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Drug treatment

Ophthalmology. 2016 Nov 8. [Epub ahead of print]

Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for Diabetic Macular Edema: TREX-DME 1 Year Outcomes.

Payne JF, Wykoff CC, Clark WL, Bruce BB, Boyer DS, Brown DM; TREX-DME Study Group.

PURPOSE: To compare monthly dosing with a treat and extend algorithm using ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation for center-involving diabetic macular edema (DME).

DESIGN: Multicenter, prospective, randomized clinical trial.

PARTICIPANTS: A total of 150 eyes from 116 subjects were randomized into 3 cohorts: Monthly (n = 30), TReat and EXtend without macular laser photocoagulation (TREX; n = 60), and treat and extend with angiography-GuIded macular LAser photocoagulation (GILA; n = 60).

METHODS: Monthly cohort eyes received ranibizumab 0.3 mg every 4 weeks. Eyes in the TREX and GILA cohorts received 4 monthly injections of ranibizumab 0.3 mg followed by a treat and extend algorithm based on disease activity. Eyes in the GILA cohort also received angiography-guided macular laser photocoagulation at month 1 and again every 3 months for microaneurysm leakage.

MAIN OUTCOME MEASURES: Change in mean best-corrected visual acuity (BCVA), mean central retinal thickness (CRT), number of injections from baseline to 1 year, and percentage gaining/losing 2 and 3 lines of vision.

RESULTS: Baseline demographics were well balanced among the cohorts. A total of 137 eyes (91%) completed the 1-year end point visit. At 1 year, the mean BCVA improved by 8.6, 9.6, and 9.5 letters in the Monthly, TREX, and GILA cohorts, respectively (P = 0.8). There was no significant difference between the cohorts in the percentage gaining/losing 2 and 3 lines of vision. The CRT improved by 123 μm, 146 μm, and 166 μm in the Monthly, TREX, and GILA cohorts, respectively (P = 0.47). The mean number of macular laser treatments in the GILA cohort at 1 year was 2.9 (range, 1-4). The number of injections was significantly reduced in both the TREX (10.7) and GILA (10.1) cohorts compared with the Monthly cohort (13.1, P < 0.001). There were no cases of endophthalmitis, and the total incidence of Anti-Platelet Trialists' Collaboration events was 4.7%.

CONCLUSIONS: This prospective, randomized trial found that treat and extend dosing of ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation significantly decreased the number of injections given while providing similar visual and anatomic outcomes compared with monthly dosing at 1 year. Adding angiography-guided laser photocoagulation to this dosing algorithm did not significantly improve outcomes at 1 year.

PMID: 27836430

Cent Eur J Immunol. 2016;41(3):311-316. Epub 2016 Oct 25.

The era of anti-vascular endothelial growth factor (VEGF) drugs in ophthalmology, VEGF and anti-VEGF therapy.

Pożarowska D, Pożarowski P.

Abstract: Angiogenesis is a clue process for tissue development and function, both in normal and pathological conditions. This process is regulated by multiple molecular systems. One of the most potent is vascular endothelial growth factor (VEGF) and its receptor (VEGFR) system. Members of this family are involved in new vessel formation in embryogenesis and maturation, as well as in reparative or pathological reactions in later stages. They play a substantial role in regeneration, inflammation, wound healing, as well as in cancer pathology. Nowadays it is possible to modulate VEGF-VEGFR interactions in many pathological conditions using anti-VEGF therapy. This therapy has already achieved a grounded position in the management of rheumatological disorders, tumour progression, and metastasis. Such drugs as bevacizumab, ranibizumab, aflibercept, and pegaptanib have also proven to be very effective in the treatment of several ocular diseases, such as age-related macular degeneration (AMD), macular oedema, or proliferative retinopathies and iris neovascularisation. The indications for the application of this therapy in ophthalmology are becoming wider and wider. It may also be used for corneal pathologies and in anti-glaucoma procedures.

PMID: 27833450 PMCID: PMC5099389

Ophthalmic Res. 2016 Nov 11. [Epub ahead of print]

Identifying Predictors of Anti-VEGF Treatment Response in Patients with Neovascular Age-Related Macular Degeneration through Discriminant and Principal Component Analysis.

Holz FG, Tadayoni R, Beatty S, Berger AR, Cereda MG, Hykin P, Hoyng CB, Wittrup-Jensen K, Altemark A, Nilsson J, Kim K, Sivaprasad S.

OBJECTIVE: AURA was an observational study that monitored visual acuity outcomes following ranibizumab use in neovascular age-related macular degeneration patients over 2 years. The aim of this analysis was to identify factors that were predictive of visual acuity outcomes in AURA.

METHODS: The correlation between the baseline characteristics, the use of resources and the visual acuity outcomes in AURA was explored using principal component analysis (PCA) and partial least-squares-discriminant analysis (PLS-DA). The response variables analysed were mean change in visual acuity over 2 years (analysed via PCA) and no decline in visual acuity at 2 years compared with baseline (analysed via PLS-DA).

RESULTS: The AURA dataset comprised 2,227 patients and 132 variables. Using PCA and PLS-DA, we found that the number of ranibizumab injections, clinic and monitoring visits, number of optical coherence tomography scans and ophthalmoscopies correlated with a change in visual acuity at Years 1 and 2, and are therefore key drivers of treatment success.

CONCLUSION: This is a novel approach to graphically explore relationships between multiple correlated covariates and outcomes in real-life ophthalmology studies. It identified a number of variables that are positively linked with treatment outcomes.

PMID: 27832661

Ophthalmologica. 2016 Nov 11. [Epub ahead of print]

Cytokines and Recurrence of Macular Edema after Intravitreal Ranibizumab in Patients with Branch Retinal Vein Occlusion.

Noma H, Mimura T, Yasuda K, Nakagawa H, Motohashi R, Kotake O, Shimura M.

Abstract: The aqueous humor levels of cytokines and growth/inflammatory factors were measured in 46 branch retinal vein occlusion (BRVO) patients with macular edema (ME) who were treated with intravitreal ranibizumab injection (IRI). Patients with recurrence of ME received further IRI as needed. The number of IRIs was significantly correlated with age, baseline best-corrected visual acuity, and baseline central macular thickness (CMT), as well as the baseline aqueous levels of 5 cytokines/factors (soluble vascular endothelial growth factor receptor-1, platelet-derived growth factor-AA [PDGF-AA], soluble intercellular adhesion molecule-1, interleukin-6 [IL-6], and IL-8). Multivariate linear regression analysis with stepwise selection confirmed that age, baseline CMT, and baseline PDGF-AA level were independent determinants of the number of IRIs. These findings suggest that inflammatory factors may influence the recurrence of ME in BRVO patients, and that PDGF-AA might be a useful indicator of the number of IRIs required to control ME.

PMID: 27832655

Surv Ophthalmol. 2016 Nov - Dec;61(6):759-768. Epub 2016 Apr 1.

Vascular endothelial growth factor and diabetic macular edema.

Lally DR, Shah CP, Heier JS.

Abstract: Diabetes mellitus is a major global health epidemic, and diabetic macular edema is the leading cause of vision loss in this population. Macular focal and/or grid laser photocoagulation applied to microaneurysms and thickened retina had long been primary therapy for diabetic macular edema. Chronically elevated serum glucose is known to cause breakdown in the inner and outer retinal blood barrier resulting in upregulation of vascular endothelial growth factor (VEGF). Intravitreal anti-vascular endothelial growth factor agents, including ranibizumab, bevacizumab, and aflibercept, have been shown in randomized clinical trials to be superior to macular laser for the treatment of clinically relevant diabetic macular edema. The READ-2, RISE/RIDE, and RESTORE trials established ranibizumab's superiority to macular laser, whereas the BOLT trial demonstrated bevacizumab's superiority to laser. The DRCR.net Protocol T results showed that intravitreal aflibercept, bevacizumab, and ranibizumab were all effective in reducing retinal thickness secondary to diabetic edema and in improving vision. When the presenting vision was 20/40 or better, visual improvement was equivalent. With eyes presenting with 20/50 or worse vision, aflibercept was superior with respect to visual improvement. Intravitreal anti-VEGF therapy can be burdensome for the patient and health care system, often requiring monthly treatment visits. To reduce burdens, anti-VEGF strategies are in development to lengthen the treatment interval.

PMID: 27045225

Other treatment & diagnosis

Retina. 2016 Nov 8. [Epub ahead of print]

CHARACTERIZATION AND DIFFERENTIATION OF POLYPOIDAL CHOROIDAL VASCULOPATHY USING SWEPT SOURCE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY.

Cheung CM, Yanagi Y, Mohla A, Lee SY, Mathur R, Chan CM, Yeo I, Wong TY.

PURPOSE: To determine the correlation and agreement between swept-source optical coherence tomography angiography (SS-OCT-A) with fluorescein angiography (FA), indocyanine green angiography (ICGA) and spectral domain OCT (SD-OCT) in characterizing polypoidal choroidal vasculopathy (PCV) and in differentiating eyes with typical age-related macular degeneration (t-AMD).

METHODS: This study included 32 and 54 eyes with t-AMD and PCV, respectively, who underwent SS-OCT-A, SD-OCT, fluorescein angiography, and indocyanine green angiography. The images from these four techniques were compared.

RESULTS: On SS-OCT-A, flow signals with vascular network configuration were detected in 81.2% and

77.8% of eyes with t-AMD and PCV, respectively. 40.4% of polyps were detected as flow signals with polypoidal configuration. Compared with indocyanine green angiography, SS-OCT-A had sensitivity and specificity of 83.0% and 57.1%, respectively, for vascular network, and 40.5% and 66.7% for polyps. Longitudinal changes were in agreement between SS-OCT-A and SD-OCT in 90% of eyes. 88.2% of eyes with dry retina on SD-OCT had persistent vascular net on SS-OCT-A. In two cases with reactivation of PCV, SS-OCT-A was more sensitive at detecting recurrence than SD-OCT.

CONCLUSION: Swept-source optical coherence tomography angiography is effective at detecting vascular network that correlate to conventional angiography in eyes with t-AMD and PCV. Swept-source optical coherence tomography angiography is inferior to indocyanine green angiography in detecting polyps and cannot replace indocyanine green angiography for differentiating PCV from t-AMD; however, SS-OCT-A may be more sensitive than SD-OCT in detecting early recurrence.

PMID: 27828911

F1000Res. 2016 Jul 5;5:1573. eCollection 2016.

Automated analysis of retinal imaging using machine learning techniques for computer vision.

De Fauw J, Keane P, Tomasev N, et al

Abstract: There are almost two million people in the United Kingdom living with sight loss, including around 360,000 people who are registered as blind or partially sighted. Sight threatening diseases, such as diabetic retinopathy and age related macular degeneration have contributed to the 40% increase in outpatient attendances in the last decade but are amenable to early detection and monitoring. With early and appropriate intervention, blindness may be prevented in many cases. Ophthalmic imaging provides a way to diagnose and objectively assess the progression of a number of pathologies including neovascular ("wet") age-related macular degeneration (wet AMD) and diabetic retinopathy. Two methods of imaging are commonly used: digital photographs of the fundus (the 'back' of the eye) and Optical Coherence Tomography (OCT, a modality that uses light waves in a similar way to how ultrasound uses sound waves). Changes in population demographics and expectations and the changing pattern of chronic diseases creates a rising demand for such imaging. Meanwhile, interrogation of such images is time consuming, costly, and prone to human error. The application of novel analysis methods may provide a solution to these challenges. This research will focus on applying novel machine learning algorithms to automatic analysis of both digital fundus photographs and OCT in Moorfields Eye Hospital NHS Foundation Trust patients. Through analysis of the images used in ophthalmology, along with relevant clinical and demographic information, Google DeepMind Health will investigate the feasibility of automated grading of digital fundus photographs and OCT and provide novel quantitative measures for specific disease features and for monitoring the therapeutic success.

PMID: 27830057 PMCID: PMC5082593

Pathogenesis

Eur Rev Med Pharmacol Sci. 2016 Oct;20(20):4196-4201.

Correlation between serum melatonin and aMT6S level for age-related macular degeneration patients.

Lv XD, Liu S, Cao Z, Gong LL, Feng XP, Gao QF, Wang J, Hu L, Cheng XC, Yu CH, Xing YQ.

OBJECTIVE: To analyze the levels of serum melatonin (MLT) and assay of 6-sulfatoxymelatonin (aMT6S) of age-related macular degeneration (AMD) patients and study their correlation with AMD risk factors.

PATIENTS AND METHODS: 58 AMD cases were selected and 58 healthy cases of the same time period were selected according to 1:1 closest matching method. ELISA method was used to test serum MLT and aMT6S level.

RESULTS: Levels of MLT and aMT6S in AMD group were lower than those in the control group, and differences were statistically significant ($p < 0.05$). Based on analysis of AMD subgroup, differences on gender had no statistical significance compared with AMD type. For cases with smoking, cardiovascular disease and corrected visual acuity lower than 0.1, MLT and aMT6S levels were reduced at 0.05). Through the regression analysis, we concluded that smoking history, cardiovascular disease history, best corrected visual acuity, MLT and aMT6S level were independent risk factors, among which MLT [OR = 3.624 (odds ratio: OR)] and aMT6S (OR = 3.201).

CONCLUSIONS: MLT and aMT6S may be related to the incidence of AMD.

PMID: 27831657

Cell Death Dis. 2016 Nov 10;7(11):e2468.

Knockout of Ccr2 alleviates photoreceptor cell death in rodent retina exposed to chronic blue light.

Hu Z, Zhang Y, Wang J, Mao P, Lv X, Yuan S, Huang Z, Ding Y, Xie P, Liu Q.

Abstract: Age-related macular degeneration (AMD), the leading cause of visual loss after the age of 60 years, is a degenerative retinal disease involving a variety of environmental and hereditary factors. Although it has been implicated that immune system is involved in the disease progression, the exact role that microglia has is still unclear. Here we demonstrated that knockout of Ccr2 gene could alleviate photoreceptor cell death in mice retinas exposed to chronic blue light. In Ccr2-/- mice, a damaged microglia recruitment was shown in retina and this could protect the visual function in electroretinogram and alleviate the photoreceptor apoptosis, which thus helped attenuate the blue light-induced retinopathy. We further found an increased co-location of NLRP3, Iba-1, and IL-1β in fluorescence and a concomitant increased protein expression of NLRP3, caspase-1, and IL-1β in western blotting in chronic blue light-induced retinopathy. Moreover, the activation of microglia and their cellular NLRP3 inflammasomes occurred as an earlier step before the structural and functional damage of the mice retinas, which collectively supported that microglial NLRP3 inflammasome might be the key to the chronic blue light-induced retinopathy.

PMID: 27831552

Mol Vis. 2016 Oct 26;22:1280-1290. eCollection 2016.

Peptide redesign for inhibition of the complement system: Targeting age-related macular degeneration.

Mohan RR, Cabrera AP, Harrison RE, Gorham RD Jr, Johnson LV, Ghosh K, Morikis D.

PURPOSE: To redesign a complement-inhibiting peptide with the potential to become a therapeutic for dry and wet age-related macular degeneration (AMD).

METHODS: We present a new potent peptide (Peptide 2) of the compstatin family. The peptide is developed by rational design, based on a mechanistic binding hypothesis, and structural and physicochemical properties derived from molecular dynamics (MD) simulation. The inhibitory activity, efficacy, and solubility of Peptide 2 are evaluated using a hemolytic assay, a human RPE cell-based assay, and ultraviolet (UV) absorption properties, respectively, and compared to the respective properties of its parent peptide (Peptide 1).

RESULTS: The sequence of Peptide 2 contains an arginine-serine N-terminal extension (a characteristic of parent Peptide 1) and a novel 8-polyethylene glycol (PEG) block C-terminal extension. Peptide 2 has significantly improved aqueous solubility compared to Peptide 1 and comparable complement inhibitory activity. In addition, Peptide 2 is more efficacious in inhibiting complement activation in a cell-based model that mimics the pathobiology of dry AMD.

CONCLUSIONS: We have designed a new peptide analog of compstatin that combines N-terminal polar amino acid extensions and C-terminal PEGylation extensions. This peptide demonstrates significantly improved aqueous solubility and complement inhibitory efficacy, compared to the parent peptide. The new

peptide overcomes the aggregation limitation for clinical translation of previous compstatin analogs and is a candidate to become a therapeutic for the treatment of AMD.

PMID: 27829783 PMCID: PMC5082644

Ophthalmic Genet. 2016 Dec;37(4):465-467. Epub 2016 Mar 3.

Evaluation of C-reactive protein and CC-cytokine ligand 2 polymorphism interaction for age-related macular degeneration.

Jabbarpoor Bonyadi MH, Mohammadian T, Bonyadi M, Soheilian M, Moein H, Yaseri M.

PMID: 26940485

Ophthalmic Genet. 2016 Dec;37(4):369-376. Epub 2016 Feb 25.

Retinal disease in the C3 glomerulopathies and the risk of impaired vision.

Savige J, Amos L, Ierino F, Mack HG, Symons RC, Hughes P, Nicholls K, Colville D.

BACKGROUND: Dense deposit disease and atypical hemolytic uremic syndrome are often caused by Complement Factor H (CFH) mutations. This study describes the retinal abnormalities in dense deposit disease and, for the first time, atypical haemolytic uremic syndrome. It also reviews our understanding of drusen pathogenesis and their relevance for glomerular disease.

METHODS: Six individuals with dense deposit disease and one with atypical haemolytic uremic syndrome were studied from 2 to 40 years after presentation. Five had renal transplants. All four who had genetic testing had CFH mutations. Individuals underwent ophthalmological review and retinal photography, and in some cases, optical coherence tomography, and further tests of retinal function.

RESULTS: All subjects with dense deposit disease had impaired night vision and retinal drusen or whitish-yellow deposits. Retinal atrophy, pigmentation, and hemorrhage were common. In late disease, peripheral vision was restricted, central vision was distorted, and there were scotoma from sub-retinal choroidal neovascular membranes and atypical serous retinopathy. Drusen were present but less prominent in the young person with atypical uremic syndrome due to a heterozygous CFH mutation.

CONCLUSIONS: Drusen are common in forms of C3 glomerulopathy caused by compound heterozygous or heterozygous CFH mutations. They are useful diagnostically but also impair vision. Drusen have an identical composition to glomerular deposits. They are also identical to the drusen of age-related macular degeneration, and may respond to the same treatments. Individuals with a C3 glomerulopathy should be assessed ophthalmologically at diagnosis, and monitored regularly for vision-threatening complications.

PMID: 26915021

Mol Neurobiol. 2016 Nov;53(9):6194-6208. Epub 2015 Nov 12.

Rotenone Induces the Formation of 4-Hydroxynonenal Aggresomes. Role of ROS-Mediated Tubulin Hyperacetylation and Autophagic Flux Disruption.

Bonet-Ponce L, Saez-Atienzar S, da Casa C, Sancho-Pelluz J, Barcia JM, Martinez-Gil N, Nava E, Jordan J, Romero FJ, Galindo MF.

Abstract: Oxidative stress causes cellular damage by (i) altering protein stability, (ii) impairing organelle function, or (iii) triggering the formation of 4-HNE protein aggregates. The catabolic process known as autophagy is an antioxidant cellular response aimed to counteract these stressful conditions. Therefore, autophagy might act as a cytoprotective response by removing impaired organelles and aggregated proteins. In the present study, we sought to understand the role of autophagy in the clearance of 4-HNE

protein aggregates in ARPE-19 cells under rotenone exposure. Rotenone induced an overproduction of reactive oxygen species (ROS), which led to an accumulation of 4-HNE inclusions, and an increase in the number of autophagosomes. The latter resulted from a disturbed autophagic flux rather than an activation of the autophagic synthesis pathway. In compliance with this, rotenone treatment induced an increase in LC3-II while upstream autophagy markers such as Beclin- 1, Vsp34 or Atg5-Atg12, were decreased. Rotenone reduced the autophagosome-to-lysosome fusion step by increasing tubulin acetylation levels through a ROS-mediated pathway. Proof of this is the finding that the free radical scavenger, N-acetylcysteine, restored autophagy flux and reduced rotenone-induced tubulin hyperacetylation. Indeed, this dysfunctional autophagic response exacerbates cell death triggered by rotenone, since 3-methyladenine, an autophagy inhibitor, reduced cell mortality, while rapamycin, an inductor of autophagy, caused opposite effects. In summary, we shed new light on the mechanisms involved in the autophagic responses disrupted by oxidative stress, which take place in neurodegenerative diseases such as Huntington or Parkinson diseases, and age-related macular degeneration.

PMID: 26558631

Epidemiology

Nurs Stand. 2001 Sep 26;16(2):10.

People taking statins less likely to lose their eyesight.

[No authors listed]

Abstract: Statins that are used to modify lipid levels might also reduce the risk of age-related macular degeneration, Southampton researchers report.

PMID: 27823297

Eye (Lond). 2016 Nov 11. [Epub ahead of print]

The association of geographic atrophy and decreased renal function in patients with age-related macular degeneration.

Leisy HB, Rastogi A, Guevara G, Ahmad M, Smith RT.

Purpose: The purpose of the study was to investigate the association between area and presence of geographic atrophy (GA) and renal function, as measured by glomerular filtration rate (GFR).

Patients and methods: We retrospectively identified patients aged 50-90 years who were assigned an ICD-9 diagnosis code for age-related macular generation (AMD) between January 2012 and January 2016. Patients met inclusion criteria if they had at least one macular spectral domain optical coherence tomography volume scan, one provider note, and one GFR value in the electronic medical record. Images were evaluated for the presence of GA, area of GA, drusen, and subretinal drusenoid deposits (SDD) and for subfoveal choroidal thickness (CTh) by standard criteria. Imaging findings were correlated with the most recent GFR from the patient's chart.

Results: We identified 107 patients who met our inclusion criteria (mean age=74 years, range 50-90 years). Overall, we found a significant correlation between the presence of GA and reduced GFR (P=0.002), which was maintained even after accounting for age and other confounders. No association between GFR and GA area was found. CTh was significantly lower in patients with GA (P=0.038) and those with decreased GFR (P=0.004). Within the SDD-positive population, GA was associated with reduced GFR (P=0.007) but only trended toward significance after controlling for age.

Conclusion: Our study findings demonstrate an association between impaired renal function and the presence, but not area, of GA within an AMD population. These findings may shed light on common pathogenic mechanisms for these two diseases.

PMID: 27834969

J West Afr Coll Surg. 2015 Apr-Jun;5(2):1-16.

RETINAL DISEASES IN A TERTIARY HOSPITAL IN SOUTHERN NIGERIA.

Uhumwangho OM, Itina EI.

BACKGROUND: Retinal diseases are an important and common cause of ophthalmic consultation.

AIM: To determine the pattern of retinal diseases in the ophthalmic department of a tertiary hospital in Southern Nigeria.

PATIENTS AND METHODS: A retrospective review of the case folders of patients with retinal pathologies seen between 2012 and 2013 was performed. Relevant demographic and clinical data was recorded. Analysis was performed for frequencies, proportions and percentages with the GraphPad Instat Software, Inc. version V2.05a program, San Diego, CA.

RESULTS: There were 185 patients made of 94 (50.8%) males and 91 (49.2%) females with a peak age group of 61-70 years, (range 1-85 years) who made consultations for retinal diseases. Age related macular degeneration, 37(15.0%), and macula hole, 10(4.0%), were the common macula pathologies while retinal detachment, 11(4.5%), was the most common condition that required emergency vitreo-retinal surgical intervention. Diabetic retinopathy/maculopathy, 31(12.6%), hypertensive retinopathy 22(8.9%), and retinal vascular occlusion 12(4.8%), were the common retinal vascular diseases found. Bilateral visual impairment (low vision and blindness) from retinal diseases was present in 28(14.4%) persons. The common vitreo-retinal treatment options were use of intravitreal antivascular endothelial growth factors 32(13.0%), laser 16 (6.5%), and vitreoretinal surgery in 22(8.9%) eyes.

CONCLUSION: Retinal diseases remain an important cause of ophthalmic consultation and visual loss. Provision of facilities to manage these conditions will improve service delivery and quality of lives of affected patients.

PMID: 27830120 PMCID: PMC5036292

Genetics

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):6107-6115.

Progression Rate From Intermediate to Advanced Age-Related Macular Degeneration Is Correlated With the Number of Risk Alleles at the CFH Locus.

Sardell RJ, Persad PJ, Pan SS, Whitehead P, Adams LD, Laux RA, Fortun JA, Brantley MA Jr, Kovach JL, Schwartz SG, Agarwal A, Haines JL, Scott WK, Pericak-Vance MA.

PURPOSE: Progression rate of age-related macular degeneration (AMD) varies substantially, yet its association with genetic variation has not been widely examined.

METHODS: We tested whether progression rate from intermediate AMD to geographic atrophy (GA) or choroidal neovascularization (CNV) was correlated with genotype at seven single nucleotide polymorphisms (SNPs) in the four genes most strongly associated with risk of advanced AMD. Cox proportional hazards survival models examined the association between progression time and SNP genotype while adjusting for age and sex and accounting for variable follow-up time, right censored data, and repeated measures (left and right eyes).

RESULTS: Progression rate varied with the number of risk alleles at the CFH:rs10737680 but not the CFH:rs1061170 (Y402H) SNP; individuals with two risk alleles progressed faster than those with one allele (hazard ratio [HR] = 1.61, 95% confidence interval [CI] = 1.08-2.40, $P < 0.02$, n = 547 eyes), although this was not significant after Bonferroni correction. This signal was likely driven by an association at the correlated protective variant, CFH:rs6677604, which tags the CFHR1-3 deletion; individuals with at least one protective allele progressed more slowly. Considering GA and CNV separately showed that the effect of CFH:rs10737680 was stronger for progression to CNV.

CONCLUSIONS: Results support previous findings that AMD progression rate is influenced by CFH, and suggest that variants within CFH may have different effects on risk versus progression. However, since CFH:rs10737680 was not significant after Bonferroni correction and explained only a relatively small portion of variation in progression rate beyond that explained by age, we suggest that additional factors contribute to progression.

PMID: 27832277 PMCID: PMC5104418

Ophthalmic Genet. 2016 Dec;37(4):459-461. Epub 2016 Mar 4.

Evaluation of CFH Y402H polymorphism and CFHR3/CFHR1 deletion in age-related macular degeneration patients from Brazil.

Dezidério Sacconi DP, Cabral de Vasconcellos JP, Endo Hirata F, MacCord Medina F, Rim PH, Barbosa de Melo M.

PMID: 26942649

Ophthalmic Genet. 2016 Dec;37(4):388-393. Epub 2016 Feb 25.

Evaluating VEGFR1 genetic polymorphisms as a predisposition to AMD in a cohort from northern China.

Xiang W, Zhuang W, Chi H, Sheng X, Zhang W, Xue Z, Pan B, Liu Y.

OBJECTIVE: The association among genetic variants in VEGFR1 and a predisposition to age-related macular degeneration (AMD) in a northern cohort from China was evaluated.

METHODS: A retrospective case-control correlation study was conducted on 432 cases and 906 gender- and ethnicity-matched controls. Whole DNA was isolated from peripheral blood samples after the individuals underwent detailed eye examinations. Eight single nucleotide polymorphisms (SNPs) in VEGFR1 genes were genotyped for all individuals using a MALDI-TOF technique. The distribution of genotypes was analyzed for Hardy-Weinberg equilibrium and the relationships among the genotype and allele frequencies with AMD were evaluated by age-adjusted logistic regression analysis. The measurement of linkage disequilibrium (LD) was carried out by Haploview 4.2. Bonferroni testing was employed to correct for multiple comparisons.

RESULTS: Among the SNPs genotyped, p values of six SNPs were less than 0.05 between AMD cases and unaffected controls. However, after Bonferroni correction, the genotype and allele distributions of only two SNPs, rs9554322 and rs9582036 differed significantly between the controls and AMD patients. Further, the rs9554322 CC genotype conferred strong susceptibility to AMD (OR = 6.057, 95% CI: 3.099-11.839). Rs9943922 was also found to be significantly associated with AMD in the distributions for the genotype and allele recessive model (p = 0.004). The specific haplotype CA of rs9582036 and rs9554320 was associated with AMD (p = 0.035), but the correlation did not remain after correction.

CONCLUSIONS: The SNPs rs9554322, rs9582036 and rs9943922 were correlated with AMD. Gene variants in VEGFR1 were linked to a pronounced emerging risk for AMD in a population in northern China.

PMID: 26914796

Ophthalmic Genet. 2016 Dec;37(4):394-399. Epub 2016 Feb 25.

ENOS polymorphisms in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in a Chinese Han population.

Zuo C, Li M, Zhang X, Chen H, Su Y, Wu K, Wen F.

PURPOSE: To investigate whether common genetic variants in the endothelial nitric oxide synthase gene (eNOS) are associated with neovascular age-related macular degeneration (nAMD) and polypoidal choroidalvasculopathy (PCV) in a Chinese Han population.

METHODS: DNA samples were obtained from 157 nAMD patients, 250 PCV patients and 204 healthy control subjects. Tag single nucleotide polymorphisms (SNPs) across the extended eNOS region were selected using data derived from the HapMap project. Genotyping of each tag SNP was performed by Multiplex SNaPshot system and direct DNA sequencing techniques. Genotypes and allele frequencies were evaluated with PLINK software for each group.

RESULTS: Seven SNPs for eNOS, rs1799983, rs1800783, rs3918186, rs3800787, rs3918188, rs7830, and rs3918227, were chosen as tag SNPs. Among these tag SNPs, rs1800783, rs3918186, rs3918188, and rs3918227 were not associated with nAMD or PCV. Rs1799983, rs3800787, and rs7830 was significantly associated with nAMD (p = 0.0192, 0.0170, and 0.0164, respectively), but not associated with PCV (p = 0.4852, 0.4568, and 0.4014, respectively). The discovered associations were no longer significant after Bonferroni correction.

CONCLUSIONS: We found no sufficient evidence to support the role of any common eNOS variants in the susceptibility to nAMD or PCV in a Chinese Han population.

PMID: 26914548

Diet, lifestyle & low vision

Subcell Biochem. 2016;81:231-259.

Vitamin A and Vision.

Saari JC.

Abstract: Visual systems detect light by monitoring the effect of photoisomerization of a chromophore on the release of a neurotransmitter from sensory neurons, known as rod and cone photoreceptor cells in vertebrate retina. In all known visual systems, the chromophore is 11-cis-retinal complexed with a protein, called opsin, and photoisomerization produces all-trans-retinal. In mammals, regeneration of 11-cis-retinal following photoisomerization occurs by a thermally driven isomerization reaction. Additional reactions are required during regeneration to protect cells from the toxicity of aldehyde forms of vitamin A that are essential to the visual process. Photochemical and phototransduction reactions in rods and cones are identical; however, reactions of the rod and cone visual pigment regeneration cycles differ, and perplexingly, rod and cone regeneration cycles appear to use different mechanisms to overcome the energy barrier involved in converting all-trans- to 11-cis-retinoid. Abnormal processing of all-trans-retinal in the rod regeneration cycle leads to retinal degeneration, suggesting that excessive amounts of the retinoid itself or its derivatives are toxic. This line of reasoning led to the development of various approaches to modifying the activity of the rod visual cycle as a possible therapeutic approach to delay or prevent retinal degeneration in inherited retinal diseases and perhaps in the dry form of macular degeneration (geographic atrophy). In spite of great progress in understanding the functioning of rod and cone regeneration cycles at a molecular level, resolution of a number of remaining puzzling issues will offer insight into the amelioration of several blinding retinal diseases.

PMID: 27830507

PeerJ. 2016 Nov 1;4:e2650. eCollection 2016.

Performance, usability and comparison of two versions of a new macular vision test: the handheld Radial Shape Discrimination test.

Ku JY, Milling AF, Pitrelli Vazquez N, Knox PC.

BACKGROUND: Central vision, critical for everyday tasks such as reading and driving, is impacted by age-

related changes in the eye and by diseases such as age-related macular degeneration. The detection of changes in macular function is therefore important. The Radial Shape Discrimination (RSD) test measures the threshold at which distortions in a radial frequency pattern can be detected and there is evidence that it is more sensitive to macular pathology than visual acuity (VA). It also provides a more quantitative measure of macular function than the commonly available Amsler grid. Recently, handheld versions of the test (hRSD) in which stimuli are presented on mobile devices (e.g., Apple iPod Touch, iPhone) have been developed. We investigated the characteristics of the hRSD test in healthy participants.

METHODS: Data were collected using both three-alternative forced choice (3AFC) and 4AFC versions of the hRSD test, presented on an Apple iPod Touch. For the 3AFC version, data from a single test session were available for 186 (72 male; mean ± SD age 42 ± 17y; range 16-90y) healthy participants. Test-retest data were available for subgroups of participants (intra-session: N = 74; tests approximately 2 months apart: N = 30; tests 39 months apart: N = 15). The 3AFC and 4AFC versions were directly compared in 106 participants who also completed a usability questionnaire. Distance and near VA and Pelli Robson Contrast Sensitivity (CS) data were collected and undilated fundoscopy performed on the majority of participants.

RESULTS: Mean (±SD) 3AFC hRSD threshold was -0.77 ± 0.14 logMAR, and was statistically significantly correlated with age (Pearson $r = 0.35$; $p < 0.001$). The linear regression of hRSD threshold on age had a slope of +0.0026 compared to +0.0051 for near VA (which also correlated with age: $r = 0.51$; $p < 0.001$). There were no statistically significant differences in hRSD thresholds for any of the test-retest subgroups. We also observed no statistically significant difference between 3AFC (-0.82 ± 0.11 logMAR) and 4AFC (-0.80 ± 0.12 logMAR) hRSD thresholds ($t = 1.85$, $p = 0.067$) and participants reported excellent test usability with no strong preference expressed between the 3AFC and 4AFC versions of the test.

DISCUSSION: The 3AFC hRSD thresholds we report are consistent with a number of previous studies, as is its greater stability in ageing compared to VA. We have also shown that in the absence of pathology, thresholds are stable over short and long timescales. The 4AFC thresholds we have reported provide a baseline for future investigations, and we have confirmed that 3AFC and 4AFC thresholds are similar, providing a basis of comparisons between studies using the different versions. As the hRSD test is easy to use and relatively inexpensive, clinical studies are now required to establish its ability to detect and monitor macular pathologies.

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Electrophysiological testing of visual function after mirror telescope implantation: a case report.

Kremláček J, Jirásková N, Nekolová J, Šikl R, Kuba M.

PURPOSE: The implantation of an intraocular telescope increases life quality in patients with end-stage age-related macular degeneration (AMD). The present study monitored changes in electrophysiological markers of visual processing before and during seventeen months after a novel mirror telescope implantation in two patients (OV-male 90 years, MZ-female 70 years) with the final-stage form of AMD.

METHODS: Visual evoked potentials were recorded to high-contrast pattern-reversal (PR-VEP for check size 40' and 10'), low-contrast motion-onset stimuli (in visual periphery M-VEP M20°, and in central part M-VEP C8°), and event-related potentials (ERPs) in the oddball visual paradigm.

RESULTS: MZ's more systematic responses showed attenuation and prolongation of the M-VEP M20° and the PR-VEP 40' immediately after the telescope implantation with a slow amplitude recovery with unchanged prolonged latency. The implantation completely eradicated the M-VEP C8° without any restoration. The PR-VEP 10' were not readable. Only a part of OV's PR-VEP 40' and M-VEP M20' were of a repeatable and expected morphology. These OV's VEPs were consistent with MZ's findings. The ERPs did not show any effect of implantation in both patients. Post-implantation visual acuity and reaction time overcame the pre-implantation levels.

CONCLUSIONS: The mirror telescope preserved peripheral vision in contrast to classic telescopes; however, the telescope concurrently reduced the luminance of the magnified retinal image, which was likely

responsible for the prolongation of the VEP latencies.

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Visual, Musculoskeletal, and Balance Complaints in AMD: A Follow-Up Study.

Zetterlund C, Richter HO, Lundqvist LO.

Purpose: To investigate whether patients with age-related macular degeneration (AMD) run a potentially higher risk of developing visual, musculoskeletal, and balance complaints than age-matched controls with normal vision.

Methods: Visual assessments, self-rated visual function, self-rated visual, musculoskeletal, and balance complaints, and perceived general health were obtained in 37 AMD patients and 18 controls, at baseline and after an average of 3.8 years later.

Results: At follow-up both groups reported decreased visual acuity (VA) and visual function, but only AMD patients reported significantly increased visual, musculoskeletal, and balance complaints. Decreased VA, need for larger font size when reading, need for larger magnification, and decreased self-rated visual function were identified as risk markers for increased complaints in AMD patients. These complaints were also identified as risk markers for decreased health. For controls, decreased VA and self-reported visual function were associated with increased visual and balance complaints.

Conclusions: Visual deterioration was a risk marker for increased visual, musculoskeletal, balance, and health complaints in AMD patients. Specifically, magnifying visual aids, such as CCTV, were a risk marker for increased complaints in AMD patients. This calls for early and coordinated actions to treat and prevent visual, musculoskeletal, balance, and health complaints in AMD patients.

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