivascular endothelial growth factor (anti-VEGF) agents.

METHODS: Unicentric retrospective review of patients with nAMD treated with anti-VEGF agents. Visual outcomes, 12 and 60 months after diagnosis, were evaluated. In an attempt to identify predictive factors of visual outcomes, multiple variables (demographic and epidemiological characteristics, angiographic and tomographic features) were analyzed, at baseline and during follow-up.

RESULTS: One hundred and seventeen patients were included. In multivariate analysis, baseline best-corrected visual acuity was associated with all visual endpoints at 12 and 60 months. Additionally, age, gender, number of injections, and development of subretinal fibrosis during follow-up were also significant predictors of visual outcomes at 60 months.

CONCLUSIONS: Several factors can be useful in clinical practice as predictors of visual outcomes in response to anti-VEGF treatment of nAMD.

PMID: 28656102 PMCID: PMC5471580


TOPIC: The aim of this article is to review and compile available information on the classification, pathophysiology, and clinical features of myopic choroidal neovascularization (CNV); to describe the latest data on the management of this disease; and to present guidance.

CLINICAL RELEVANCE: In the United States, myopia affects approximately 34 million people (2010), and similar figures have been reported in Europe. Pathologic myopia (PM), a possible consequence of myopia, is estimated to affect up to 3% of the global population. One of the most serious complications of PM is myopic CNV, which often leads to a sudden onset but progressive decline in central vision and is associated with a poor prognosis unless treated. Furthermore, 35% of patients with myopic CNV develop
bilateral disease in the fellow eye within 8 years. Although intravitreal anti-vascular endothelial growth factor (VEGF) therapies have had a major impact on the management of patients with myopic CNV, there remain significant gaps in our understanding of this condition and how to best administer treatment. Additionally, the long-term safety and efficacy of these treatments are largely unknown.

METHODS: We carried out a literature review (September 2015) of all English-language articles in PubMed resulting from searches of the following terms: "choroidal neovascularization" AND "myopia" OR "myopic macular degeneration" OR "degenerative myopia" OR "myopic maculopathy" OR "myopic retinopathy" OR "pathological myopia" OR "pathologic myopia."

RESULTS: We screened a total of 566 abstracts, and 250 articles were deemed relevant for full publication review. We excluded a further 71, but an additional 44 articles were identified. This resulted in 223 articles being used to develop this review.

CONCLUSIONS: Highly myopic patients experiencing a sudden loss of central vision should be referred for further examination. Once a diagnosis of myopic CNV has been confirmed, after fluorescein angiography, treatment initiation should be prompt and anti-VEGF agents considered as first-line therapy, unless contraindicated. Continued monitoring of patients is required to assess any progression or recurrence of the condition.

PMID: 28655539


Prediction of Anti-VEGF Treatment Requirements in Neovascular AMD Using a Machine Learning Approach.


PURPOSE: The purpose of this study was to predict low and high anti-VEGF injection requirements during a pro re nata (PRN) treatment, based on sets of optical coherence tomography (OCT) images acquired during the initiation phase in neovascular AMD.

METHODS: Two-year clinical trial data of subjects receiving PRN ranibizumab according to protocol specified criteria in the HARBOR study after three initial monthly injections were included. OCT images were analyzed at baseline, month 1, and month 2. Quantitative spatio-temporal features computed from automated segmentation of retinal layers and fluid-filled regions were used to describe the macular microstructure. In addition, best-corrected visual acuity and demographic characteristics were included. Patients were grouped into low and high treatment categories based on first and third quartile, respectively. Random forest classification was used to learn and predict treatment categories and was evaluated with cross-validation.

RESULTS: Of 317 evaluable subjects, 71 patients presented low (≤5), 176 medium, and 70 high (≥16) injection requirements during the PRN maintenance phase from month 3 to month 23. Classification of low and high treatment requirement subgroups demonstrated an area under the receiver operating characteristic curve of 0.7 and 0.77, respectively. The most relevant feature for prediction was subretinal fluid volume in the central 3 mm, with the highest predictive values at month 2.

CONCLUSIONS: We proposed and evaluated a machine learning methodology to predict anti-VEGF treatment needs from OCT scans taken during treatment initiation. The results of this pilot study are an important step toward image-guided prediction of treatment intervals in the management of neovascular AMD.

PMID: 28660277

Change in vision-related quality of life and influencing factors in Asians receiving treatment for neovascular age-related macular degeneration.


AIM: To assess the change in vision-related quality of life (VRQoL) after treatment for neovascular age-related macular degeneration (nAMD) and factors influencing this change in an Asian population.

METHODS: In this longitudinal study, 116 patients (mean age±SD=66.5±9.9 years; 59.5% male) who underwent treatment for nAMD were recruited from a tertiary eye centre in Singapore. Best-corrected visual acuity (BCVA) and the Impact of Vision Impairment (IVI) questionnaire were evaluated at baseline and month 12. We defined three categories of BCVA change in the treated eye: BCVA gain ≥2 lines; no change in BCVA; BCVA loss ≥2 lines. The main outcome measures were the Rasch-derived IVI Reading, Mobility, and Emotional Scores. Multivariable linear regression analyses assessed the influence of sociodemographic, clinical and treatment-related factors on change in VRQoL.

RESULTS: Following treatment, mean treated-eye BCVA improved by almost 2 lines (-0.22±0.40 logMAR, p<0.001) and 43% (n=50) patients reported a gain in BCVA of ≥2 lines. Mean±SD scores for Reading, Mobility and Emotional demonstrated positive changes of 0.43±1.73, 0.45±1.54 and 0.66±1.6, respectively (p<0.001 for all). In multivariable models, a ≥2 line improvement in BCVA was independently associated with a 47% (β=0.20; CI 0.01 to 0.39) increase in Reading Scores, but was not independently associated with Mobility or Emotional Scores.

CONCLUSION: Nearly half of patients undergoing treatment for nAMD reported a 2-line improvement in vision which was, in turn, associated with substantial positive increases in Reading Scores. Improvements in Mobility and Emotional Scores appear to be driven by factors other than visual acuity.

PMID: 28659392


Effect of intravitreal ranibizumab on the ocular circulation of the untreated fellow eye.

Sugimoto M, Nunome T, Sakamoto R, Kobayashi M, Kondo M.

PURPOSE: To evaluate the effects of unilateral intravitreal ranibizumab (IVR) on the ocular circulation of the fellow eyes.

METHODS: Fifteen eyes of 15 patients with macular edema (average age 69.6 ± 11.8 years) were studied. Eleven eyes had diabetic macular edema (DME) and four eyes had macular edema associated with a branch retinal vein occlusion. Each eye received 0.5 mg of IVR. The blood circulation on the optic nerve head of the treated and untreated eyes were determined by laser speckle flowgraphy (LSFG, Softcare Co., Ltd) before, 1 day, and 1 week after the IVR. The mean blur rate (MBR) and the relative changes of the MBRs determined as dMBR(%) = 100 × (MBR before/MB after) × 100 were evaluated. The central macular thickness (CMT) and the rate of reduction in the thickness (dCMT = 100 × (CMT before/CMT after) × 100) were also evaluated.

RESULTS: The mean dMBR was significantly higher in the treated eyes than the untreated eyes at 1 day (-16.4 ± 17.0% vs 2.31 ± 19.3%) and at 1 week (-12.0 ± 14.6% vs 4.50 ± 25.9%) after the IVR (P = 0.02, paired t tests).

CONCLUSION: These findings indicate that if ranibizumab enters the systemic circulation, the concentration is not high enough to affect the ocular circulation of the fellow eyes.

PMID: 28656342

Short-term efficacy of intravitreal Aflibercept injections for retinal angiomatous proliferation.

Chou HD, Wu WC, Wang NK, Chuang LH, Chen KJ, Lai CC.

BACKGROUND: To evaluate the short-term efficacy of intravitreal injections of aflibercept (IVA) to treat retinal angiomatous proliferation (RAP) and identify factors related to functional outcomes.

METHODS: This retrospective case series consisted of 19 eyes in 19 patients with RAP. All 19 eyes received 3 monthly consecutive IVA. The primary outcome measures were best-corrected visual acuity (BCVA) and central retinal thickness (CRT) after the last IVA.

RESULTS: Of the 19 treated eyes, 8 (42%) were pre-treated with 1 dose of bevacizumab one month prior to the initiation of treatment with aflibercept. BCVA was significantly improved and CRT was significantly reduced after 3 consecutive IVAs (P = 0.014 and P = 0.0002, respectively). Stabilization or improvement in BCVA was observed in 17 eyes (90%) treated with IVA. Eyes with baseline fibrovascular pigment epithelial detachment (PED) showed no significant gain in BCVA, and fibrovascular PED was negatively correlated with final BCVA (Spearman's correlation coefficient = -0.481, P = 0.037). The mean follow-up was 3.5 ± 0.5 months.

CONCLUSIONS: In this short-term study, three consecutive IVAs showed efficacy for improving vision and reducing retinal edema in RAP patients. Eyes with fibrovascular PED showed poorer responses, and the presence of fibrovascular PED at baseline was negatively correlated with visual outcomes.

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PREDICTORS OF ONE-YEAR VISUAL OUTCOMES AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.


PURPOSE: To determine predictors of best-corrected visual acuity (BCVA) outcomes 1 year after ranibizumab or bevacizumab treatment for neovascular age-related macular degeneration, within the French Study Group Avastin versus Lucentis for neovascular age-related macular degeneration (GEFAL).

METHODS: Patients aged ≥50 years presenting subfoveal neovascular age-related macular degeneration were randomized to receive ranibizumab or bevacizumab (3 monthly intravitreal injections followed by an as-needed regimen). The main outcome measures were BCVA and its change from baseline at 1 year. Variables with a P value <0.20 in the univariate model and/or which were clinically relevant were included in the multivariate analysis.

RESULTS: The following baseline factors were associated with a lower BCVA score at 1 year and with less improvement in BCVA (multivariate analysis): intraretinal fluid, thickness of central subfield macular ≤277 μm, predominantly classic choroidal neovascularization, and total area of choroidal neovascularization (all P ≤ 0.01). Pigment epithelium detachment and high baseline BCVA were associated with less improvement in BCVA (P = 0.03, P = 0.05, respectively). Patients who met retreatment criteria but did not receive the corresponding injection had significantly poorer outcomes (only tested in the univariate analysis).

CONCLUSION: This study confirms the predictors of BCVA score at 1 year posttreatment; the presence of intraretinal fluid was associated with a poor prognosis.

PMID: 28654629
PROGNOSTIC VALUE OF SUBRETINAL HYPERREFLECTIVE MATERIAL IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH BEVACIZUMAB.

Pokroy R, Mimouni M, Barayev E, Segev F, Geffen N, Nemet AY, Segal O.

PURPOSE: To study the correlation between subretinal hyperreflective material (SHRM) seen on spectral domain optical coherence tomography at baseline and visual outcomes after intravitreal bevacizumab injection in neovascular age-related macular degeneration.

METHODS: Consecutive patient charts with treatment-naive center-involved neovascular age-related macular degeneration treated with 3 monthly intravitreal bevacizumab's, continued as needed, from 2011 to 2014 were reviewed. Baseline spectral domain optical coherence tomography SHRM parameters (height, width, area, reflectivity, border definition, and homogeneity) and established optical coherence tomography biomarkers of neovascular activity (intraretinal fluid, subretinal fluid, retinal volume, central retinal thickness, and pigment epithelial detachment presence) were collected. These baseline parameters were correlated with visual acuity at baseline, 3 and 12 months.

RESULTS: Seventy-three eyes of 73 patients, 47 (64.4%) having central SHRM at baseline, were studied. Mean age was 79.2 ± 8.9 years. Mean best-corrected visual acuity was 0.70 ± 0.57 logarithm of the minimum angle of resolution (20/100), 0.73 ± 0.55 (20/107), and 0.76 ± 0.63 (20/115) at baseline, 3 and 12 months, respectively. Baseline parameters with a significant predictive value of 12-month visual acuity by univariate analysis were presence of intraretinal fluid, presence of SHRM, highly reflective SHRM, well-defined SHRM borders, and thick SHRM. These parameters, with the exception of high reflectivity, were significant on multivariate regression analysis. The most predictive baseline parameter was well-defined SHRM borders.

CONCLUSION: This study supports the use of SHRM as a prognostic biomarker when interpreting optical coherence tomography in neovascular age-related macular degeneration. Baseline parameters predicting poorer vision 1 year after intravitreal bevacizumab treatment were as follows: presence of central SHRM, well-defined SHRM borders, intraretinal fluid, and thicker SHRM.

PMID: 28654630


No improvement in injection frequency or in visual outcome over time in two cohorts of patients from the same Swedish county treated for wet age-related macular degeneration.

Schroeder M, Rung L, Lövestam-Adrian M.

BACKGROUND: Although ranibizumab has been used for the treatment of wet age-related macular degeneration (AMD) since 2007, real-world studies still report undertreatment resulting in a less favorable visual outcome. In this study, two different time cohorts of patients treated with ranibizumab for wet AMD in routine care were analyzed to observe whether there was a change over time regarding visual outcome, injection frequency, and quality of life (QoL).

METHODS: We compared patients with treatment-naive wet AMD in two observational follow-up cohorts 2007-2010 (n=50 patients) and 2009-2013 (n=26). After a loading dose of three intravitreal ranibizumab injections, the patients were treated under the pro re nata regimen. Visual acuity (VA) was examined by Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The National Eye Institute Visual Functioning Questionnaire 25 was answered by patients at baseline and at 37±7 months (cohort 1) and at 45±4 months (cohort 2).

RESULTS: At baseline, the cohorts were homogeneous considering mean age (76±7 vs 75±8 years), mean VA (53±14 vs 52±15 ETDRS letters), and mean self-reported symptom duration (14±11 vs 13±11 weeks). Mean VA decreased in both cohorts over time, from 53±14 to 45±24 letters (P=0.011) and from 52±15 to
46±22 letters (P=0.175), respectively. The patients received a mean of 8±5 and 9±7 injections, respectively. The mean composite score change from baseline to follow-up decreased in cohort 1 from 64±21 to 59±25 scores (P=0.04) but increased in cohort 2 from 64±28 to 67±23 scores (P=0.38).

CONCLUSION: We could not demonstrate any improvement in the number of injections in two different time cohorts of patients treated with ranibizumab for wet AMD in a Swedish county. Visual outcomes decreased after 3 years of follow-up, but QoL scores were divergent.

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Evaluation of pain during intravitreal aflibercept injections.
Doguizi S, Sekeroglu MA, Inanc M, Anayol MA, Yilmazbas P.

PURPOSE: To evaluate the pain associated with intravitreal aflibercept injections.

METHODS: The study included 119 patients who received intravitreal aflibercept injection at a single institution. Pain was evaluated by visual analog scale (VAS) immediately after the injection of 2 mg/0.05 mL aflibercept into the vitreous cavity using a 27-G needle. Additional variables including age, sex, indication for the injection, injection site by quadrant (superotemporal or inferotemporal), position during injection (sitting or supine), number of previous intravitreal injections in the study eye, presence of diabetes mellitus or hypertension, and lens status (phakic or pseudophakic) were recorded and assessed with self-reported pain scores.

RESULTS: Pain scores on the VAS ranged from 9 to 70, with a median of 18. Indications for injection included diabetic macular edema (21.0%), macular edema secondary to central retinal vein occlusion (12.6%), and neovascular age-related macular degeneration (66.38%). Pain did not significantly correlate with any of the recorded variables.

CONCLUSIONS: This is the first series evaluating the pain associated with intravitreal aflibercept injections. We demonstrated that pain associated with intravitreal aflibercept injection is generally mild with low pain scores.

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Int Ophthalmol. 2017 Jun 23. [Epub ahead of print]

A comparison of three different intravitreal treatment modalities of macular edema due to branch retinal vein occlusion.
Kaldırım HE, Yazgan S.

PURPOSE: To compare the efficacy of intravitreal injection of ranibizumab, dexamethasone implant and aflibercept for the management of macular edema (ME) related to branch retinal vein occlusion (BRVO).

METHODS: This retrospective and comparative study included 62 eyes of 62 patients with BRVO and ME. Patients received one of the following treatments: 0.5 mg ranibizumab (group 1, n = 22), 0.7 mg dexamethasone implant (group 2, n = 20) and 2 mg aflibercept (group 3, n = 20). The 6-month treatment protocol in groups 1 and 3 consisted of 3-dose loading treatment for the first 3 months and followed by repeat injections based on clinical necessity. Group 2 received only single dose of 0.7 mg dexamethasone implant for 6 months. Visual acuity (VA), central macular thickness (CMT), serous retinal detachment (SRD) height and intraocular pressure (IOP) measurements were done at baseline and first 6 months of follow-up.

RESULTS: At baseline, the groups did not differ in age, gender, duration of ME, VA, CMT, IOP and SRD height (p > 0.05). Mean number of injections per eye within six months were 3.64 ± 0.49 (range 3-4) in
group 1, only 1 in group 2 and 3.35 ± 0.49 (range 3-4) in group 3. VA was significantly better in group 2 in first 3 months but it became the worst among three groups in sixth month. CMT did not differ between groups in first 3 months, but it was significantly higher in group 2 at sixth month. SRD height was significantly lower in group 2 in first 3 months, but there was no difference between the groups at the end of the sixth month. IOP was significantly higher in group 2 in third and sixth months.

CONCLUSION: In the treatment of ME associated with BRVO, dexamethasone implant appears to be more advantageous in terms of VA and SRD height for the first 3 months. However, at the end of the sixth month of treatment, anti-VEGF drugs were more efficient in maintaining the increased visual acuity and reduced CMT. A dexamethasone implant may be the first treatment option in BRVO cases with high SRD.

PMID: 28646440

Other treatment & diagnosis


Structural Changes in Optical Coherence Tomography Underlying Spots of Increased Autofluorescence in the Perilesional Zone of Geographic Atrophy.


PURPOSE: To investigate structural correlates corresponding to the appearance of increased fundus autofluorescence (FAF) in the perilesional area of geographic atrophy (GA) secondary to age-related macular degeneration.

METHODS: Serial FAF images of 181 eyes with GA of 134 patients participating in the Directional Spread in Geographic Atrophy study (NCT02051998) were screened for increased FAF spots that had developed during the review period. Thickness and reflectivity of the retinal pigment epithelium (RPE)-basal lamina complex, as well as the integrity of the external limiting membrane (ELM) and the ellipsoid zone (EZ), respectively, in corresponding optical coherence tomography (OCT) scans were compared between the time points before and after the appearance of increased FAF. Adjacent areas without development of abnormal FAF were assessed as internal control.

RESULTS: A total of 36 areas (15 eyes) with de novo developed increased FAF spots and 54 control areas were included. Analysis of the corresponding OCT images revealed an increase in RPE-basal lamina complex thickness (31.8 ± 7.3 to 42.1 ± 11.9 μm [P < 0.001]) and reflectivity (reflectivity ratio: 1.42 ± 0.11 to 1.54 ± 0.27 [P = 0.009]) corresponding to an increased FAF signal while there was no significant change in control areas. Development of increased FAF spots was associated with disruption of the ELM and the EZ.

CONCLUSIONS: Increase of RPE-basal lamina complex thickness and reflectivity was spatially and temporally associated with the development of increased FAF spots in eyes with GA. In addition, outer retinal disruption may contribute to the corresponding increased FAF signal.

PMID: 28666281


Quantifying melanin concentration in retinal pigment epithelium using broadband photoacoustic microscopy.

Shu X, Li H, Dong B, Sun C, Zhang HF.

Abstract: Melanin is the dominant light absorber in retinal pigment epithelium (RPE). The loss of RPE melanin is a sign of ocular senescence and is both a risk factor and a symptom of age-related macular degeneration (AMD). Quantifying the RPE melanin concentration provides insight into the pathological role
of RPE in ocular aging and the onset and progression of AMD. The main challenge in accurate quantification of RPE melanin concentration is to distinguish this ten-micrometer-thick cell monolayer from the underlying choroid, which also contains melanin but carries different pathognomonic information. In this work, we investigated a three-dimensional photoacoustic microscopic (PAM) method with high axial resolution, empowered by broad acoustic detection bandwidth, to distinguish RPE from choroid and quantify melanin concentrations in the RPE ex vivo. We first conducted numerical simulation on photoacoustic generation in the RPE, which suggested that a PAM system with at least 100-MHz detection bandwidth provided sufficient axial resolution to distinguish the melanin in RPE from that in choroid. Based on simulation results, we integrated a transparent broadband micro-ring resonator (MRR) based detector in a homebuilt PAM system. We imaged ex vivo RPE-choroid complexes (RCCs) from both porcine and human eyes and quantified the absolute melanin concentrations in the RPE and choroid, respectively. In our study, the measured melanin concentrations were 14.7 mg/mL and 17.0 mg/mL in human and porcine RPE, and 12 mg/mL and 61 mg/mL in human and porcine choroid, respectively. This study suggests that broadband PAM is capable of quantifying the RPE melanin concentration from RCCs ex vivo.

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**Biomed Opt Express. 2017 Apr 27;8(5):2732-2744. eCollection 2017 May 1.**

**Automatic segmentation of nine retinal layer boundaries in OCT images of non-exudative AMD patients using deep learning and graph search.**


Abstract: We present a novel framework combining convolutional neural networks (CNN) and graph search methods (termed as CNN-GS) for the automatic segmentation of nine layer boundaries on retinal optical coherence tomography (OCT) images. CNN-GS first utilizes a CNN to extract features of specific retinal layer boundaries and train a corresponding classifier to delineate a pilot estimate of the eight layers. Next, a graph search method uses the probability maps created from the CNN to find the final boundaries. We validated our proposed method on 60 volumes (2915 B-scans) from 20 human eyes with non-exudative age-related macular degeneration (AMD), which attested to effectiveness of our proposed technique.

PMID: 28663902 PMCID: PMC5480509


**Automated intraretinal segmentation of SD-OCT images in normal and age-related macular degeneration eyes.**

de Sisternes L, Jonna G, Moss J, Marmor MF, Leng T, Rubin DL.

Abstract: This work introduces and evaluates an automated intra-retinal segmentation method for spectral-domain optical coherence (SD-OCT) retinal images. While quantitative assessment of retinal features in SD-OCT data is important, manual segmentation is extremely time-consuming and subjective. We address challenges that have hindered prior automated methods, including poor performance with diseased retinas relative to healthy retinas, and data smoothing that obscures image features such as small retinal drusen. Our novel segmentation approach is based on the iterative adaptation of a weighted median process, wherein a three-dimensional weighting function is defined according to image intensity and gradient properties, and a set of smoothness constraints and pre-defined rules are considered. We compared the segmentation results for 9 segmented outlines associated with intra-retinal boundaries to those drawn by hand by two retinal specialists and to those produced by an independent state-of-the-art automated software tool in a set of 42 clinical images (from 14 patients). These images were obtained with a Zeiss Cirrus SD-OCT system, including healthy, early or intermediate AMD, and advanced AMD eyes. As a qualitative evaluation of accuracy, a highly experienced third independent reader blindly rated the quality of the outlines produced by each method. The accuracy and image detail of our method was superior in
healthy and early or intermediate AMD eyes (98.15% and 97.78% of results not needing substantial editing) to the automated method we compared against. While the performance was not as good in advanced AMD (68.89%), it was still better than the manual outlines or the comparison method (which failed in such cases). We also tested our method’s performance on images acquired with a different SD-OCT manufacturer, collected from a large publicly available data set (114 healthy and 255 AMD eyes), and compared the data quantitatively to reference standard markings of the internal limiting membrane and inner boundary of retinal pigment epithelium, producing a mean unsigned positioning error of 6.04 ± 7.83µm (mean under 2 pixels). Our automated method should be applicable to data from different OCT manufacturers and offers detailed layer segmentations in healthy and AMD eyes.

PMID: 28663874 PMCID: PMC5480589


Reflectance-based projection-resolved optical coherence tomography angiography [Invited].

Wang J, Zhang M, Hwang TS, Bailey ST, Huang D, Wilson DJ, Jia Y.

Abstract: Optical coherence tomography angiography (OCTA) is limited by projection artifacts from the superficial blood vessels onto deeper layers. We have recently described projection-resolved (PR) OCTA that solves the ambiguity between in situ flow and flow projection along each axial scan and suppresses the artifact on both en face and cross-sectional angiograms. While this method significantly improved the depth resolution of OCTA, the vascular integrity of the deeper layers was not fully preserved. In this study, we propose a novel reflectance-based projection-resolved (rbPR) OCTA algorithm which uses OCT reflectance to enhance the flow signal and suppress the projection artifacts in 3-dimensional OCTA. We demonstrated quantitatively that rbPR improved the vascular connectivity and improved the discrimination of the deeper plexus angiograms in healthy eyes, compared to prior PR-OCTA method. We also demonstrated qualitatively that rbPR removes flow projection artifacts more completely from the outer retinal slab in the eyes with age-related macular degeneration, and preserves vascular integrity of the intermediate and deep capillary plexuses in the eyes with diabetic retinopathy. Additionally, this method improves the resolution of the choriocapillaris and demonstrates details comparable to scanning electron microscopy.

PMID: 28663848 PMCID: PMC5480563


Machine Learning of the Progression of Intermediate Age-Related Macular Degeneration Based on OCT Imaging.

Bogunovic H, Montuoro A, Baratsits M, Karantonis MG, Waldstein SM, Schlanitz F, Schmidt-Erfurth U.

PURPOSE: To develop a data-driven interpretable predictive model of incoming drusen regression as a sign of disease activity and identify optical coherence tomography (OCT) biomarkers associated with its risk in intermediate age-related macular degeneration (AMD).

METHODS: Patients with AMD were observed every 3 months, using Spectralis OCT imaging, for a minimum duration of 12 months and up to a period of 60 months. Segmentation of drusen and the overlying layers was obtained using a graph-theoretic method, and the hyperreflective foci were segmented using a voxel classification method. Automated image analysis steps were then applied to identify and characterize individual drusen at baseline, and their development was monitored at every follow-up visit. Finally, a machine learning method based on a sparse Cox proportional hazard regression was developed to estimate a risk score and predict the incoming regression of individual drusen.

RESULTS: The predictive model was trained and evaluated on a longitudinal dataset of 61 eyes from 38 patients using cross-validation. The mean follow-up time was 37.8 ± 13.8 months. A total of 944 drusen were identified at baseline, out of which 249 (26%) regressed during follow-up. The prediction performance
was evaluated as area under the curve (AUC) for different time periods. Prediction within the first 2 years achieved an AUC of 0.75.

CONCLUSIONS: The predictive model proposed in this study represents a promising step toward image-guided prediction of AMD progression. Machine learning is expected to accelerate and contribute to the development of new therapeutics that delay the progression of AMD.

PMID: 28658477

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QUANTITATIVE ANALYSIS OF THE INNER RETINAL LAYER THICKNESSES IN AGE-RELATED MACULAR DEGENERATION USING CORRECTED OPTICAL COHERENCE TOMOGRAPHY SEGMENTATION.

Muftuoglu IK, Ramkumar HL, Bartsch DU, Meshi A, Gaber R, Freeman WR.

PURPOSE: To characterize inner retinal damage in patients with dry age-related macular degeneration (AMD) using high-resolution spectral domain optical coherence tomography images.

METHODS: Sixty eyes of 60 patients with AMD were categorized using the Age-Related Eye Disease Study (AREDS) severity scale. Spectral domain optical coherence tomography images of these patients were quantified by manually correcting the segmentation of each retinal layer, including the retinal nerve fiber layer, ganglion cell layer, and inner plexiform layer to ensure accurate delineation of layers. The mean ganglion cell complex thickness values (ganglion cell layer + inner plexiform layer + retinal nerve fiber layer) were compared with 30 eyes of 30 healthy subjects.

RESULTS: Ninety percent of eyes (81 eyes) required manual correction of segmentation. Compared with healthy subjects, mean ganglion cell complex thicknesses significantly decreased in more advanced dry AMD eyes, and this decrease was predominantly related to a change in inner plexiform layer thickness. There was no significant difference in thickness-related measurements between milder dry AMD (AREDS-2) eyes and healthy eyes (P > 0.05).

CONCLUSION: In patients with dry AMD, automatic optical coherence tomography segmentation algorithms may be erroneous. As the severity of dry AMD increases, the inner plexiform layer layer becomes thinned, suggesting that transsynaptic degeneration may be occurring, as the photoreceptor layer is affected by AMD.

PMID: 28650925


New precision metrics for contrast sensitivity testing.

Dorr M, Elze T, Hui W, Lu ZL, Bex PJ, Lesmes LA.

Abstract: Visual sensitivity is comprehensively described by the Contrast Sensitivity Function (CSF), but current routine clinical care does not include its assessment because of the time-consuming need to estimate thresholds for a large number of spatial frequencies. The quick CSF method, however, dramatically reduces testing times by using a Bayesian information maximization rule. We evaluate the test-retest variability of a tablet-based quick CSF implementation in a study with 100 subjects who repeatedly assessed their vision with and without optical correction. We first discuss two commonly used measures of repeatability, intra-class correlation and the Bland-Altman Coefficient of Repeatability, and show that they are vulnerable to artifacts. Instead, we propose to formulate precision as an information retrieval task: from all repeat test scores, can we retrieve a certain individual based on their first test score? We then use rank-based analyses such as Mean Average Precision as a better measure to compare different test metrics,
and show that the highest test-retest precision is achieved using a summary statistic, the Area Under the Log CSF (AULCSF). This demonstrates the benefit of assessment of the whole CSF compared to sensitivity at individual spatial frequencies only. AULCSF also yields best discrimination performance (99.2%) between measurements that were taken with and without glasses, respectively, even better than CSF Acuity. The tablet-based quick CSF thus enables the rapid and reliable home monitoring of visual function, which has the potential to improve early diagnosis and treatment of ophthalmic pathologies such as diabetic retinopathy or age-related macular degeneration.

PMID: 28650831

Surv Ophthalmol. 2017 Jun 22. [Epub ahead of print]

Optical Coherence Tomography Angiography in Dry Age-related Macular Degeneration.

Cicinelli MV, Rabiolo A, Sacconi R, Carnevali A, Querques L, Bandello F, Querques G.

Abstract: Optical coherence tomography angiography (OCT-A) is a new imaging modality that provides non-invasive characterization and quantification of the microvasculature in different retinal conditions. The purpose of this paper is to give an updated review of the features of dry age-related macular degeneration investigated by means of new generation OCT-A. We searched PubMed and Medline using the terms "optical coherence tomography angiography" associated with "age-related macular degeneration", "drusen", "reticular pseudodrusen," and "geographic atrophy" and reviewed publications up to January, 2017.

PMID: 28648383


The Current State of Teleophthalmology in the United States.

Rathi S, Tsui E, Mehta N, Zahid S, Schuman JS.

Abstract: Telemedicine services facilitate the evaluation, diagnosis, and management of the remote patient. Telemedicine has rapidly flourished in the United States and has improved access to care, outcomes, and patient satisfaction. However, the use of telemedicine in ophthalmology is currently in its infancy and has yet to gain wide acceptance. Current models of telemedicine in ophthalmology are largely performed via "store and forward" methods, but remote monitoring and interactive modalities exist. Although studies have examined the effects of telemedicine, few reports have characterized its current status. We perform a descriptive analysis of the current state of teleophthalmology in the United States. We describe the use of teleophthalmology in the hospital and outpatient settings. We also review the applications to retinopathy of prematurity, diabetic retinopathy, age-related macular degeneration, and glaucoma, as well as anticipated barriers and hurdles for the future adoption of teleophthalmology. With ongoing advances in teleophthalmology, these models may provide earlier detection and more reliable monitoring of vision-threatening diseases.

PMID: 28647202

Pathogenesis


Lutein Activates the Transcription Factor Nrf2 in Human Retinal Pigment Epithelial Cells.

Frede K, Ebert F, Kipp A, Schwerdtle T, Baldermann S.

Abstract: The degeneration of the retinal pigment epithelium caused by oxidative damage is a stage of
development in age-related macular degeneration (AMD). The carotenoid lutein is a major macular pigment that may reduce the incidence and progression of AMD, but the underlying mechanism is currently still not fully understood. Carotenoids are known to be direct antioxidants. However, carotenoids can also activate cellular pathways resulting in indirect antioxidant effects. Here, we investigate the influence of lutein on the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) target genes in human retinal pigment epithelial cells (ARPE-19 cells) using lutein-loaded Tween40 micelles. The micelles were identified as a suitable delivery system since they were non-toxic in APRE-19 cells up to 0.04% Tween40 and led to a cellular lutein accumulation of 62 µM ± 14 µM after 24 h. Lutein significantly enhanced Nrf2 translocation to the nucleus 1.5 ± 0.4-fold compared to unloaded micelles after 4 h. Furthermore, lutein treatment for 24 h significantly increased the transcripts of NAD(P)H:quinone oxidoreductase 1 (NQO1) by 1.7 ± 0.1-fold, glutamate-cysteine ligase regulatory subunit (GCLm) by 1.4 ± 0.1-fold, and heme oxygenase-1 (HO-1) by 1.8 ± 0.3-fold. Moreover, we observed a significant enhancement of NQO1 activity by 1.2 ± 0.1-fold. Collectively, this study indicates that lutein not only serves as a direct antioxidant, but also activates Nrf2 in ARPE-19 cells.

PMID: 28665123


Abstract: Oxidative damage is a key factor for the pathogenesis of age-related macular degeneration (AMD), therefore, anti-oxidative stress is a valuable method for the prevention or treatment of AMD. The aim of the present study was to reveal the protective mechanism of lutein on retinal pigment epithelium (RPE) cells subjected to oxidative stress. Acute retinal pigment epithelial 19 (ARPE-19) cells were exposed to oxidative stress induced by H2O2 following lutein pretreatment. The activities of caspases, level of intracellular reactive oxygen species (ROS) and cell cycle were analyzed using flow cytometry. The expression levels of cell cycle regulatory proteins and inflammation-associated genes were detected using western blot and reverse transcription-polymerase chain reaction analyses, respectively. The data showed that oxidative stress reduced cell viability, and increased total apoptosis and ROS generation, however, lutein prevented cells from oxidative stress-induced damage. In addition, oxidative damage triggered G2/M phase arrest of the ARPE-19 cells, which was reversed by lutein in a concentration-dependent manner, through the activation of cyclin-dependent kinase 1 and cell division cycle 25C, and degradation of cyclin B1. These results demonstrated that lutein may be an effective antioxidant, which can be applied in the prevention of AMD, or other age-related diseases associated with oxidative damage.

PMID: 28656238


Intravitreal itraconazole inhibits laser-induced choroidal neovascularization in rats.

Bae JH, Hwang AR, Kim CY, Yu HG, Koh HJ, Yang WI, Chang HR, Lee SC.

Abstract: Choroidal neovascularization (CNV) is a major cause of severe visual loss in patients with age-related macular degeneration (AMD). Recently, itraconazole has shown potent and dose-dependent inhibition of tumor-associated angiogenesis. We evaluated the anti-angiogenic effect of itraconazole in a rat model of laser-induced CNV. After laser photocoagulation in each eye to cause CNV, right eyes were administered intravitreal injections of itraconazole; left eyes received balanced salt solution (BSS) as controls. On day 14 after laser induction, fluorescein angiography (FA) was used to assess abnormal vascular leakage. Flattened retinal pigment epithelium (RPE)-choroid tissue complex was stained with Alexa Fluor 594-conjugated isolectin B4 to measure the CNV area and volume. Vascular endothelial growth
factor receptor 2 (VEGFR2) mRNA and protein expression was determined 1, 4, 7, and 14 days after intravitreal injection by quantitative RT-PCR or Western blot. VEGF levels were analyzed by enzyme-linked immunosorbent assay (ELISA). Intravitreal itraconazole significantly reduced leakage from CNV as assessed by FA and CNV area and volume on flat mounts compared with intravitreal BSS (p = 0.002 for CNV leakage, p<0.001 for CNV area and volume). Quantitative RT-PCR showed significantly lower expression of VEGFR2 mRNA in the RPE-choroid complexes of itraconazole-injected eyes than those of BSS-injected eyes on days 7 and 14 (p = 0.003 and p = 0.006). Western blots indicated that VEGFR2 was downregulated after itraconazole treatment. ELISA showed a significant difference in VEGF level between itraconazole-injected and BSS-injected eyes on days 7 and 14 (p = 0.04 and p = 0.001). Our study demonstrated that intravitreal itraconazole significantly inhibited the development of laser-induced CNV in rats. Itraconazole had anti-angiogenic activity along with the reduction of VEGFR2 and VEGF levels. Itraconazole may prove beneficial for treating CNV as an alternative or adjunct to other therapies.

PMID: 28666022


Anaphylatoxins Activate Ca2+, Akt/PI3-Kinase, and FOXO1/FoxP3 in the Retinal Pigment Epithelium.


PURPOSE: The retinal pigment epithelium (RPE) is a main target for complement activation in age-related macular degeneration (AMD). The anaphylatoxins C3a and C5a have been thought to mostly play a role as chemoattractants for macrophages and immune cells; here, we explore whether they trigger RPE alterations. Specifically, we investigated the RPE as a potential immunoregulatory gate, allowing for active changes in the RPE microenvironment in response to complement.

DESIGN: In vitro and in vivo analysis of signaling pathways.

METHODS: Individual activities of and interaction between the two anaphylatoxin receptors were tested in cultured RPE cells by fluorescence microscopy, western blot, and immunohistochemistry.

MAIN OUTCOME MEASURES: Intracellular free calcium, protein phosphorylation, immunostaining of tissues/cells, and multiplex secretion assay.

RESULTS: Similar to immune cells, anaphylatoxin exposure resulted in increases in free cytosolic Ca2+, PI3-kinase/Akt activation, FoxP3 and FOXO1 phosphorylation, and cytokine/chemokine secretion. Differential responses were elicited depending on whether C3a and C5a were co-administered or applied consecutively, and response amplitudes in co-administration experiments ranged from additive to driven by C5a (C3a + C5a = C5a) or being smaller than those elicited by C3a alone (C3a + C5a < C3a).

CONCLUSION: We suggest that this combination of integrative signaling between C3aR and C5aR helps the RPE to precisely adopt its immune regulatory function. These data further contribute to our understanding of AMD pathophysiology.

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Effects of white light-emitting diode (LED) exposure on retinal pigment epithelium in vivo.


Abstract: Ageing and alteration of the functions of the retinal pigment epithelium (RPE) are at the origin of
lost of vision seen in age-related macular degeneration (AMD). The RPE is known to be vulnerable to high-energy blue light. The white light-emitting diodes (LED) commercially available have relatively high content of blue light, a feature that suggest that they could be deleterious for this retinal cell layer. The aim of our study was to investigate the effects of "white LED" exposure on RPE. For this, commercially available white LEDs were used for exposure experiments on Wistar rats. Immunohistochemical stain on RPE flat mount, transmission electron microscopy and Western blot were used to exam the RPE. LED-induced RPE damage was evaluated by studying oxidative stress, stress response pathways and cell death pathways as well as the integrity of the outer blood-retinal barrier (BRB). We show that white LED light caused structural alterations leading to the disruption of the outer blood-retinal barrier. We observed an increase in oxidized molecules, disturbance of basal autophagy and cell death by necrosis. We conclude that white LEDs induced strong damages in rat RPE characterized by the breakdown of the BRB and the induction of necrotic cell death.

PMID: 28661040

The role and therapeutic potential of melatonin in age-related ocular diseases.
Crooke A, Huete-Toral F, Colligris B, Pintor J.
Abstract: The eye is continuously exposed to solar UV radiation and pollutants, making it prone to oxidative attacks. In fact, oxidative damage is a major cause of age-related ocular diseases including cataract, glaucoma, age-related macular degeneration and diabetic retinopathy. Since the nature of lens cells, trabecular meshwork cells, retinal ganglion cells, retinal pigment epithelial cells and photoreceptors is post-mitotic, autophagy plays a critical role in their cellular homeostasis. In age-related ocular diseases, this process is impaired, thus, oxidative damage becomes irreversible. Other conditions such as low-grade chronic inflammation and angiogenesis also contribute to the development of retinal diseases (glaucoma, age-related macular degeneration and diabetic retinopathy). As melatonin is known to have remarkable qualities such as antioxidant/antinitridergic, mitochondrial protector, autophagy modulator, anti-inflammatory and anti-angiogenic, it can represent a powerful tool to counteract all these diseases. The present review analyzes the role and therapeutic potential of melatonin in age-related ocular diseases, focusing on nitro-oxidative stress, autophagy, inflammation and angiogenesis mechanisms.

PMID: 28658514

Probing the Role of Inflammation in Age-Related Macular Degeneration.
Curcio CA, Huisingh C.

PMID: 28654970

Epidemiology
Combined influence of poor health behaviours on the prevalence and 15-year incidence of age-related macular degeneration.
Abstract: We aimed to establish the collective influence of four lifestyle practices (physical activity, diet,
smoking and alcohol consumption) on the prevalence and incidence of AMD. At baseline, 2428 participants aged 49+ with complete lifestyle and AMD data were examined, and of these, 1903 participants were re-examined 15 years later. AMD was assessed from retinal photographs. A health behaviour score was calculated, allocating 1 point for each poor behaviour: current smoking; fruits and vegetables consumed <4 serves daily; <3 episodes of physical activity per week; and >2 alcoholic drinks per day. Cross-sectional analysis showed that participants who engaged in all 4 poor health behaviours (n = 29) versus those who did not engage in unhealthy behaviours (reference group; n = 677) had greater odds of any and late AMD: multivariable-adjusted OR, 5.14 (95% CI, 1.04-25.45) and OR 29.53 (95% CI 2.72-321.16), respectively. A marginally non-significant association was observed between increasing number of poor health behaviours and 15-year incidence of early AMD (multivariable-adjusted P-trend = 0.08). Our data suggests that motivating patients with AMD to eat better, exercise more, limit alcohol intake and avoid smoking seems advisable to decelerate the development or worsening of existing AMD.

PMID: 28659620

The Prevalence of Age-Related Eye Disease in an Elderly Population.
Hashemi H, Khabazkhoob M, Nabovati P, Ostadimoghaddam H, Shafaee S, Doostdar A, Yekta A.
PURPOSE: To determine the prevalence of cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) in Iranians over the age of 54 years.
METHODS: Through a cross-sectional study using randomized cluster sampling, 60 clusters were selected in Sari, a city in the North of Iran. In each cluster, 20 people over 54 years of age were chosen systematically and were invited to participate in the study. After enrollment, all participants had optometric and ophthalmologic exams including slit lamp biomicroscopy and fundoscopy.
RESULTS: Of the 1185 selected persons, 937 (79.1%) participated in this study (age range 55-87 years). The prevalence of cataracts, AMD, glaucoma, and DR in at least one eye was 29.6% (95% confidence interval [CI] 26.6-32.5), 5.8% (95% CI: 4.3-7.3), 3.7% (95% CI: 2.5-5.0), and 2.7% (95% CI: 1.6-3.7), respectively. All prevalences significantly increased with aging. AMD was more prevalent in men (7.4%) than women (4.4%) (p = 0.054). Overall, 35.8% (95% CI: 32.7-38.8) of participants had at least one of the four conditions; this rate was 27.4% for the 55-59-year old age group and 52.4% for those over 75 years of age.
CONCLUSION: Overall, 35.8% of the studied population had at least one of the four diseases. Cataracts, followed by AMD, are the most common age-related eye diseases in the Iranian population, and thus, precise planning along with enhanced diagnostic and therapeutic facilities are necessary.
PMID: 28658589

Neovascular Age-Related Macular Degeneration in the Very Old (≥90 Years): Epidemiology, Adherence to Treatment, and Comparison of Efficacy.
Subhi Y, Sørensen TL.
PURPOSE: To investigate neovascular age-related macular degeneration (AMD) in patients aged ≥90 years from several perspectives for a comprehensive overview: prevalence, presenting characteristics, treatment adherence, reasons for discontinuation, and efficacy of antivascular endothelial growth factor (VEGF) treatment comparing Ranibizumab and Aflibercept.
METHODS: In this retrospective chart review, we determined the prevalence and presenting characteristics
by reviewing all data for patients referred to our department with treatment-naïve neovascular AMD. By looking at historical cohorts, we determined adherence to treatment, reasons for discontinuation, and treatment outcomes after loading dose, 12 months, and 24 months.

RESULTS: Patients aged ≥90 years constituted 7% of the patients. Treatment was discontinued in 51%, primarily because of death and treatment burden. Mean change in best-corrected visual acuity was 3.2, 1.5, and -2.2 ETDRS letters at 4, 12, and 24 months, respectively. Aflibercept was superior to Ranibizumab in visual and anatomic outcomes. After two years of treatment, patients losing ≥15 ETDRS letters made up 19% in the Aflibercept group and 26% in the Ranibizumab group.

CONCLUSIONS: We propose that the very old patients with neovascular AMD may constitute a distinctive group warranting special attention and possibilities for individualized therapy. Possible differences between anti-VEGF agents need further investigations.

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Retina. 2017 Jun 29. [Epub ahead of print]


Xin X, Sun Y, Li S, Xu H, Zhang D.

PURPOSE: We evaluated the association between age-related macular degeneration (AMD) and the risk of all-cause and cardiovascular mortality by meta-analyses of data from prospective studies.

METHODS: A literature search was performed in PubMed, Web of Science, Embase, Cochrane Library, and China National Knowledge Infrastructure for relevant articles published up to December 2016. We estimated hazard ratios with 95% confidence intervals with fixed-effect models and conducted meta-regression to explore the potential sources of heterogeneity. Small-study effect was estimated by Egger's test and funnel plot.

RESULTS: We identified 13 population-based prospective cohort studies that examined the relationship between AMD and all-cause and cardiovascular mortality. Overall, the hazard ratios (95% confidence intervals) of all-cause mortality and cardiovascular mortality associated with any AMD were 1.15 (1.05-1.27) and 1.05 (95% confidence intervals: 0.87-1.26), respectively. The risk of all-cause mortality and cardiovascular mortality associated with early AMD were 1.08 (1.00-1.18) and 1.05 (0.89-1.24), and the associations with late AMD were 1.23 (1.11-1.36) and 1.28 (1.04-1.57), respectively. No evidence of small-study effect was found.

CONCLUSION: This meta-analysis indicated that AMD, especially late AMD, was associated with increased risk of all-cause mortality and cardiovascular mortality based on comparisons with people who did not have AMD and who were of similar age and sex.

PMID: 28665868


Age-Related Macular Degeneration in Patients With Chronic Myeloproliferative Neoplasms.

Bak M, Sørensen TL, Flachs EM, Zwisler AD, Juel K, Frederiksen H, Hasselbalch HC.

IMPORTANCE: It has been suggested that systemic inflammation increases the risk of age-related macular degeneration (AMD). Given that chronic immune modulation is present in patients with myeloproliferative neoplasms (MPNs), the risk of AMD in these patients may be increased.

OBJECTIVE: To compare the risk of AMD in patients with MPNs with the risk of AMD in matched controls
from the general population.

DESIGN, SETTING, AND PARTICIPANTS: A nationwide population-based cohort study using Danish registers was conducted of all patients in Denmark who received a diagnosis between January 1, 1994, and December 31, 2013, of essential thrombocythemia, polycythemia vera, myelofibrosis, or unclassifiable MPNs. For each patient, 10 age- and sex-matched controls were included. All patients without prior AMD were followed up from the date of diagnosis (or corresponding entry date for the controls) until the first AMD diagnosis, death or emigration, or December 31, 2013, whichever occurred first. Data analysis was performed from April 1, 2015, to October 31, 2016.

MAIN OUTCOMES AND MEASURES: Incidence of AMD recorded in specialized hospital-based care. The rates and absolute risk of AMD were calculated. Using Cox proportional hazards regression models, smoking and risk-time adjusted hazard ratios (HRs) between patients and controls were calculated. In addition, HRs of neovascular AMD after 2006 were calculated since antivascular endothelial growth factor treatment was introduced nationwide at hospitals thereafter.

RESULTS: A total of 7958 patients with MPNs (4279 women [53.8%] and 3679 men [46.2%]; mean [SD] age at diagnosis, 66.4 [14.3] years) were included in the study. The rate of AMD per 1000 person-years at risk was 5.2 (95% CI, 4.6-5.9) for patients with MPNs (2628 with essential thrombocythemia, 3063 with polycythemia vera, 547 with myelofibrosis, and 1720 with unclassifiable MPNs) and 4.3 (95% CI, 4.1-4.4) for the 77445 controls, while the 10-year risk of AMD was 2.4% (95% CI, 2.1%-2.8%) for patients with MPNs and 2.3% (95% CI, 2.2%-2.4%) for the controls. The risk of AMD was increased overall for patients with MPNs (adjusted HR, 1.3; 95% CI, 1.1-1.5), with adjusted HRs for the subtypes of 1.2 (95% CI, 1.0-1.6) for essential thrombocythemia, 1.4 (95% CI, 1.2-1.7) for polycythemia vera, 1.7 (95% CI, 0.8-4.0) for myelofibrosis, and 1.5 (95% CI, 1.1-2.1) for unclassifiable MPNs. In addition, patients with MPNs had a higher risk of neovascular AMD (adjusted HR, 1.4; 95% CI, 1.2-1.6).

CONCLUSIONS AND RELEVANCE: Our results suggest that patients with MPNs are at increased risk of AMD, supporting the possibility that systemic inflammation is involved in the pathogenesis of AMD.

PMID: 28655032

Genetics


Specific correlation between the major chromosome 10q26 haplotype conferring risk for age-related macular degeneration and the expression of HTRA1.


PURPOSE: A region within chromosome 10q26 has a set of single nucleotide polymorphisms (SNPs) that define a haplotype that confers high risk for age-related macular degeneration (AMD). We used a bioinformatics approach to search for genes in this region that may be responsible for risk for AMD by assessing levels of gene expression in individuals carrying different haplotypes and by searching for open chromatin regions in the retinal pigment epithelium (RPE) that might include one or more of the SNPs.

METHODS: We surveyed the PubMed and the 1000 Genomes databases to find all common (minor allele frequency > 0.01) SNPs in 10q26 strongly associated with AMD. We used the HaploReg and LDlink databases to find sets of SNPs with alleles in linkage disequilibrium and used the Genotype-Tissue Expression (GTEx) database to search for correlations between genotypes at individual SNPs and the relative level of expression of the genes. We also accessed Encyclopedia of DNA Elements (ENCODE) to find segments of open chromatin in the region with the AMD-associated SNPs. Predicted transcription factor binding motifs were identified using HOMER, PROMO, and RegulomeDB software programs.

RESULTS: There are 34 polymorphisms within a 30-kb region that are in strong linkage disequilibrium (r2>0.8) with the reference SNP rs10490924 previously associated with risk for AMD. The expression of
three genes in this region, PLEKHA1, ARMS2, and HTRA1 varies between people who have the low-AMD-risk haplotype compared with those with the high-AMD-risk haplotype. For PLEKHA1, 44 tissues have an expression pattern with the high-AMD-risk haplotype associated with low expression (rs10490924 effect size -0.43, p = 3.8 x 10^-5 in ovary). With regard to ARMS2, the variation is most pronounced in testes: homozygotes with the high-AMD-risk haplotype express ARMS2 at lower levels than homozygotes with the low-AMD-risk haplotype; expression in heterozygotes falls in between (rs10490924 effect size -0.79, p = 7.5 x 10^-24). For HTRA1, the expression pattern is the opposite; the high-AMD-risk haplotype has higher levels of expression in 27 tissues (rs10490924 effect size 0.40, p = 1.5 × 10^-7 in testes). None of the other 22 genes within one megabase of rs10490924, or any gene in the entire genome, have mRNA expression levels that correlate with the high-AMD-risk haplotype. More than 100 other SNPs in the 10q26 region affect the expression of PLEKHA1 and ARMS2 but not that of HTRA1; none of these SNPs affects the risk for AMD according to published genome-wide association studies (GWASs). Two of the AMD-risk SNPs (rs36212732 and rs36212733) affect transcription factor binding sites in proximity to a DNase I hypersensitive region (i.e., a region of open chromatin) in RPE cells.

CONCLUSIONS: SNPs in chromosome 10q26 that influence the expression of only PLEKHA1 or ARMS2 are not associated with risk for AMD, while most SNPs that influence the expression of HTRA1 are associated with risk for AMD. Two of the AMD-risk SNPs affect transcription factor binding sites that may control expression of one of the linked genes in the RPE. These findings suggest that the variation in the risk for AMD associated with chromosome 10q26 is likely due to variation in HTRA1 expression. Modulating HTRA1 activity might be a potential therapy for AMD.

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Improving power for rare-variant tests by integrating external controls.

Lee S, Kim S, Fuchsberger C.

Abstract: Due to the drop in sequencing cost, the number of sequenced genomes is increasing rapidly. To improve power of rare-variant tests, these sequenced samples could be used as external control samples in addition to control samples from the study itself. However, when using external controls, possible batch effects due to the use of different sequencing platforms or genotype calling pipelines can dramatically increase type I error rates. To address this, we propose novel summary statistics based single and gene- or region-based rare-variant tests that allow the integration of external controls while controlling for type I error. Our approach is based on the insight that batch effects on a given variant can be assessed by comparing odds ratio estimates using internal controls only vs. using combined control samples of internal and external controls. From simulation experiments and the analysis of data from age-related macular degeneration and type 2 diabetes studies, we demonstrate that our method can substantially improve power while controlling for type I error rate.

PMID: 28657150


Identification of pathogenic genes and upstream regulators in age-related macular degeneration.

Zhao B, Wang M, Xu J, Li M, Yu Y.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in older individuals. Our study aims to identify the key genes and upstream regulators in AMD.

METHODS: To screen pathogenic genes of AMD, an integrated analysis was performed by using the microarray datasets in AMD derived from the Gene Expression Omnibus (GEO) database. The functional annotation and potential pathways of differentially expressed genes (DEGs) were further discovered by
Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. We constructed the AMD-specific transcriptional regulatory network to find the crucial transcriptional factors (TFs) which target the DEGs in AMD. Quantitative real time polymerase chain reaction (qRT-PCR) was performed to verify the DEGs and TFs obtained by integrated analysis.

RESULTS: From two GEO datasets obtained, we identified 1280 DEGs (730 up-regulated and 550 down-regulated genes) between AMD and normal control (NC). After KEGG analysis, steroid biosynthesis is a significantly enriched pathway for DEGs. The expression of 8 genes (TNC, GRP, TRAF6, ADAMTS5, GPX3, FAP, DHCR7 and FDFT1) was detected. Except for TNC and GPX3, the other 6 genes in qRT-PCR played the same pattern with that in our integrated analysis.

CONCLUSIONS: The dysregulation of these eight genes may involve with the process of AMD. Two crucial transcription factors (c-rel and myogenin) were concluded to play a role in AMD. Especially, myogenin was associated with AMD by regulating TNC, GRP and FAP. Our finding can contribute to developing new potential biomarkers, revealing the underlying pathogenesis, and further raising new therapeutic targets for AMD.

PMID: 28651595

**Stem cells**


**Induced pluripotent stem cell-based therapy for age-related macular degeneration.**

Bracha P, Moore NA, Ciulla TA.

INTRODUCTION: In age-related macular degeneration (AMD), stem cells could possibly replace or regenerate disrupted pathologic retinal pigment epithelium (RPE), and produce supportive growth factors and cytokines such as brain-derived neurotrophic factor. Induced pluripotent stem cells (iPSCs)-derived RPE was first subretinally transplanted in a neovascular AMD patient in 2014. Areas covered: Induced PSCs are derived from the introduction of transcription factors to adult cells under specific cell culture conditions, followed by differentiation into RPE cells. Induced PSC-derived RPE cells exhibit ion transport, membrane potential, polarized VEGF secretion and gene expression that is similar to native RPE. Despite having similar in vitro function, morphology, immunostaining and microscopic analysis, it remains to be seen if iPSC-derived RPE can replicate the myriad of in vivo functions, including immunomodulatory effects, of native RPE cells. Historically, adjuvant RPE transplantation during CNV resections were technically difficult and complicated by immune rejection. Autologous iPSCs are hypothesized to reduce the risk of immune rejection, but their production is time-consuming and expensive. Alternatively, allogenic transplantation using human leukocyte antigen (HLA)-matched iPSCs, similar to HLA-matched organ transplantation, is currently being investigated. Expert opinion: Challenges to successful transplantation with iPSCs include surgical technique, a pathologic subretinal microenvironment, possible immune rejection, and complications of immunosuppression.

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