Macular Degeneration Foundation
Our focus is your vision

MD Research News

Issue 73

Monday March 26 , 2012

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with ‘Subscribe to MD Research News’ in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your ‘unsubscribe’ request.

Drug treatment

Retina. 2012 Mar 21. [Epub ahead of print]

EVEREST STUDY: Efficacy and Safety of Verteporfin Photodynamic Therapy in Combination with Ranibizumab or Alone Versus Ranibizumab Monotherapy in Patients with Symptomatic Macular Polypoidal Choroidal Vasculopathy.

Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, Lai TY, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, Lim TH.

*Eye & Retina Surgeons Clinic, Camden Medical Centre, Singapore, Singapore †Department of Ophthalmology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea ‡Department of Ophthalmology, Mackay Memorial Hospital, Taipei, Taiwan §Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan ¶School of Medicine, National Yang-Ming University, Taipei, Taiwan **Clinical Research and Development, Retina, Allergan, Inc., Irvine, California ††Department of Ophthalmology, Kangnam Sacred Heart Hospital, Hallym University, Seoul, Korea ‡‡Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China §§Novartis Pharma AG, Basel, Switzerland ¶¶Department of Ophthalmology, Rajavithi Hospital, Bangkok, Thailand ***Novartis Pharmaceuticals Corporation, East Hanover, New Jersey †††National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Singapore.

PURPOSE: To assess the effects of verteporfin photodynamic therapy (PDT) combined with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy.

METHODS: In this multicenter, double-masked, primarily indocyanine green angiography-guided trial, 61 Asian patients were randomized to verteporfin PDT (standard fluence), ranibizumab 0.5 mg, or the combination. Patients were administered with verteporfin PDT/placebo and initiated with three consecutive monthly ranibizumab/sham injections starting Day 1, and re-treated (Months 3-5) as per predefined criteria. The primary endpoint was the proportion of patients with indocyanine green angiography-assessed complete regression of polyps at Month 6. Secondary endpoints included mean change in best-corrected visual acuity at Month 6 and safety.

RESULTS: At Month 6, verteporfin combined with ranibizumab or alone was superior to ranibizumab monotherapy in achieving complete polyp regression (77.8% and 71.4% vs. 28.6%; $P < 0.01$); mean change ± standard deviation in best-corrected visual acuity (letters) was 10.9 ± 10.9 (verteporfin PDT + ranibizumab), 7.5 ± 10.6 (verteporfin PDT), and 9.2 ± 12.4 (ranibizumab). There were no new safety findings with either drug used alone or in combination.

CONCLUSION: Verteporfin PDT combined with ranibizumab 0.5 mg or alone was superior to ranibizumab monotherapy in achieving complete regression of polyps in this 6-month study in patients with symptomatic macular polypoidal choroidal vasculopathy. All treatments were well tolerated over 6 months.

PMID: 22426346 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Mar 16. [Epub ahead of print]

Verteporfin plus Ranibizumab for Choroidal Neovascularization in Age-related Macular Degeneration: Twelve-month MONT BLANC Study Results.

Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A; MONT BLANC Study Group. Department of Ophthalmology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark.

PURPOSE: To compare the efficacy and safety of same-day verteporfin photodynamic therapy (PDT) and intravitreal ranibizumab combination treatment versus ranibizumab monotherapy in neovascular age-related macular degeneration.

DESIGN: Prospective, multicenter, double-masked, randomized, active-controlled trial.

PARTICIPANTS: We included 255 patients with all types of active subfoveal choroidal neovascularization.

METHODS: Patients were randomized 1:1 to as-needed (pro re nata; PRN) combination (standard-fluence verteporfin 6 mg/m(2) PDT and ranibizumab 0.5 mg) or PRN ranibizumab monotherapy (sham infusion [5% dextrose] PDT and ranibizumab 0.5 mg). Patients received 3 consecutive monthly injections followed by PRN retreatments based on protocol-specific retreatment criteria.

MAIN OUTCOME MEASURES: Mean change in best-corrected visual acuity (BCVA) from baseline to month 12, and the proportion of patients with treatment-free interval ≥3 months at any timepoint after month 2.

RESULTS: The mean change in BCVA at month 12 was +2.5 and +4.4 letters in the combination and monotherapy groups, respectively (P = 0.0048; difference: -1.9 letters [95% confidence interval, -5.76 to 1.86], for having achieved noninferiority with a margin of 7 letters). The proportion of patients with a treatment-free interval of ≥3 months at any timepoint after month 2 was high, but did not show a clinically relevant difference between the treatment groups. Secondary efficacy endpoints included the mean number of ranibizumab retreatments after month 2 (1.9 and 2.2 with combination and monotherapy, respectively [P = 0.1373]). The time to first ranibizumab retreatment after month 2 was delayed by 34 days (about 1 monthly visit) with combination (month 6) versus monotherapy (month 5). At month 12, mean ± standard error central retinal thickness decreased by 115.3±9.04 μm in the combination group and 107.7±11.02 μm in the monotherapy group. The mean number of verteporfin/sham PDT treatments was comparable in the 2 groups (combination, 1.7; monotherapy, 1.9). The safety profiles of the 2 groups were comparable, with a low incidence of ocular serious adverse events.

CONCLUSIONS: The combination PRN treatment regimen with verteporfin PDT and ranibizumab was effective in achieving BCVA gain comparable with ranibizumab monotherapy; however, the study did not show benefits with respect to reducing the number of ranibizumab retreatment over 12 months. The combination therapy was well tolerated.

PMID: 22424834 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Mar 21. [Epub ahead of print]

Sustained elevation of intraocular pressure after intravitreal injections of bevacizumab in eyes with

neovascular age-related macular degeneration.

Mathalone N, Arodi-Golan A, Sar S, Wolfson Y, Shalem M, Lavi I, Geyer O.

Department of Ophthalmology, Carmel Medical Center, 7 Michal St., Haifa, Israel, matnurit@yahoo.com.

BACKGROUND: The use of intravitreal anti-VEGF agents in general, and of bevacizumab (Avastin) in particular, has become the common first-line treatment of neovascular age-related macular degeneration (AMD). Several reports addressed the possible elevation of intraocular pressure (IOP) following intravitreal injection of anti-VEGF. The aim of this study was to determine the prevalence of sustained IOP elevation following intravitreal bevacizumab injections for neovascular AMD and identify possible risk factors for the development of increased IOP.

METHODS: This retrospective cohort study included 174 consecutive patients (201 eyes) receiving intravitreal bevacizumab (1.25 mg/0.05 ml) as treatment for neovascular AMD. The records of the study patients were reviewed for age, gender, history of glaucoma, phakic status, IOP levels, length of follow-up, total number of injections, intervals between injections, and IOP management in eyes that exhibited IOP elevation. Sustained IOP elevation was defined as IOP ≥22 mmHg and a change from baseline of ≥6 mmHg recorded on at least two consecutive visits and lasting ≥30 days. Risk factors for an IOP increase were identified from the association between the studied variables and IOP elevations.

RESULTS: Sustained IOP elevation was found in 22 of 201 eyes (11%). The increased IOP was controlled with topical medications in all eyes. Among the variables studied, only male gender [OR = 3.1, 95% CI (1.1, 8.5) p = 0.029] and length of interval between injections <8 weeks [OR = 3.0, 95%CI (1.1, 7.9), p = 0.028] emerged as risk factors for IOP elevation in a multivariable model. The prevalence of IOP elevation was significantly higher when the interval between injections was <8 weeks than ≥8 weeks (17.6 and 6%, respectively, p = 0.009). Pre-existing glaucoma was not associated with IOP elevation (p = 0.9).

CONCLUSIONS: Sustained IOP elevations can occur in normotensive eyes undergoing intravitreal bevacizumab treatment for neovascular AMD. This phenomenon was related to shorter intervals between injections, with 8 weeks being taken as the cut-off point. AMD eyes that receive intravitreal bevacizumab injections need to be monitored for IOP changes, especially those in which the intervals between injections are <8 weeks.

PMID: 22434210 [PubMed - as supplied by publisher]

Prescrire Int. 2012 Mar;21(125):66.

Ranibizumab and diabetic macular oedema: after laser therapy.

[No authors listed]

Abstract

Diabetic retinopathy is sometimes accompanied by macular oedema, leading to a marked decline in visual acuity. The standard treatment, in addition to glycaemic and blood pressure control, is laser photocoagulation, despite its modest efficacy. Ranibizumab (Lucentis, Novartis), a VEGF (vascular endothelial growth factor) inhibitor, was initially authorised for age-related macular degeneration (AMD) in the European Union. It is now also approved for the treatment of visual loss due to macular oedema in diabetic patients. In this setting, clinical evaluation of ranibizumab is mainly based on two double-blind randomised trials comparing ranibizumab + laser photocoagulation versus placebo + laser photo-coagulation in a total of about 1000 patients. Compared with placebo, addition of ranibizumab to laser therapy led to a marked improvement in visual acuity in approximately 15% of patients after 12 months of treatment. The improvement appeared to persist after 24 months of treatment. In a trial that included a group treated with ranibizumab alone, efficacy did not differ from that of the ranibizumab + laser combination. Uncertainties remain concerning the long-term efficacy of ranibizumab and its benefits in

patients with poorly controlled diabetes or proliferative retinopathy. The adverse effect profile of ranibizumab in patients with diabetic macular oedema is similar to that reported in patients with AMD, and mainly includes ocular adverse effects such as pain, bleeding and increased intraocular pressure. A risk of systemic adverse effects, particularly cardiovascular disorders, should be kept in mind in case of long-term treatment. Ranibizumab can cause birth defects, even after intravitreal injection during pregnancy. Monthly treatment with ranibizumab is inconvenient, difficult and expensive. In practice, laser therapy remains the standard treatment for diabetic patients with significantly reduced visual acuity due to macular oedema. Ranibizumab, which requires intravitreal injections, should be restricted to second-line use.

PMID: 22428185 [PubMed - in process]

Acta Ophthalmol. 2012 Mar 16. doi: 10.1111/j.1755-3768.2011.02372.x. [Epub ahead of print]

Vitreomacular traction in a case of exudative age-related macular degeneration resistant to anti-VEGF therapy.

Shah SU, Haller JA.

Retina Service, Wills Eye Institute, Philadelphia, Pennsylvania, USA.

PMID: 22429537 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2012 Mar 20. [Epub ahead of print]

Hyporeflective Wedge-Shaped Band in Geographic Atrophy Secondary to Age-Related Macular Degeneration: An Underreported Finding.

Monés J, Biarnés M, Trindade F.

Institut de la Màcula i de la Retina and Barcelona Macula Foundation, Centro Médico Teknon, Barcelona, Spain.

OBJECTIVE: To describe and interpret the frequently observed spectral-domain optical coherence tomography (SD-OCT) finding of a marked hyporeflective wedge-shaped structure at the boundaries of the areas of atrophy.

DESIGN: A prospective, longitudinal follow-up study.

PARTICIPANTS: Consecutive patients (n = 71) 50 years of age and older with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) were examined between January 2010 and June 2011.

METHODS: Patients were evaluated with the use of imaging techniques that included 35° fundus photography, infrared, fundus autofluorescence (FAF), and SD-OCT. Visualization of the fundus with FAF was done simultaneously with OCT. Two acquisition protocols were followed: a macular cube for coverage (19 horizontal B-scans centered on the fovea) and high-resolution horizontal B-scan for qualitative foveal detail.

MAIN OUTCOMES MEASURES: Estimation of the prevalence of a hyporeflective wedge-shaped band among patients with GA.

RESULTS: A marked hyporeflective wedge-shaped structure, with its base on Bruch's membrane and its apex pointing toward the inner limit of the outer plexiform layer (OPL) adjacent to the margin between the

atrophied area and the preserved retina, was observed in 72.9% of eyes (70/96; 95% confidence interval, 63.9-82.0). This hyporeflective band appeared to be within the OPL. Using eccentric SD-OCT acquisition, the boundaries between the outer nuclear layer (ONL) and Henle's fiber layer (HFL) were well defined, showing that the ONL ends before the margin of atrophy of the retinal pigment epithelium (RPE). A narrow hyperreflective band separated the margin of the ONL and RPE from the hyporeflective band, already within the atrophic area.

CONCLUSIONS: A hyporeflective wedge-shaped structure appears frequently within the boundaries of the OPL in patients with GA secondary to AMD, corresponding to an increase in the width of the HFL, presumably because of axonal swelling or interaxonal edema. This finding may improve the interpretation of SD-OCT images of the outer layers, may help in understanding better the interactions between photoreceptor cells and the RPE, and may help in the development of monitoring techniques and therapies for GA secondary to AMD.

PMID: 22440276 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Mar 16. doi: 10.1111/j.1755-3768.2012.02398.x. [Epub ahead of print]

Impact of scanning density on spectral domain optical coherence tomography assessments in neovascular age-related macular degeneration.

Barañano AE, Keane PA, Ruiz-Garcia H, Walsh AC, Sadda SR.

Doheny Image Reading Center, Doheny Eye Institute, Keck School of Medicine of the University of Southern California, Los Angeles, California, USA NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

Purpose: To determine the effect of optical coherence tomography (OCT) B-scan density on the qualitative assessment of neovascular age-related macular degeneration (AMD).

Methods: Data were collected from 59 patients imaged with Topcon 3D OCT-1000 (128 B-scans × 512 A-scans). Custom software was used to generate less dense subsets of scans: 1/16 (eight B-scans), 1/8 (16 B-scans), 1/4 (32 B-scans) and 1/2 (64 B-scans). At each B-scan density, scans were assessed for cystoid spaces, subretinal fluid (SRF), subretinal tissue (SRT) and pigment epithelium detachment (PED). For each sampling density, sensitivity, specificity and predictive values were calculated using the full volume scan (128 B-scans) as the reference standard.

Results: For cystoid spaces, the detection sensitivity was 76.3% at 1/16 density; this rose to 89.5% with a 1/4 density. For SRF, the detection sensitivity was 75.0% at a 1/16 density; this increased to 91.1% with 1/4 density. For PED, even at the lowest sampling density (1/16) the detection sensitivity was 86.4%; this rose to 94.9% at 1/4 density. For SRT, detection sensitivity at a 1/16 density was 64.7% and only rose above 90% with the densest sampling subset (1/2).

Conclusions: Use of scanning protocols with reduced sampling densities resulted in decreased detection of key features of neovascular AMD; despite this, a sampling density reduced to 1/4 appeared to allow accurate assessment for most features. Current management of neovascular AMD is dependent on qualitative assessment of OCT images; with the recent proliferation of OCT systems, optimization and standardization of scanning protocols may be of value.

PMID: 22429902 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Mar 16. [Epub ahead of print]

Assessment of 180 degree rotation of the choroid as a novel surgical treatment for age-related

macular degeneration.

Lee E, Singh MS, Jones HE, Ahmed B, Andolina IM, Clements J, Luong V, Munro P, Lawton M, Grieve K, Aylward GW, Sillito A, Maclaren RE.

Genetics, UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL, United Kingdom.

Purpose: Our objective was to examine the feasibility of rotating choriocapillaris, Bruch's membrane (BM) and retinal pigment epithelium (RPE) through 180 degrees on a vascular pedicle and to assess revascularisation and tissue preservation post-operatively. Such an approach could be used in the treatment of age-related macular degeneration where there is focal disease at the macula with healthy tissues located peripherally.

Methods: Surgery was performed in six rhesus macaque monkeys which have a very similar choroidal blood supply to humans. After inducing a retinal detachment, the recurrent branch of the long posterior ciliary artery was used as a pedicle around which a graft stretching to the temporal equator was rotated. Retina was reattached over the rotated graft and eyes were followed up for up to 6 months with repeated angiography and optical coherence tomography (OCT). The morphology of retinal cells and BM were assessed by immunohistochemistry and electron microscopy.

Results: Revascularisation of the choroid was limited, with reestablishment of drainage to the vortex veins seen in only one case. There was a secondary loss of the RPE and outer retina evident on histological analysis three months after surgery. The underlying BM however remained intact.

Conclusions: Pedicled choroidal rotation surgery is technically feasible but re-establishing blood flow remains challenging, despite good apposition of transplanted and host tissues. The ability to rotate autologous BM from the equator to the macula, may provide a viable substrate to support submacular RPE replacement in combination with other cell therapy approaches.

PMID: 22427591 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Mar 16. [Epub ahead of print]

Explaining the Relationship Between Three Eye Diseases and Depressive Symptoms in Older Adults.

Popescu M, Boisjoly H, Schmaltz H, Kergoat MJ, Rousseau J, Moghadaszadeh S, Djafari F, Freeman EE.

Research Center, Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada.

Purpose: To examine whether patients with age-related eye diseases like age-related macular degeneration (AMD), glaucoma, or Fuchs corneal dystrophy are more likely to show signs of depression compared to a control group of older adults with good vision, and to determine whether reduced life space mediates these relationships.

Methods: We recruited 315 eligible patients (81 with AMD, 55 with Fuchs, 91 with glaucoma, and 88 controls) from the ophthalmology clinics of a Montreal hospital from September 2009 until December 2011. Depressive symptoms were assessed using the Geriatric Depression Scale Short Form (GDS-15). Life space was measured using the Life Space Assessment. Logistic regression was used to adjust for demographic, health, and social factors, and mediation was assessed using the methods of Baron and Kenny.

Results: There were 78 people meeting the criteria for depression in the cohort (25%). All 3 groups with eye disease were more likely to be depressed than the control group after adjusting for age, gender, ethnicity, education, cognitive score, limitations in activities of daily living, social support, and lens opacity ($p<0.05$). Life space appeared to mediate the relationship between eye disease and depression.

Conclusions: Visually limiting eye disease is associated with depression in older adults. Further research on interventions to prevent depression in patients with eye disease is warranted and should consider strategies to alleviate mobility limitation. Greater attention from families, physicians, and society to the mental health needs and mobility challenges of patients with eye disease is needed.

PMID: 22427589 [PubMed - as supplied by publisher]

Insight. 2012 Winter;37(1):9-11.

The impact of vision loss from age-related macular degeneration: a review (Part 2).

Orticio LP.

Impatient & Ambulatory Surgery Services, Bascom Palmer Eye Institute/Anne Bates Leach Eye Hospital, Miami, FL, USA. lorticio@med.miami.edu

PMID: 22439351 [PubMed - in process]

Pathogenesis

Photochem Photobiol. 2012 Mar 16. doi: 10.1111/j.1751-1097.2012.01143.x. [Epub ahead of print]

Retinal Photodamage Mediated by All-trans-retinal(†).

Maeda T, Golczak M, Maeda A.

Department of Ophthalmology and Visual Sciences Department of Pharmacology, Case Western Reserve University, Cleveland, OH, 44106, U.S.A.

Abstract

Accumulation of all-trans-retinal (all-trans-RAL), reactive vitamin A aldehyde, is one of the key factors in initiating retinal photodamage. This photodamage is characterized by progressive retinal cell death evoked by light exposure in both an acute and chronic fashion. Photo-activated rhodopsin releases all-trans-RAL which is subsequently transported by ATP-binding cassette transporter 4 and reduced to all-trans-retinol by all-trans-retinol dehydrogenases located in photoreceptor cells. Any interruptions in the clearing of all-trans-RAL in the photoreceptors can cause an accumulation of this reactive aldehyde and its toxic condensation products. This accumulation may result in the manifestation of retinal dystrophy including human retinal degenerative diseases such as Stargardt's disease and age-related macular degeneration. Here, we discuss the mechanisms of all-trans-RAL clearance in photoreceptor cells by sequential enzymatic reactions, the visual (retinoid) cycle, and potential molecular pathways of retinal photodamage. We also review recent imaging technologies to monitor retinal health status as well as novel therapeutic strategies preventing all-trans-RAL-associated retinal photodamage.

PMID: 22428905 [PubMed - as supplied by publisher]

Epidemiology

Eye (Lond). 2012 Mar 23. doi: 10.1038/eye.2012.51. [Epub ahead of print]

The Cataract National Dataset electronic multi-centre audit of 55 567 operations: risk indicators for monocular visual acuity outcomes.

Sparrow JM, Taylor H, Qureshi K, Smith R, Birnie K, Johnston RL.

1] Department of Ophthalmology, Bristol Eye Hospital, Bristol, UK [2] International Centre for Eye Health, London School of Hygiene & Tropical Medicine, London, UK.

Aims: To report risk factors for visual acuity (VA) improvement and harm following cataract surgery using electronically collected multi-centre data conforming to the Cataract National Dataset (CND).

Methods: Routinely collected anonymised data were remotely extracted from the electronic patient record systems of 12 participating NHS Trusts undertaking cataract surgery. Following data checks and cleaning, analyses were performed to identify risk indicators for: (1) a good acuity outcome (VA 6/12 or better), (2) the pre- to postoperative change in VA, and (3) VA loss (doubling or worse of the visual angle).

Results: In all, 406 surgeons from 12 NHS Trusts submitted data on 55 567 cataract operations. Preoperative VA was known for 55 528 (99.9%) and postoperative VA outcome for 40 758 (73.3%) operations. Important adverse preoperative risk indicators found in at least 2 of the 3 analyses included older age (3), short axial length (3), any ocular comorbidity (3), age-related macular degeneration (2), diabetic retinopathy (3), amblyopia (2), corneal pathology (2), previous vitrectomy (2), and posterior capsule rupture (PCR) during surgery (3). PCR was the only potentially modifiable adverse risk indicator and was powerfully associated with VA loss (OR=5.74).

Conclusion: Routinely collected electronic data conforming to the CND provide sufficient detail for identification and quantification of preoperative risk indicators for VA outcomes of cataract surgery. The majority of risk indicators are intrinsic to the patient or their eye, with a notable exception being PCR during surgery.

Eye advance online publication, 23 March 2012; doi:10.1038/eye.2012.51.

PMID: 22441022 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Mar 16. [Epub ahead of print]

Measurement of macular pigment optical density in a healthy Chinese population sample.

Yu J, Johnson EJ, Shang F, Lim A, Zhou H, Cui L, Xu J, Snellingen T, Liu X, Wang N, Liu N.

Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Sciences Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

Purpose: Macular pigment may protect against age-related macular degeneration (AMD) by its capacity to absorb blue light and scavenge free radicals. Current information on human macular pigment density has been largely from studies on Caucasian populations. The purpose of this study was to assess macular pigment density and its determinant factors in a Chinese population sample.

Methods: Macular pigment optical density (MPOD) was measured in a healthy Chinese population using heterochromatic flicker photometry (HFP). Participants received a standard ophthalmic examination and only subjects who were confirmed not to have any eye diseases except mild age-related cataract were included in the study. Demographic and lifestyle data and general health status were recorded by questionnaire.

Results: A total of 281 unrelated healthy Chinese individuals including 96 males and 185 females, with age ranging from 17 to 85 years, participated in the study. The mean and standard deviation of MPOD levels were 0.56 ± 0.19, 0.49 ± 0.18, 0.36 ± 0.15, and 0.19 ± 0.12, respectively, at 0.25°, 0.5°, 1.0°, and 1.75° eccentricity points. A significant age-related decline in MPOD was observed at 0.25° (p=0.014). Females tended to have relatively lower levels of MPOD than males at 0.25º (p=0.21), 0.5º (p=0.025), and 1.0º (p=0.16). No statistically significant association of MPOD was observed with body mass index or smoking

status.

Conclusions: Macular pigment density measured by HFP tends to decline with aging in this healthy Chinese population sample. Females may have lower levels of MPOD than males.

PMID: 22427543 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2012;7(3):e33576. Epub 2012 Mar 15.

Morpholino-mediated increase in soluble flt-1 expression results in decreased ocular and tumor neovascularization.

Owen LA, Uehara H, Cahoon J, Huang W, Simonis J, Ambati BK.

Department Of Ophthalmology, Moran Eye Center, University of Utah, Salt Lake City, Utah, United States of America.

BACKGROUND: Angiogenesis is a key process in several ocular disorders and cancers. Soluble Flt-1 is an alternatively spliced form of the Flt-1 gene that retains the ligand-binding domain, but lacks the membrane-spanning and intracellular kinase domains of the full-length membrane bound Flt-1 (mbFlt-1) protein. Thus, sFlt-1 is an endogenous inhibitor of VEGF-A mediated angiogenesis. Synthetic mopholino oligomers directed against splice site targets can modulate splice variant expression. We hypothesize that morpholino -induced upregulation of sFlt-1 will suppress angiogenesis in clinically relevant models of macular degeneration and breast cancer.

METHODS AND FINDINGS: In vivo morpholino constructs were designed to target murine exon/intron 13 junction of the Flt-1 transcript denoted VEGFR1_MOe13; standard nonspecific morpholino was used as control. After nucleofection of endothelial and breast adenocarcinoma cell lines, total RNA was extracted and real-time RT-PCR performed for sFlt-1 and mbFlt-1. Intravitreal injections of VEGFR1_MOe13 or control were done in a model of laser-induced choroidal neovascularization and intratumoral injections were performed in MBA-MD-231 xenografts in nude mice. VEGFR1_MOe13 elevated sFlt-1 mRNA expression and suppressed mbFlt-1 mRNA expression in vitro in multiple cellular backgrounds ($p<0.001$). VEGFR1_MOe13 also elevated sFlt/mbFlt-1 ratio in vivo after laser choroidal injury 5.5 fold ($p<0.001$) and suppressed laser-induced CNV by 50% ($p=0.0179$). This latter effect was reversed by RNAi of sFlt-1, confirming specificity of morpholino activity through up-regulation of sFlt-1. In the xenograft model, VEGFR1_MOe13 regressed tumor volume by 88.9%, increased sFlt-1 mRNA expression, and reduced vascular density by 50% relative to control morpholino treatment ($p<0.05$).

CONCLUSIONS: Morpholino oligomers targeting the VEGFR1 mRNA exon/intron 13 junction promote production of soluble FLT-1 over membrane bound FLT-1, resulting in suppression of lesional volume in laser induced CNV and breast adenocarcinoma. Thus, morpholino manipulation of alternative splicing offers translational potential for therapy of angiogenic disorders.

PMID: 22438952 [PubMed - in process]

PLoS One. 2012;7(3):e33244. Epub 2012 Mar 15.

MFGE8 Does Not Influence Chorio-Retinal Homeostasis or Choroidal Neovascularization in vivo.

Raoul W, Poupel L, Tregouet DA, Lavalette S, Camelo S, Keller N, Krumeich S, Calippe B, Guillonneau X, Behar-Cohen F, Cohen SY, Baatz H, Combadière C, Théry C, Sennlaub F.

INSERM, U968, Paris, France.

PURPOSE: Milk fat globule-epidermal growth factor-factor VIII (MFGE8) is necessary for diurnal outer segment phagocytosis and promotes VEGF-dependent neovascularization. The prevalence of two single nucleotide polymorphisms (SNP) in MFGE8 was studied in two exsudative or "wet" Age-related Macular Degeneration (AMD) groups and two corresponding control groups. We studied the effect of MFGE8 deficiency on retinal homeostasis with age and on choroidal neovascularization (CNV) in mice.

METHODS: The distribution of the SNP (rs4945 and rs1878326) of MFGE8 was analyzed in two groups of patients with "wet" AMD and their age-matched controls from Germany and France. MFGE8-expressing cells were identified in Mfge8(+/-) mice expressing ß-galactosidase. Aged Mfge8(+/-) and Mfge8(-/-) mice were studied by funduscopy, histology, electron microscopy, scanning electron microscopy of vascular corrosion casts of the choroid, and after laser-induced CNV.

RESULTS: rs1878326 was associated with AMD in the French and German group. The Mfge8 promoter is highly active in photoreceptors but not in retinal pigment epithelium cells. Mfge8(-/-) mice did not differ from controls in terms of fundus appearance, photoreceptor cell layers, choroidal architecture or laser-induced CNV. In contrast, the Bruch's membrane (BM) was slightly but significantly thicker in Mfge8(-/-) mice as compared to controls.

CONCLUSIONS: Despite a reproducible minor increase of rs1878326 in AMD patients and a very modest increase in BM in Mfge8(-/-) mice, our data suggests that MFGE8 dysfunction does not play a critical role in the pathogenesis of AMD.

PMID: 22438901 [PubMed - in process]

Curr Eye Res. 2012 Apr;37(4):259-271.

CFB/C2 Gene Polymorphisms and Risk of Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis.

Sun C, Zhao M, Li X.

Department of Ophthalmology, Peking University People's Hospital , Beijing , China.

Purpose: To investigate whether the polymorphisms of CFB/C2 gene are associated with age-related macular degeneration (AMD), and to evaluate the magnitude of gene effect.

Methods: We performed a meta-analysis of the association between four SNPs in CFB/C2 gene (rs9332739, rs547154, rs4151667, and rs641153) and risk of AMD using data from 15 case-control studies involving 8905 subjects. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed- and random-effects models. The Q and I(2) statistics were used to evaluate between-study heterogeneity. Harbord's modified test was used to detect small study effects. Sensitivity analysis, cumulative meta-analysis, and meta-regression were also performed.

Results: For rs9332739, rs547154, rs4151667, and rs641153, the pooled ORs in a dominant genetic model were 0.474 (fixed effects, $P < 0.001$, 95% CI 0.378-0.596), 0.399 (random effects, 95% CI 0.289-0.551, $P < 0.001$), 0.496 (fixed effects, 95% CI 0.390-0.632, $P < 0.001$), and 0.557 (random effects, $P = 0.008$, 95% CI 0.362-0.856), respectively. These results suggested that variant alleles of all the four SNPs has significant protective effect against AMD. Contour-enhanced funnel plots and Harbord's test showed moderate small study effects for rs9332739 and rs4151667. Heterogeneity were found for rs547154 and rs641153, subgroup analysis suggested that ethnicity was the main source for heterogeneity. Stratification by ethnicity indicated stronger protective effects of rare alleles in Caucasians. Genotype distribution analysis also suggested that frequencies of rare homozygous genotype were higher in Caucasian group.

Conclusions: Our meta-analysis indicated strong protective effects of the variant alleles of four SNPs in CFB/C2 gene (rs9332739, rs547154, rs4151667, and rs641153) against AMD. The disease risk descended to nearly one half for individuals carrying at least one copy of the rare alleles. The protective effects

seemed to be stronger in Caucasians, of which the genotype frequencies were also higher.

PMID: 22440158 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Mar 16. [Epub ahead of print]

A subgroup of age-related macular degeneration is associated with mono-allelic sequence variants in the ABCA4 gene.

Fritsche LG, Fleckenstein M, Fiebig BS, Schmitz-Valckenberg S, Bindewald-Wittich A, Keilhauer CN, Renner AB, Mackensen F, Moessner A, Pauleikhoff D, Adrion C, Mansmann U, Scholl HP, Holz FG, Weber BH.

Institute of Human Genetics, University Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg, 93053, Germany.

Purpose: Age-related macular degeneration (AMD) is a heterogenous condition of high prevalence and complex etiology involving genetic as well as environmental factors. By fundus autofluorescence (FAF) imaging AMD can be classified into several distinct phenotypes with one subgroup characterized by fine granular pattern with peripheral punctate spots (GPS[+]). Some features of GPS[+] overlap with Stargardt disease (STGD1), a recessive macular dystrophy caused by biallelic sequence variants in the ATP-binding cassette transporter 4 (ABCA4) gene. The aim of this study was to investigate the role of ABCA4 in GPS[+].

Methods: The ABCA4 gene was sequenced in 25 patients with the GPS[+] phenotype and 29 patients with geographic atrophy (GA)-AMD but no signs of GPS (GPS[-]). In addition, frequencies of risk increasing alleles at three known AMD susceptibility loci including complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), and complement component 3 (C3), were evaluated.

Results: Here, we demonstrate that GPS[+] is significantly associated with monoallelic ABCA4 sequence variants. Moreover, frequencies of AMD risk increasing alleles at CFH, ARMS2 and C3 are similar in GPS [+] and STGD1 patients, with risk allele frequencies in both subcategories comparable to population-based control individuals estimated from 3,510 individuals from the NHLBI Exome Sequencing Project.

Conclusions: Our data suggest that the GPS[+] phenotype is accounted for by monoallelic variants in ABCA4 and unlikely by the well established AMD risk increasing alleles at CFH, ARMS2 and C3. These findings provide support for a complex role of ABCA4 in the etiology of a minor fraction of AMD patients.

PMID: 22427542 [PubMed - as supplied by publisher]

Gene. 2012 Mar 8. [Epub ahead of print]

Contribution of complement factor H Y402H polymorphism to sudden sensorineural hearing loss risk and possible interaction with diabetes.

Nishio N, Teranishi M, Uchida Y, Sugiura S, Ando F, Shimokata H, Sone M, Otake H, Kato K, Yoshida T, Tagaya M, Hibi T, Nakashima T.

Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Otorhinolaryngology, Social Insurance Chukyo Hospital, Aichi, Japan.

Abstract

Sudden sensorineural hearing loss (SSNHL) is one of the most common diseases encountered by otolaryngologists; however, the etiology is unclear. The aim of this study was to assess the association between SSNHL and polymorphism of complement factor H (CFH) Y402H, which is implicated in age-

related macular degeneration. We conducted a case-control study, in which the cases were 72 SSNHL patients and the controls were 2161 residents selected randomly from the resident register. The odds ratio (OR) for SSNHL risk was determined using the additive-genetic model of CFH Y402H polymorphism. The OR for SSNHL risk was 1.788 (95% confidence interval [CI]: 1.008-3.172) with no adjustments and 1.820 (CI: 1.025-3.232) after adjusting for age and sex. Of the three lifestyle-related diseases hypertension, dyslipidemia, and diabetes, only diabetes was significantly associated with SSNHL risk. We classified both the controls and SSNHL patients into those with or without diabetes, and the OR for SSNHL risk was 6.326 (CI: 1.885-21.225) in diabetic subjects and 1.214 (CI: 0.581-2.538) in nondiabetic subjects. We conclude that CFH Y402H polymorphism and SSNHL risk are significantly related, and that diabetic CFH Y402H minor allele carriers may be susceptible to SSNHL.

PMID: 22426290 [PubMed - as supplied by publisher]

Am J Pathol. 2012 Mar 16. [Epub ahead of print]

Evidence for Baseline Retinal Pigment Epithelium Pathology in the Trp1-Cre Mouse.

Thanos A, Morizane Y, Murakami Y, Giani A, Mantopoulos D, Kayama M, In Roh M, Michaud N, Pawlyk B, Sandberg M, Young LH, Miller JW, Vavvas DG.

Retina Service, Angiogenesis Laboratory, Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.

Abstract

The increasing popularity of the Cre/loxP recombination system has led to the generation of numerous transgenic mouse lines in which Cre recombinase is expressed under the control of organ- or cell-specific promoters. Alterations in retinal pigment epithelium (RPE), a multifunctional cell monolayer that separates the retinal photoreceptors from the choroid, are prevalent in the pathogenesis of a number of ocular disorders, including age-related macular degeneration. To date, six transgenic mouse lines have been developed that target Cre to the RPE under the control of various gene promoters. However, multiple lines of evidence indicate that high levels of Cre expression can be toxic to mammalian cells. In this study, we report that in the Trp1-Cre mouse, a commonly used transgenic Cre strain for RPE gene function studies, Cre recombinase expression alone leads to RPE dysfunction and concomitant disorganization of RPE layer morphology, large areas of RPE atrophy, retinal photoreceptor dysfunction, and microglial cell activation in the affected areas. The phenotype described herein is similar to previously published reports of conditional gene knockouts that used the Trp1-Cre mouse, suggesting that Cre toxicity alone could account for some of the reported phenotypes and highlighting the importance of the inclusion of Cre-expressing mice as controls in conditional gene targeting studies.

PMID: 22429967 [PubMed - as supplied by publisher]

Diet

Acta Biochim Pol. 2012 Mar 17. [Epub ahead of print]

Structural aspects of the antioxidant activity of lutein in a model of photoreceptor membranes.

Wisniewska-Becker A, Nawrocki G, Duda M, Subczynski WK.

Department of Biophysics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Kraków, Poland.

Abstract

It was shown that in membranes containing raft domains, the macular xanthophylls lutein and zeaxanthin are not distributed uniformly, but are excluded from saturated raft domains and about ten times more concentrated in unsaturated bulk lipids. The selective accumulation of lutein and zeaxanthin in direct proximity to unsaturated lipids, which are especially susceptible to lipid peroxidation, could be very important as far as their antioxidant activity is concerned. Therefore, the protective role of lutein against lipid peroxidation was investigated in membranes made of raft-forming mixtures and in models of photoreceptor outer segment membranes and compared with their antioxidant activity in homogeneous membranes composed of unsaturated lipids. Lipid peroxidation was induced by photosensitized reactions using rose Bengal and monitored by an MDA-TBA test, an iodometric assay, and oxygen consumption (using EPR spectroscopy and the mHCTPO spin label as an oxygen probe). The results show that lutein protects unsaturated lipids more effectively in membranes made of raft-forming mixtures than in homogeneous membranes. This suggests that the selective accumulation of macular xanthophylls in the most vulnerable regions of photoreceptor membranes may play an important role in enhancing their antioxidant properties and ability to prevent age-related macular diseases (such as age-related macular degeneration [AMD]).

PMID: 22428148 [PubMed - as supplied by publisher]