

Issue 144

Tuesday 20 August, 2013

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".

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Drug treatment

Am J Ophthalmol. 2013 Aug 9. pii: S0002-9394(13)00418-2. doi: 10.1016/j.ajo.2013.06.020. [Epub ahead of print]

Long-term Stability of Vascular Endothelial Growth Factor Suppression Time Under Ranibizumab Treatment in Age-Related Macular Degeneration.

Muether PS, Hermann MM, Dröge K, Kirchhof B, Fauser S.

Department of Ophthalmology, University of Cologne, Cologne, Germany.

PURPOSE: To determine intra-individual long-term stability of vascular endothelial growth factor (VEGF) suppression time in eyes with neovascular age-related macular degeneration (AMD) treated with ranibizumab.

DESIGN: Nonrandomized, prospective clinical study.

METHODS: Eighty-three eyes of 83 patients with neovascular AMD undergoing intravitreal ranibizumab injections were included in the study. A total of 859 aqueous humor specimens were taken before each intravitreal ranibizumab injection. Vascular endothelial growth factor A was measured by multiplex bead analysis.

RESULTS: Ranibizumab resulted in complete VEGF suppression within a mean period of 36.4 days (standard deviation ± 6.7 days; range, 26-69 days). Intra-individual suppression time was stable within a period of up to 3 years. Among 859 VEGF measurements, only 5 (0.58%) deviated from this pattern. Nonsuppressed VEGF levels did not differ significantly between baseline and recurrence (68.0 pg/mL vs 69.3 pg/mL) and did not correlate with choroidal neovascularization size and lesion type.

CONCLUSIONS: Both the long-term stability and the broad range of individual suppression times after ranibizumab injections would allow and justify adjustment of continuous injections individually in order to achieve permanent VEGF suppression in patients.

PMID: 23938122 [PubMed - as supplied by publisher]

Doc Ophthalmol. 2013 Aug 13. [Epub ahead of print]

Single-session photodynamic therapy combined with intravitreal ranibizumab for neovascular age-related macular degeneration: a comprehensive functional retinal assessment.

Parravano M, Parisi V, Ziccardi L, Chiaravalloti A, Tedeschi M, Cacciamani A, Boccassini B, Boninfante A,

Varano M.

Fondazione G.B. Bietti-IRCCS, Via Livorno n 3, 00198, Rome, Italy, criparra@tin.it.

PURPOSE: To explore functional retinal changes in neovascular AMD patients (nAMD) treated with ranibizumab 0.5 mg combined with photodynamic therapy (PDT) 3 days after the first injection in the long term.

METHODS: Patients with no prior treatment for nAMD were treated with 3 injections of ranibizumab 0.5 mg 1 month apart and a single session of standard PDT 3 days after the first injection. Best-corrected visual acuity and time-domain OCT at baseline and every 28 ± 2 days were performed; microperimetry at 3, 6, and 12 months and multifocal electroretinogram (mfERG) at 3 and 12 months were repeated. Fluorescein angiography and vision-related quality-of-life questionnaire were performed at baseline and 12 months.

RESULTS: 12/15 nAMD patients completed the 12 months study and received an average of 3.4 ± 0.7 injections. Mean VA changed from 54.67 ± 15.72 to 59.0 ± 24.77 letters ($p = 0.371$), while mean retinal sensitivity from 5.5 ± 4.8 to 6.6 ± 6.0 dB ($p = 0.216$). mfERG N1-P1 response amplitude densities (RADs) were significantly different from baseline ($p < 0.01$) in the central 0° - 2.5° , whereas in the peripheral retinal areas (2.5° - 20°), not significant ($p > 0.01$) changes in N1-P1 RADs were detected. The "general vision" VFQ-25 subscale showed a statistically significant improvement at 3 and 12 months.

CONCLUSIONS: Ranibizumab 0.5 mg combined with standard PDT 3 days after the first injection determines an improvement of mfERG values in the retinal central area in nAMD patients in long-term follow-up.

PMID: 23943132 [PubMed - as supplied by publisher]

Isr Med Assoc J. 2013 Jul;15(7):352-5.

Persistent elevation of intraocular pressure following intravitreal injection of bevacizumab.

Segal O, Ferencz JR, Cohen P, Nemet AY, Neshet R.

Department of Ophthalmology, Meir Medical Center, Kfar Saba, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel. orisegal@gmail.com

BACKGROUND: The number of patients treated with intravitreal injections has increased significantly over the past few years, mainly following the introduction of anti-vascular endothelial growth factor antibody intraocular drugs. Bevacizumab is mostly used in this group of medications.

OBJECTIVES: To describe persistent elevation of intraocular pressure (IOP) following intravitreal injection of bevacizumab.

METHODS: We reviewed consecutive cases of persistent IOP elevation after intravitreal bevacizumab injection for exudative age-related macular degeneration (AMD). A total of 424 patients (528 eyes) met the inclusion criteria and received 1796 intravitreal injections of bevacizumab. Persistent IOP elevation was found in 19 eyes (3.6%, 19/528) of 18 patients (4.2%, 18/424) with IOP elevated 30-70 mmHg 3-30 days after injection.

RESULTS: Mean IOP was 42.6 mmHg (range 30-70); IOP elevations occurred after an average of 7.8 injections of bevacizumab (range 3-13). Injected eyes (19/528) had a significantly higher incidence of elevated IOP than uninjected eyes (fellow eyes), 1/328, $P < 0.001$.

CONCLUSIONS: Like other anti-vascular endothelial growth factor (VEGF) substances reported in a few recent studies, intravitreal injection of bevacizumab for neovascular AMD may be associated with persistent IOP elevation. Providers should be aware that significant IOP elevation might occur after repeated treatments.

PMID: 23943979 [PubMed - in process]

Can J Ophthalmol. 2013 Aug;48(4):317-23. doi: 10.1016/j.jcjo.2013.03.004.

Ranibizumab injection for diabetic macular edema: meta-analysis of systemic safety and systematic review.

Abouammoh MA.

King Saud University, Riyadh, Saudi Arabia. Electronic address: dr.abouammoh@gmail.com.

OBJECTIVE: To conduct a systematic review on the safety of ranibizumab injections for diabetic macular edema by meta-analysis of recently conducted level 1 randomized clinical trials.

DESIGN: A meta-analysis and systematic review.

METHODS: Main outcome measures of permissible studies were extracted and reported. The relative risk (RR) for thromboembolic events (TEEs) was calculated for those studies that met this study's inclusion criteria. The fixed-effects model (Mantel-Haenszel method) was appropriately used to calculate the pooled RR. The quality of trials was assessed using the Jadad score.

RESULTS: Of the 2072 patients who were included from 4 eligible randomized clinical trials, 1295 patients received intravitreal ranibizumab injections. The pooled RR for TEEs after ranibizumab intravitreal injection was 0.74 (95% CI 0.52-1.06).

CONCLUSIONS: Intravitreal ranibizumab for the treatment of diabetic macular edema did not increase the risk for TEEs as shown by this meta-analysis of 4 randomized, controlled clinical trials.

PMID: 23931473 [PubMed - in process]

Pharmacogenomics. 2013 Aug;14(11):1239-42. doi: 10.2217/pgs.13.100.

Pharmacogenetic labyrinth of neovascular age-related macular degeneration therapy: how to escape and move forward?

Lazzeri S, Nardi M, Bocci G.

Dipartimento di Patologia Chirurgica, Medica, Molecolare e dell'Area Critica, Università di Pisa, Pisa, Italy.

PMID: 23930669 [PubMed - in process]

Other treatment & diagnosis

Clin Exp Optom. 2013 Aug 15. doi: 10.1111/cxo.12102. [Epub ahead of print]

Australian general medical practitioner referral pathways for people with different ocular conditions.

Jamous KF, Jalbert I, Kalloniatis M, Boon MY.

School of Optometry and Vision Science, University of New South Wales, Kensington, New South Wales, Australia; Department of Ophthalmology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia.

BACKGROUND: The aim was to obtain an overview of general medical practitioner (GP) referral pathways to ocular health care and allied services for people identified with age-related macular degeneration (AMD), diabetic retinopathy (DR) or glaucoma (GL).

METHODS: A questionnaire was developed to survey GPs in Australia. Questions included demographic

information and referral patterns to ocular and health service providers. The survey was posted to 1,050 randomly selected GPs across Australia.

RESULTS: Fifty-eight GPs participated in this study amounting to a 6.5 per cent response rate. Nearly all GPs referred patients to ophthalmologists (AMD: 98 per cent; DR: 98 per cent; GL: 95 per cent). A smaller proportion of GPs also referred to low vision rehabilitation (LVR) services (AMD: 34 per cent; DR: 33 per cent; GL: 22 per cent), optometrists (AMD: 26 per cent; DR: 34 per cent; GL: 31 per cent), or support services (AMD: 17 per cent; DR: 40 per cent; GL: 19 per cent). For the three tested conditions, there were no statistically significant differences in the proportions of GPs, who referred to ophthalmologists ($p = 0.43$), optometrists ($p = 0.48$) or to low vision rehabilitation services ($p = 0.31$). The proportion of GPs who referred to support services was significantly higher for patients diagnosed with DR than AMD or GL ($p < 0.05$).

CONCLUSION: The majority of GPs referred patients with AMD, DR or GL to ophthalmologists. Fewer GPs considered referrals to optometrists, low vision rehabilitation or support services. General practitioners may need to be more aware about the central role of optometrists in the delivery of primary eye health care. In the interest of optimising eye care, closer working relationships between GPs and optometrists should be fostered.

PMID: 23944239 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Aug 9;54(8):5408-15. doi: 10.1167/iovs.12-12026.

Dual tasking and balance in those with central and peripheral vision loss.

Kotecha A, Chopra R, Fahy RT, Rubin GS.

National Institute for Health Research Biomedical Research Center for Ophthalmology, Moorfields Eye Hospital National Health Service Foundation Trust, and University College London (UCL) Institute of Ophthalmology, London, United Kingdom.

PURPOSE: To investigate the effects of a secondary task on standing balance in patients with glaucoma or AMD compared with age-similar control subjects.

METHODS: Twelve AMD, 12 glaucoma, and 12 control participants underwent posturography under two standing conditions (eyes open on a firm or foam-rubber surface) and two tasks: quiet standing and undertaking a mental arithmetic task. Center of foot-pressure average displacement (root mean square [RMS]; in millimeters) was calculated.

RESULTS: The mean (SD) age of the participants in each group was as follows: controls 66.2 (6.4) years, glaucoma 69.2 (4.3) years, and AMD 72.2 (5.3) years. There were significant differences in RMS between controls and AMD patients when undertaking the mental arithmetic task standing on the firm surface (mean difference [SE]: 2.8 [0.8] mm, $P = 0.005$). There were significant differences between controls and AMD patients when undertaking the mental arithmetic task on the foam surface, with the difference between controls and glaucoma patients approaching significance (mean difference [SE]: control versus AMD = 3.1 [0.9] mm, $P = 0.005$; control versus glaucoma = 2.2 [0.9] mm, $P = 0.06$).

CONCLUSIONS: Postural instability increases with the addition of a secondary task in older persons, which may put them at greater risk of falls. Patients with central losses exhibit greater instability with the addition of a secondary task, particularly during somatosensory perturbations. The negative effects of secondary tasks on balance control in those with peripheral visual losses become more apparent under somatosensory perturbations.

PMID: 23934661 [PubMed - in process]

Can J Ophthalmol. 2013 Aug;48(4):274-8. doi: 10.1016/j.jcjo.2013.03.006.

Residual colour detection abilities in age-related macular degeneration.

Shima N, Markowitz SN, Reyes SV.

Low Vision Service (University Health Network Hospitals), Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ont.

OBJECTIVE: To quantify residual abilities to identify a target's colour in cases with age-related macular degeneration (AMD).

METHODS: Subjects with AMD with best corrected visual acuity (BCVA) of 20/50 to 20/400 in the better eye (test eye) and age older than 55 years were recruited. A separate matching control group was recruited with subjects with BCVA of 20/40 or better. Each subject was presented sequentially with square-shaped colour targets corresponding in size to optotype sizes used in standard Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing protocols, all against a white background. Four major colour hues were selected for testing: blue, yellow, green, and red. The same subjects were tested with standard ETDRS targets (black on white), and results served as control group references. The primary outcome measure selected for analysis was the minimum angle of resolution (MAR) required to correctly identify the hue presented.

RESULTS: Forty study subjects (14 males and 26 females) aged 55 to 95 years (mean 79.45 years, SD 8.82) were recruited. Thirty similar subjects were recruited for a control group. Red on white estimates were better than for other colours and related best to standard black on white ETDRS estimates (20/121 vs 20/132, respectively). Also, red on white estimates seem not to be affected by age. Estimates for colour detection for the control group were not different among colours tested and were not affected by age.

CONCLUSIONS: Ranking abilities according to the MAR required to identify a hue can serve as a quantifying measure for residual colour vision. Our findings reflect functional abilities rather than psychophysical measurements.

PMID: 23931466 [PubMed - in process]

Can J Ophthalmol. 2013 Aug;48(4):269-73. doi: 10.1016/j.jcjo.2013.03.007.

Prevalence and impact of depressive symptoms in patients with age-related macular degeneration.

Jivraj J, Jivraj I, Tennant M, Rudnisky C.

Departments of Pediatrics and Ophthalmology, University of Alberta, Royal Alexandra Hospital, Edmonton, Alta.. Electronic address: jivraj.jamil@gmail.com.

OBJECTIVE: This study sought to identify the point prevalence of depressive symptoms, quality-of-life (QOL) impairment, and demographic parameters associated with depression in patients with age-related macular degeneration (AMD) attending a retina clinic in Edmonton, Alberta.

DESIGN: A cross-sectional design was used.

METHODS: Consecutive patients with AMD were invited to participate in the study. Demographic data, as well as ophthalmic, medical, and psychiatric histories, were collected. Participants completed the Center for Epidemiological Studies Depression Scale (CES-D) and the Visual Function Questionnaire (VFQ-25) scales to quantify the burden of depressive symptoms and vision-related QOL impairment.

RESULTS: The study enrolled 101 patients, of whom 7 (6.9%) had a previous history of depression. Twenty (21.3%) of the remaining patients endorsed severe symptoms of depression that had not yet been diagnosed. Significant differences in vision-related QOL between depressed and not depressed patients

were identified. Depressed patients were also found to have worse visual acuity ($p = 0.047$) and were less likely to live with others ($p = 0.020$) than those who were not depressed.

CONCLUSIONS: After excluding patients with a history of diagnosed depression, 20 (21.3%) patients demonstrated severe symptoms of depression. Development of depression screening protocols for patients with AMD would improve identification and referral of patients at risk. The finding that patients who lived with others had a lower prevalence of depressive symptoms suggests that further research into the relationship between mood symptoms and environmental supports is merited.

PMID: 23931465 [PubMed - in process]

Pathogenesis

Prog Retin Eye Res. 2013 Aug 8. pii: S1350-9462(13)00045-1. doi: 10.1016/j.preteyeres.2013.07.003. [Epub ahead of print]

Aging Is Not a Disease: Distinguishing Age-Related Macular Degeneration from Aging.

Ardeljan D, Chan CC.

Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD 20892; Johns Hopkins University School of Medicine, Baltimore, MD 21205.

Abstract: Age-related macular degeneration (AMD) is a disease of the outer retina, characterized most significantly by atrophy of photoreceptors and retinal pigment epithelium accompanied with or without choroidal neovascularization. Development of AMD has been recognized as contingent on environmental and genetic risk factors, the strongest being advanced age. In this review, we highlight pathogenic changes that destabilize ocular homeostasis and promote AMD development. With normal aging, photoreceptors are steadily lost, Bruch's membrane thickens, the choroid thins, and hard drusen may form in the periphery. In AMD, many of these changes are exacerbated in addition to the development of disease-specific factors such as soft macular drusen. Para-inflammation, which can be thought of as an intermediate between basal and robust levels of inflammation, develops within the retina in an attempt to maintain ocular homeostasis, reflected by increased expression of the anti-inflammatory cytokine IL-10 coupled with shifts in macrophage plasticity from the pro-inflammatory M1 to the anti-inflammatory M2 polarization. In AMD, imbalances in the M1 and M2 populations together with activation of retinal microglia are observed and potentially contribute to tissue degeneration. Nonetheless, the retina persists in a state of chronic inflammation and increased expression of certain cytokines and inflammasomes is observed. Since not everyone develops AMD, the vital question to ask is how the body establishes a balance between normal age-related changes and the pathological phenotypes in AMD.

PMID: 23933169 [PubMed - as supplied by publisher]

Mol Vis. 2013 Aug 6;19:1826-33. eCollection 2013.

Increase in peripheral blood mononuclear cell Toll-like receptor 2/3 expression and reactivity to their ligands in a cohort of patients with wet age-related macular degeneration.

Zhu Y, Liang L, Qian D, Yu H, Yang P, Lei B, Peng H.

Department of Ophthalmology, the First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, Chongqing Eye Institute, Chongqing, China.

PURPOSE: To investigate Toll-like receptor (TLR) expression and reactivity in patients with the wet form age-related macular degeneration (AMD).

METHODS: Blood samples were collected from 25 patients with wet AMD and 25 age-matched healthy controls. Peripheral blood mononuclear cells (PBMCs) were isolated with Ficoll-Hypaque density gradient centrifugation. Expression of TLR1 to TLR10 mRNAs in PBMCs from 15 patients with wet AMD and 15 controls was assessed with real-time PCR. TLR2 and TLR3 protein levels in PBMCs from six patients with wet AMD and six controls were measured with flow cytometry. After PBMCs were stimulated with peptidoglycan (PGN) and poly(I:C), the specific ligands of TLR2 and TLR3, cytokines interleukin-6 (IL-6), IL-8, VEGF, and monocyte chemoattractant protein-1 (MCP-1) production in 11 patients with wet AMD and 11 controls were assessed.

RESULTS: TLR2 and TLR3 mRNA and protein expression in the PBMCs of the patients with wet AMD was significantly higher than that in the controls. However, the difference in TLR1 and TLR4-10 mRNA expression between the two groups was not significant. The PBMCs of the patients with wet AMD produced more IL-6 and IL-8 proteins than the controls in response to PGN, a ligand for TLR2, and more IL-6 protein than the controls in response to poly(I:C), the ligand for TLR3. However, there was no significant difference in vascular endothelial growth factor and monocyte chemoattractant protein-1 production between the wet AMD group and the control group when the PBMCs were stimulated with PGN or poly(I:C).

CONCLUSIONS: Our data suggested that upregulation of TLR2 and TLR3 may be associated with the pathogenesis of wet AMD.

PMID: 23946637 [PubMed - in process]

Epidemiology

Curr Med Res Opin. 2013 Aug 14. [Epub ahead of print]

An epidemiological study of neovascular age-related macular degeneration in Germany.

Krause L, Yousif T, Pohl K; on behalf of CAPTAIN study group.

Municipal Hospital Dessau, Dessau, Germany.

Objective: Neovascular or wet age-related macular degeneration (AMD) is one of the leading causes of blindness in industrialized countries; however, there is a lack of recent epidemiological data from Germany. The aim of this study was to collect epidemiological data from patients in Germany with suspected neovascular AMD and evaluate the diagnostic procedures performed and treatments used at clinics.

Methods: This was a Germany-based, multicentre, retrospective review of data from patients with suspected neovascular AMD visiting ophthalmology clinics over an 18-month period in 2008-10. Clinical characteristics, functional symptoms and examination results were recorded. In addition, ophthalmologists completed a questionnaire on neovascular AMD diagnosis and treatment.

Results: Ten sites collected data from 2498 patients (64.0% female) with a mean decimal visual acuity of 0.4 ± 0.3 at the time of diagnosis of neovascular AMD. The mean age at the time of diagnosis was 76.9 ± 8.9 years for patients with the right eye affected and 77.0 ± 8.3 years for patients with the left eye affected. The most frequent pathological findings detected by routine ophthalmic examination were old lesions (31.2%), intra/subretinal fluid (18.1%), new lesions (13.0%), and intra/subretinal haemorrhage (11.4%). A confirmed diagnosis of neovascular AMD was most frequently based on fundoscopy (67.3%), fluorescein angiography (39.6%), and biomicroscopy (35.7%) tests but rarely on optical coherence tomography (8.9%). The most frequently documented comorbidity with neovascular AMD was hypertension and other cardiovascular diseases (57.5%). Seven ophthalmologists completed the questionnaire with the majority of ophthalmologists agreeing that regular ophthalmic examination can prevent the development of late stage neovascular AMD.

Conclusion: Neovascular AMD is a frequent diagnosis in German ophthalmology clinics. As visual acuity is

already poor in most patients with suspected neovascular AMD, regular preventive ophthalmologic examinations should be considered in high risk patients. Study limitations: Limitations of the study include the lack of a comparator cohort, which limited the amount of analyses that could be performed. Additionally, a study eye was not defined and information was collected separately for each affected eye and therefore analysed separately. Furthermore, a small number of ophthalmologists completed the questionnaire, limiting the objectivity.

PMID: 23944372 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Aug 9. pii: S0002-9394(13)00395-4. doi: 10.1016/j.ajo.2013.06.007. [Epub ahead of print]

Prevalence and Characteristics of Age-Related Macular Degeneration in the Japanese Population: The Nagahama Study.

Nakata I, Yamashiro K, Nakanishi H, Akagi-Kurashige Y, Miyake M, Tsujikawa A, Matsuda F, Yoshimura N; the Nagahama Cohort Research Group.

Department of Ophthalmology, Kyoto University Graduate School of Medicine, Kyoto, Japan; Center for Genomic Medicine/Inserm U.852, Kyoto University Graduate School of Medicine, Kyoto, Japan.

PURPOSE: To estimate the age- and sex-specific prevalence of early age-related macular degeneration (AMD; drusen and retinal pigment abnormalities) and late AMD (exudative AMD and geographic atrophy) in the Japanese population.

DESIGN: Community-based, cross-sectional study.

METHODS: The study was held in Nagahama, Japan, and included 6065 Japanese individuals (aged ≥ 50 years) recruited in 2008-2010. We graded fundus photographs of both eyes for the AMD phenotype based on drusen size, the presence of retinal pigment abnormalities, and late AMD. The associations between smoking and AMD phenotypes were also evaluated.

RESULTS: We assessed 5595 subjects (women, 65%) with a gradable macular condition. Early and late AMD prevalence increased from 16.1% and 0.27% at 50-59 years to 31.2% and 0.98%, respectively, at 70-74 years and was predominant in male subjects in each age group. Smoking was associated with both early and late AMD stages and retinal pigment abnormalities ($P < .0001$), but not with drusen ($P = .305$). The prevalence of retinal pigment abnormalities was significantly higher in men ($P < .0001$), which was associated with high rates of cigarette smoking. We found no sex difference for the prevalence of large drusen ($P = .264$).

CONCLUSIONS: The prevalence of early AMD among adult Japanese persons was similar to the rates in white populations. The prevalence of late AMD in Japanese people aged < 70 years was similar to that observed in white populations, whereas that in Japanese people aged ≥ 70 years was relatively lower.

PMID: 23938127 [PubMed - as supplied by publisher]

JAMA Intern Med. 2013 Aug 12;173(15):1476-7. doi: 10.1001/jamainternmed.2013.8131.

Is 81-mg Aspirin Associated With Age-Related Macular Degeneration Risk?-Reply.

Wang JJ, Liew G, Mitchell P.

Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia²Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia.

PMID: 23939526 [PubMed - in process]

JAMA Intern Med. 2013 Aug 12;173(15):1476. doi: 10.1001/jamainternmed.2013.8147.

Is 81-mg Aspirin Associated With Age-Related Macular Degeneration Risk?

Keller DL.

Providence Medical Group, Torrance, California.

PMID: 23939525 [PubMed - in process]

Genetics

Invest Ophthalmol Vis Sci. 2013 Aug 13. pii: iovs.13-12273v1. doi: 10.1167/iov.13-12273. [Epub ahead of print]

AMD-associated variants at the chromosome 10q26 locus and the stability of ARMS2 transcripts.

Minor EA, Court BL, Dubovy S, Wang G.

University of Miami, 1501 NW 10th Avenue, Miami, FLORIDA, 33136, United States.

Purpose: To analyze the effect of variants including age-related macular degeneration (AMD)-associated indel at 3'UTR of ARMS2 and possibly associated R38X on the stability of ARMS2 transcripts.

Methods: ARMS2 transcription from minigene vectors carrying different alleles at variants R38X and the indel were assessed in mouse embryonic fibroblasts (MEFs). Dual luciferase assays were applied to evaluate the effect of the indel on gene expression. RT-PCR and quantitative RT-PCR (qRT-PCR) were used to measure the two ARMS2 transcripts (isoform-A and isoform-B) in MEFs and human retina-RPE-choroid samples (n = 83).

Results: Allele X at variant R38X decreased exogenous ARMS2 transcripts in MEFs compared to allele R. In contrast, the indel did not change the level of exogenous ARMS2 transcripts. After blocking transcription by actinomycin-D, R38X appeared to accelerate the degradation of ARMS2 transcripts, while the indel did not obviously affect the stability of ARMS2 transcripts compared to the wild type (WT) allele. Dual luciferase assays further indicated the indel did not influence gene expression. qRT-PCR results showed there was no significant difference in two ARMS2 transcript splice isoforms among retina-RPE-choroid samples carrying different genotypes at variants R38X and the indel.

Conclusions: Variant R38X, not the indel, decreases the stability of ARMS2 transcripts in vitro. However, genotypes at R38X and the indel do not obviously affect the level of ARMS2 transcripts in retina-RPE-choroid samples. These results suggest that variants R38X and the indel are less likely to play a pathogenic role in AMD by changing the level of ARMS2 transcripts.

PMID: 23942973 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Aug 9. pii: S0002-9394(13)00392-9. doi: 10.1016/j.ajo.2013.06.004. [Epub ahead of print]

Associations of Candidate Genes to Age-Related Macular Degeneration Among Racial/Ethnic Groups in the Multi-Ethnic Study of Atherosclerosis.

Klein R, Li X, Kuo JZ, Klein BE, Cotch MF, Wong TY, Taylor KD, Rotter JI.

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin. Electronic address: kleinr@epi.opth.wisc.edu.

PURPOSE: To describe the relationships of selected candidate genes to the prevalence of early age-related macular degeneration (AMD) in a cohort of whites, blacks, Hispanics, and Chinese Americans.

DESIGN: Cross-sectional study.

METHODS: setting: Multicenter study. study population: A total of 2456 persons aged 45-84 years with genotype information and fundus photographs. procedures: Twelve of 2862 single nucleotide polymorphisms (SNPs) from 11 of 233 candidate genes for cardiovascular disease were selected for analysis based on screening with marginal unadjusted P value <.001 within 1 or more racial/ethnic groups. Logistic regression models tested for association in case-control samples. main outcome measure: Prevalence of early AMD.

RESULTS: Early AMD was present in 4.0% of the cohort and varied from 2.4% in blacks to 6.0% in whites. The odds ratio increased from 2.3 for 1 to 10.0 for 4 risk alleles in a joint effect analysis of Age-Related Maculopathy Susceptibility 2 rs10490924 and Complement Factor H Y402H (P for trend = 4.2×10^{-7}). Frequencies of each SNP varied among the racial/ethnic groups. Adjusting for age and other factors, few statistically significant associations of the 12 SNPs with AMD were consistent across all groups. In a multivariate model, most candidate genes did not attenuate the comparatively higher odds of AMD in whites. The higher frequency of risk alleles for several SNPs in Chinese Americans may partially explain their AMD frequency's approaching that of whites.

CONCLUSIONS: The relationships of 11 candidate genes to early AMD varied among 4 racial/ethnic groups, and partially explained the observed variations in early AMD prevalence among them.

PMID: 23938121 [PubMed - as supplied by publisher]

Am J Epidemiol. 2013 Aug 13. [Epub ahead of print]

RE: "THE ASSOCIATION BETWEEN COMPLEMENT COMPONENT 2/COMPLEMENT FACTOR B POLYMORPHISMS AND AGE-RELATED MACULAR DEGENERATION: A HuGE REVIEW AND META-ANALYSIS"

Tillmann S, Grasskamp A, Wulf M, Martis LS, Domani M, Sand PG.

Experimental and Clinical Neurosciences Graduate Program, University of Regensburg, Regensburg 93053, Germany.

PMID: 23942214 [PubMed - as supplied by publisher]

Br J Pharmacol. 2013 Aug 13. doi: 10.1111/bph.12330. [Epub ahead of print]

Small interfering RNAs (siRNAs) as a promising tool for ocular therapy.

Guzman-Aranguiz A, Loma P, Pintor J.

Department of Biochemistry and Molecular Biology IV, Faculty of Optics and Optometry, Universidad Complutense de Madrid, Spain.

Abstract: RNA interference (RNAi) permits the inhibition of gene expression in vitro or in vivo, thereby providing an extremely useful tool for investigating gene function. Progress in the understanding of RNAi-based mechanisms has opened wide perspectives in therapeutics for the treatment of several diseases including ocular disorders. The eye is currently considered a good target for RNAi therapy mainly because

it is a confined compartment and local delivery of siRNAs by topical instillation or direct injection is possible. However, delivery strategies allowing protection against degradation and long-term delivery would be helpful to improve the efficiency of RNAi-based therapies for ocular pathologies. siRNAs targeting critical molecules involved in the pathogenesis of glaucoma, retinitis pigmentosa and neovascular eye diseases (age-related macular degeneration, diabetic retinopathy or corneal neovascularization) have been tested in experimental animal models and clinical trials have been conducted with some of them. This review provides an update on the progress of RNAi for ocular therapeutics, discussing the advantages and drawbacks of RNAi-based therapeutics over previous treatments.

PMID: 23937539 [PubMed - as supplied by publisher]

Hum Mol Genet. 2013 Aug 13. [Epub ahead of print]

Mouse genetics and proteomic analyses demonstrate a critical role for complement in a model of DHRD/ML, an inherited macular degeneration.

Garland DL, Fernandez-Godino R, Kaur I, Speicher KD, Harnly JM, Lambris JD, Speicher DW, Pierce EA.

Ocular Genomics Institute, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA.

Abstract: Macular degenerations, inherited and age-related, are important causes of vision loss. Human genetic studies have suggested perturbation of the complement system is important in the pathogenesis of age-related macular degeneration. The mechanisms underlying the involvement of the complement system are not understood, although complement and inflammation have been implicated in drusen formation. Drusen are an early clinical hallmark of inherited and age-related forms of macular degeneration. We studied one of the earliest stages of macular degeneration which precedes and leads to the formation of drusen, ie the formation of basal deposits. The studies were done using a mouse model of the inherited macular dystrophy Doyme Honeycomb Retinal Dystrophy/Malattia Leventinese (DHRD/ML) which is caused by a p.Arg345Trp mutation in EFEMP1. The hallmark of DHRD/ML is the formation of drusen at an early age, and gene targeted Efemp1R345 W/R345 W mice develop extensive basal deposits. Proteomic analyses of Bruch's membrane/choroid and Bruch's membrane in the Efemp1R345 W/R345 W mice indicate that the basal deposits are composed of normal extracellular matrix components present in abnormal amounts. The proteomic analyses also identified significant changes in proteins with immune-related function, including complement components, in the diseased tissue samples. Genetic ablation of the complement response via generation of Efemp1R345 W/R345 W:C3^{-/-} double mutant mice inhibited the formation of basal deposits. The results demonstrate a critical role for the complement system in basal deposit formation, and suggest that complement-mediated recognition of abnormal extracellular matrix may participate in basal deposit formation in DHRD/ML and perhaps other macular degenerations.

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Diet

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Saffron Pre-Treatment Offers Neuroprotection to Nigral and Retinal Dopaminergic Cells of MPTP-Treated mice.

Purushothuman S, Nandasena C, Peoples CL, El Massri N, Johnstone DM, Mitrofanis J, Stone J.

Discipline of Physiology, University of Sydney, Australia.

Background: There is growing evidence that the spice saffron, which contains powerful anti-oxidants, offers

protection against neurodegenerative disorders, including age-related macular degeneration and Alzheimer's disease.

Objective: We examined whether saffron pre-treatment protects dopaminergic cells of the substantia nigra pars compacta (SNc) and retina in an acute MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model of Parkinson's disease.

Methods: BALB/c mice received MPTP or saline injections over a 30 hour period, followed by six days survival. For five days prior to injections, the drinking water of the saffron groups was supplemented with saffron (0.01% w/v), while non-saffron groups received normal tap water. After the survival period was complete, brains were processed for tyrosine hydroxylase (TH) immunohistochemistry and the number of TH+ cells was analysed using the optical fractionator method.

Results: In both the SNc and retina, non-conditioned MPTP-injected mice had a reduced number of TH+ cells (30-35%) compared to the saline-injected controls. Saffron pre-conditioning mitigated the reduction, with pre-conditioned MPTP-injected mice having SNc and retinal TH+ cell numbers close to control levels, significantly (25-35%) higher than in non-conditioned MPTP-injected mice.

Conclusions: Our results indicated that saffron pre-treatment of mice saved many dopaminergic cells of the SNc and retina from parkinsonian (MPTP) insult.

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