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MD Research News

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Drug treatment

Invest Ophthalmol Vis Sci. 2012 Aug 21. [Epub ahead of print]

Retinal nerve fiber layer thickness changes in patients with age-related macular degeneration treated with intravitreal ranibizumab.

Martinez-de-la-Casa JM, Ruiz-Calvo A, Saenz-Frances F, Reche-Frutos J, Calvo-Gonzalez C, Donate-Lopez J, Garcia-Feijoo J.

Madrid and Instituto de Investigaciones Oftalmologicas Ramon Castroviejo, Universidad Complutense, Hospital Clinico San Carlos, Madrid, 28040, Spain.

Purpose: To assess the effects of intravitreal ranibizumab therapy on intraocular pressure (IOP) and retinal nerve fiber (RNFL) thickness.

Methods: 49 eyes of 49 patients with neovascular age-related macular degeneration (AMD) treated with intravitreal ranibizumab injections and 27 fellow eyes not requiring treatment were followed for one year. RNFL thickness, as measured by Fourier domain optical coherence tomography, and IOP were determined pre- and post injection.

Results: After 12 months, the mean number of injections received was 4.8 ± 1.6. The incidence of IOP elevations (>5 mmHg over baseline) observed at the time of injection was 0.4%. Baseline RNFL thickness was 105.7 ± 12.2 µm in the treatment group compared to 101.8 ± 11.6 µm in the control group (p=0.176). At the end of follow up, significant RNFL thinning was noted in the treatment group (100.2 ± 11.0 µm, p<0.001), while no differences were found in the control group (100.5 +/- 10.8 µm, p=0.477).

Conclusion: Intravitreal ranibizumab injections used to treat AMD caused a significant change in RNFL thickness after 12 months of follow up.

PMID: 22915037 [PubMed - as supplied by publisher]

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

Anti-Vascular Endothelial Growth Factor Pharmacotherapy for Diabetic Macular Edema: A Report by the American Academy of Ophthalmology.

Ho AC, Scott IU, Kim SJ, Brown GC, Brown MM, Ip MS, Recchia FM.

American Academy of Ophthalmology, San Francisco, California.

OBJECTIVE: To review the evidence regarding the safety and efficacy of current anti-vascular endothelial growth factor (VEGF) pharmacotherapies for the treatment of diabetic macular edema (DME).

METHODS: Literature searches last were conducted in September 2011, in PubMed with no date restrictions, limited to articles published in English, and in the Cochrane Library without a language limitation. The combined searches yielded 532 citations, of which 45 were deemed clinically relevant for the authors to review in full text and to assign ratings of level of evidence to each of the selected studies with the guidance of the panel methodologists.

RESULTS: At this time, there are 5 studies that provide level I evidence for intravitreal ranibizumab, alone or in combination with other treatments for DME. There is also 1 study that provides level I evidence for intravitreal pegaptanib sodium for DME. Nine studies reviewed were rated as level II, and 2 additional studies reviewed were graded as level III. Most studies do not provide information about long-term results (i.e., more than 2 years of follow-up) or the comparative efficacy of anti-VEGF pharmacotherapies.

CONCLUSIONS: Review of the available literature indicates that anti-VEGF pharmacotherapy, delivered by intravitreal injection, is a safe and effective treatment over 2 years for DME. Further evidence is required to support the long-term safety of these pharmacotherapies and their comparative efficacy.

PMID: 22917890 [PubMed - as supplied by publisher]

Ther Clin Risk Manag. 2012;8:343-51. Epub 2012 Jul 11.

Profile of ranibizumab: efficacy and safety for the treatment of wet age-related macular degeneration.

Chen Y, Han F.

Department of Ophthalmology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China.

Abstract

Wet age-related macular degeneration (AMD) causes severe vision loss due to the development of choroidal neovascularization (CNV). The critical role of vascular endothelial growth factor in the pathogenesis of CNV is well understood. Ranibizumab plays an inhibitory role with CNV and reduces vascular permeability by binding to vascular endothelial growth factor. Intravitreal ranibizumab reduces the risk of visual acuity (VA) loss and increases the chance of VA gain compared with no treatment or photodynamic therapy for CNV in AMD. Some high-quality research has shown that the optimal timing for ranibizumab treating wet AMD is the first 3 months. It is recommended that ranibizumab is intravitreally injected monthly in the initiation for at least 3 months. Subsequent managing of regimens should be made dependent on the VA change, fundus examination, and image of optical coherence topography. An individualized strategy or combined method with photodynamic therapy is beneficial to the active lesion in the consecutive treatment of ranibizumab for CNV, and may be a good choice in order to decrease injection times. Regarding the safety profile, ranibizumab has been well tolerated in clinical trials. The principal ocular adverse event detected in clinical trials is a low frequency of ocular inflammation. Key serious ocular adverse events occurred in <5% of ranibizumab-treated patients in large-scale clinical trials. It appears unlikely that treatment with ranibizumab increases the risk of vascular events significantly. Less frequent injections on an as-needed schedule, based on monthly monitoring may have the most optimal risk:benefit ratio.

PMID: 22911433 [PubMed] PMCID: PMC3404592

Other treatment & diagnosis

J Drug Deliv. 2012;2012:527516. Epub 2012 Jul 18.

Design of an implantable device for ocular drug delivery.

Lee JH, Pidaparti RM, Atkinson GM, Moorthy RS.

Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA 23284, USA.

Abstract

Ocular diseases, such as, glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, and retinitis pigmentosa require drug management in order to prevent blindness and affecting million of adults in USA and worldwide. There is an increasing need to develop devices for drug delivery to address ocular diseases. This study focuses on the design, simulation, and development of an implantable ocular drug delivery device consisting of micro-/nanochannels embedded between top and bottom covers with a drug reservoir made from polydimethylsiloxane (PDMS) which is silicon-based organic and biodegradable polymer. Several simulations were carried out with six different micro-channel configurations in order to see the feasibility for ocular drug delivery applications. Based on the results obtained, channel design of osmotic I and osmotic II satisfied the diffusion rates required for ocular drug delivery. Finally, a prototype illustrating the three components of the drug delivery design is presented. In the future, the device will be tested for its functionality and diffusion characteristics.

PMID: 22919500 [PubMed] PMCID: PMC3418683

Ophthalmologe. 2012 Aug;109(8):749-57.

[Morphological features of myopic choroidal neovascularization : Differences to neovascular age-related macular degeneration]. [Article in German]

Inhoffen W, Ziemssen F.

Department für Augenheilkunde, Universität Tübingen, Schleichstr. 12-16, 72076, Tübingen, Deutschland, Werner.Inhoffen@med.uni-tuebingen.de.

Abstract

Choroidal neovascularization due to pathological myopia (mCNV) differs in important characteristics from lesions seen in age-related macular degeneration (ARMD). Myopic CNV is associated with typical phenomena, such as lacquer cracks or patchy atrophy drusen or pigment epithelium detachment are rare occurrences. The dimensions of mCNV and the extent of leakage are substantially smaller. The heterogeneous combination of thinning and concomitant staphyloma often complicates the early detection of neovascular lesions. Diagnosis and evaluation of the clinical progress are only possible using the combination of different imaging modalities, e.g. funduscopy, fluorescein angiography (FLA) and spectral domain optical coherence tomography (SD-OCT). Special forms, such as periconal mCNV or dome-shaped variants exhibit a typical progression and response to therapy. In the course of the disease a progressive pigmentation and secondary atrophy occur and later, depigmentation of the mCNV complicates the demarcation of the original mCNV within the zone of atrophy. Extensive information and counselling seem to be mandatory in order to allow a better self-assessment. Sometimes, patients notice the first symptoms of recurrent mCNV activity before confirmation is possible by objective diagnostics.

PMID: 22911352 [PubMed - in process]

Appl Psychophysiol Biofeedback. 2012 Aug 18. [Epub ahead of print]

MP-1 Biofeedback: Luminous Pattern Stimulus Versus Acoustic Biofeedback in Age Related Macular degeneration (AMD).

Vingolo EM, Salvatore S, Limoli PG.

Department of Ophthalmology, University La Sapienza of Rome, Polo Pontino, A. Fiorini Hospital, Terracina, LT, Italy.

Abstract

In this study we evaluated the efficacy of visual rehabilitation by means of two different types of biofeedback techniques in patients with age related macular degeneration (AMD). Thirty patients, bilaterally affected by AMD, were randomly divided in two groups: one group was treated with an acoustic biofeedback (AB group), the other was treated with luminous biofeedback of a black and white checkerboard flickering during the examination (LB group). All patients underwent a complete ophthalmological examination. Rehabilitation consisted of 12 training sessions of 10 min for each eye performed once a week for both groups. Both groups showed better visual performance after rehabilitation and luminous flickering biofeedback stimulus showed a statistically significant improvement in training the patients to modify their preferred retinal locus in comparison to acoustic biofeedback. This suggests that it might be possible in the damaged retina to override dead photoreceptor and outer retinal layers and involve residual surviving cells, as well as amplify and integrate retinal and brain cortex plasticity by using other spared channels towards associative pathways.

PMID: 22903517 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2012 Aug 17. [Epub ahead of print]

[Retinal Angiomatous Proliferations.] [Article in German]

Heußen FM, Ouyang Y, Joussen AM.

Charité Universitätsmedizin Berlin, Klinik für Augenheilkunde, Berlin.

Abstract

Retinal angiomatous proliferations, also known as type 3 neovascularisation, are a common entity amongst patients with age-related macular degeneration. Their prevalence is being estimated at around 12-15 % in this group of patients. Certain funduscopic signs like an extravofeal, intraretinal haemorrhage, cystoid macular oedema or a retinal anastomosis of the lesion are considered to be pathognomonic. Verification of the diagnosis should be based on ICG angiography, although OCT is gaining popularity. Interestingly, RAP lesions seem to have distinctive demographic characteristics and respond differently to established therapies, differentiating them from regular type 1 or type 2 neovascularisation. Current therapies of choice are VEGF inhibitors. Nonetheless, combination therapies, combining different approaches like anti-VEGF treatment and photodynamic therapy, have received more attention recently.

PMID: 22903355 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Aug 16. [Epub ahead of print]

Use of Prescribed Optical Devices in Age-Related Macular Degeneration.

Decarlo DK, McGwin G Jr, Searcey K, Gao L, Snow M, Stevens L, Owsley C.

Department of Ophthalmology, School of Medicine (DKD, GMc, KS, LG, LS, CO), Department of

Optometry, School of Optometry (DKD, MS), Department of Epidemiology, School of Public Health (GMc), and Section of Trauma, Burns, and Surgical Critical Care, Division of General Surgery, Department of Surgery, School of Medicine (GMc), University of Alabama at Birmingham, Birmingham, Alabama.

PURPOSE: To evaluate prescribed optical device use in terms of frequency and perceived usefulness among people with age-related macular degeneration (AMD). We also sought to determine the tasks for which they were using their prescribed low vision device(s).

METHODS: One hundred ninety-nine patients with AMD presenting for the first time to the low vision service were recruited from a university-based clinic. Prior to the low vision evaluation and device prescription, they completed the National Eye Institute Visual Function Questionnaire 25, Center for Epidemiological Studies Depression Scale, Short Portable Mental Status Questionnaire, and a general health questionnaire. The low vision evaluation included best-corrected early treatment of diabetic retinopathy study visual acuity, MNREAD testing, microperimetry, prescription, and dispensing of optical low vision devices. Telephone follow-up interviews were conducted about device usage 1-week, 1-months, and 3-months postintervention.

RESULTS: One hundred eighty-one participants were prescribed low vision devices. Of them, 93% completed all 3 follow-up interviews. Intensive users (≥1 hours/day) of devices were similar in demographic and visual characteristics to non-intensive users (<1 hours/day), except for habitual reading acuity and speed as well as contrast sensitivity. Overall, device use increased slightly over 3 months of follow-up. Magnifiers were reported to be moderately-to-extremely useful by >80% of participants at all time points except the 1-month follow-up for hand magnifiers (75%). High plus spectacles were the least frequently prescribed device and rated as moderately-to-extremely useful by 70%, 74%, and 59% at 1 week, 1 month, and 3 months, respectively. Most participants used their devices for leisure reading, followed by managing bills. Very few devices (n = 3, <1%) were not used at any time point.

CONCLUSIONS: Patients with AMD who are provided with prescribed optical low vision devices do use them and perceive them as useful, especially for leisure reading activities. High rates of usage were maintained over 3 month.

PMID: 22902420 [PubMed - as supplied by publisher]

J Cataract Refract Surg. 2012 Sep;38(9):1706.

Magnification for age-related macular degeneration patients having cataract surgery.

Novis C, Lipshitz I.

Benoni, Gauteng, South Africa.

PMID: 22906466 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 Aug 23. [Epub ahead of print]

Correlation of SD-OCT Features and Retinal Sensitivity in Neovascular Age-related Macular Degeneration.

Sulzbacher F, Kiss C, Kaider A, Eisenkoelbl S, Munk M, Roberts P, Sacu S, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

Purpose: To correlate retinal sensitivity in patients with neovascular age-related macular degeneration (AMD) with specific characteristics of retinal morphology.

Methods: Thirty eyes of 30 patients presenting with active choroidal neovascularization were examined by spectral domain optical coherence tomography (SD-OCT) and microperimetry (MP1). Image processing software was used to match a fundus photographic (FP) MP1 image with an infrared+OCT SD-OCT image. Each MP test point for retinal sensitivity was positioned at the corresponding SD-OCT location, and the microperimetric results were evaluated.

Results: An intact retinal configuration was associated with a median retinal sensitivity of 15.5 dB [quartiles: 12dB, 18dB]. The median retinal sensitivities were 0 dB [quartiles: 0dB, 1dB] for the neovascular complex, 4 dB [0 dB, 9 dB] for the subretinal fluid, 1 dB [0 dB, 6 dB] for the intraretinal fluid, and 0 dB [0 dB, 3 dB] for intraretinal cysts. Pigment epithelium detachment was associated with a median retinal sensitivity of 3 dB [0 dB, 8 dB], and subretinal drusen had a median value of 8 dB [5 dB, 12 dB]. Deep retinal layer analyses gave low median retinal sensitivities of 0 dB [0 dB, 3 dB] for an absent retinal pigment epithelium layer and 1 dB [0 dB, 5 dB] for an absent photoreceptor layer.

Conclusions: Superimposition of morphological SD-OCT features and microperimetric retinal sensitivity allowed exact determination of the differential impact of retinal alteration on the corresponding sensitivity. Individual OCT-related indicators of neurosensory integrity were distinctly correlated with visual function. "Morphofunctional" findings could be relevant as prognostic factors and for (re)treatment decisions.

PMID: 22918631 [PubMed - as supplied by publisher]

N Engl J Med. 2012 Aug 23;367(8):768-70.

Eyeing macular degeneration--few inflammatory remarks.

Rosenbaum JT.

Department of Ophthalmology, Oregon Health and Science University, Portland, USA.

PMID: 22913688 [PubMed - in process]

Pathogenesis

Invest Ophthalmol Vis Sci. 2012 Aug 23. [Epub ahead of print]

Effects of Simvastatin on the expression of Heme Oxygenase-1 in Human Retinal Pigment Epithelial Cells.

Kim KJ, Kim KS, Kim NR, Chin HS.

Department of Ophthalmology and Inha Vision Science Laboratory, Inha University School of Medicine, Incheon, Korea (South), Republic of.

Purpose: Chronic oxidative stress can lead to the impairment of retinal pigment epithelial (RPE) cells, indicating it to be a risk factor for age-related macular degeneration (AMD). The cholesterol-independent, pleiotropic effects of statins have protective effects on several cell types via unknown mechanisms. This study examined the role of heme oxygenase-1 as a target and potential mediator of statins in cultured human RPE cells.

Methods: The RPE cell viability was measured using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay. After 24 hours incubation, RT-PCR and western blot was performed to measure the levels of HO-1 mRNA and protein expression, respectively, in RPE cells. Intracellular ROS production was measured using a fluorescence-activated cell sorter.

Results: In cultured human RPE cells, simvastatin showed no toxicity up to 10 µM. Simvastatin increased

the HO-1 mRNA and protein levels in a concentration-dependent manner up to 10 µM. HO-1 protein induction by simvastatin was unaffected by mevalonate or N-nitro-L-arginine methyl ester, showing that the isoprenoid- and NO-dependent pathways are not involved. Simvastatin-dependent HO-1 protein induction was reduced significantly by pharmacological inhibition of the phosphotidylinositol-3-kinase (PI3K)/Akt pathways. The simvastatin-induced inhibition of free radical formation was recovered by the presence of a HO inhibitor, zinc protoporphyrin.

Conclusions: These results demonstrate that HO-1 is a target site and an antioxidant mediator of simvastatin in human RPE cells. The simvastatin-dependent up-regulation of HO-1 occurs mainly via PI3K/Akt-dependent signaling pathways. These results suggest that simvastatin might have some clinical benefits in preventing retinal diseases associated with oxidative stress, such as AMD.

PMID: 22918643 [PubMed - as supplied by publisher]

EMBO Mol Med. 2012 Aug 20. doi: 10.1002/emmm.201101084. [Epub ahead of print]

β-Secretase (BACE1) inhibition causes retinal pathology by vascular dysregulation and accumulation of age pigment.

Cai J, Qi X, Kociok N, Skosyrski S, Emilio A, Ruan Q, Han S, Liu L, Chen Z, Bowes Rickman C, Golde T, Grant MB, Saftig P, Serneels L, de Strooper B, Joussen AM, Boulton ME.

Department of Anatomy & Cell Biology, University of Florida, Gainesville, FL, USA.

Abstract

β-Secretase (BACE1) is a major drug target for combating Alzheimer's disease (AD). Here we show that BACE1(-/-) mice develop significant retinal pathology including retinal thinning, apoptosis, reduced retinal vascular density and an increase in the age pigment, lipofuscin. BACE1 expression is highest in the neural retina while BACE2 was greatest in the retinal pigment epithelium (RPE)/choroid. Pigment epithelial-derived factor, a known regulator of γ-secretase, inhibits vascular endothelial growth factor (VEGF)-induced in vitro and in vivo angiogenesis and this is abolished by BACE1 inhibition. Moreover, intravitreal administration of BACE1 inhibitor or BACE1 small interfering RNA (siRNA) increases choroidal neovascularization in mice. BACE1 induces ectodomain shedding of vascular endothelial growth factor receptor 1 (VEGFR1) which is a prerequisite for γ-secretase release of a 100 kDa intracellular domain. The increase in lipofuscin following BACE1 inhibition and RNAI knockdown is associated with lysosomal perturbations. Taken together, our data show that BACE1 plays a critical role in retinal homeostasis and that the use of BACE inhibitors for AD should be viewed with extreme caution as they could lead to retinal pathology and exacerbate conditions such as age-related macular degeneration.

PMID: 22903875 [PubMed - as supplied by publisher]

PLoS One. 2012;7(8):e43173. Epub 2012 Aug 20.

αA Crystallin May Protect against Geographic Atrophy-Meta-Analysis of Cataract vs. Cataract Surgery for Geographic Atrophy and Experimental Studies.

Zhou P, Ye HF, Jiang YX, Yang J, Zhu XJ, Sun XH, Luo Y, Dou GR, Wang YS, Lu Y.

Department of Ophthalmology, Eye and ENT Hospital of Fudan University, Shanghai, People's Republic of China.

BACKGROUND: Cataract and geographic atrophy (GA, also called advanced "dry" age-related macular degeneration) are the two major causes of visual impairment in the developed world. The association between cataract surgery and the development of GA was controversial in previous studies.

METHODS/PRINCIPAL FINDINGS: We performed a meta-analysis by pooling the current evidence in literature and found that cataract is associated with an increased risk of geographic atrophy with a summary odds ratio (OR) of 3.75 (95% CI: 95% CI: 1.84-7.62). However, cataract surgery is not associated with the risk of geographic atrophy (polled OR=3.23, 95% CI: 0.63-16.47). Further experiments were performed to analyze how the αA-crystallin, the major component of the lens, influences the development of GA in a mouse model. We found that theαA-crystallin mRNA and protein expression increased after oxidative stress induced by NaIO(3) in immunohistochemistry of retinal section and western blot of posterior eyecups. Both functional and histopathological evidence confirmed that GA is more severe in αA-crystallin knockout mice compared to wild-type mice.

CONCLUSIONS: Therefore, αA-crystallin may protect against geographic atrophy. This study provides a better understanding of the relationship between cataract, cataract surgery, and GA.

PMID: 22916220 [PubMed - in process] PMCID: PMC3423426

Apoptosis. 2012 Aug 22. [Epub ahead of print]

Enhanced apoptosis in retinal pigment epithelium under inflammatory stimuli and oxidative stress.

Wang Y, Shen D, Wang VM, Yu CR, Wang RX, Tuo J, Chan CC.

Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, 10 Center Dr., 10/10N103, NIH/NEI, Bethesda, MD, 20892-1857, USA.

Abstract

Age-related macular degeneration (AMD) is a neurodegenerative disease that causes irreversible central vision loss in the elderly. Retinal pigment epithelium (RPE) has been found to be a key component in AMD pathogenesis. The Ccl2 (-/-) /Cx3cr1 (-/-) (DKO) mouse on Crb1 (rd8) background is created as an AMD model, developing AMD-like retinal lesions. Our study aimed to examine RPE apoptosis in DKO mouse and human ARPE-19 cell line. DKO RPE expressed higher apoptotic proteins when compared with age-matched wild type (WT) RPE in physiological conditions. Apoptosis of primary cultured mouse RPE was evaluated under stimulation with lipopolysaccharide for inflammatory stimulation and 2,3,7,8-tetrachlorodibenzo-p-dioxin or H(2)O(2) for oxidative stress. Compared with WT RPE, DKO RPE was more susceptible to Fas ligand (FasL)-mediated apoptosis under both inflammatory and oxidative stress, with less cell viability and higher expression of apoptotic transcripts and proteins. Decreased cell viability was also observed in ARPE-19 cells under each stimulus. Furthermore, we also investigated the anti-apoptotic effects of decoy receptor 3 (DcR3), a decoy receptor for FasL, on ARPE-19 cells under inflammatory and oxidative stress. DcR3 pre-incubated ARPE-19 cells showed decreased apoptosis, with increased cell viability and decreased expression of apoptotic transcripts and proteins under the stimuli. On the contrary, knockdown of DcR3 in ARPE-19 cells showed totally opposite results. Our study demonstrates that FasL-mediated RPE apoptosis may play a pivotal role in AMD pathogenesis.

PMID: 22911474 [PubMed - as supplied by publisher]

Genetics

Physiol Genomics. 2012 Aug 21. [Epub ahead of print]

Constructing the Angiome - a Global Angiogenesis Protein Interaction Network.

Chu LH, Rivera CG, Popel AS, Bader JS.

Johns Hopkins University.

Abstract

Angiogenesis is the formation of new blood vessels from preexisting microvessels. Excessive and insufficient angiogenesis have been associated with many diseases including cancer, age-related macular degeneration, ischemic heart, brain, and skeletal muscle diseases. A comprehensive understanding of angiogenesis regulatory processes is needed to improve treatment of these diseases. To identify proteins related to angiogenesis, we developed a novel integrative framework for diverse sources of high throughput data. The system called GeneHits was used to expand on known angiogenesis pathways to construct the angiome, a protein-protein interaction network for angiogenesis. The network consists of 478 proteins and 1,488 interactions. The network was validated through cross-validation and analysis of five gene expression datasets from in vitro angiogenesis assays. We calculated the topological properties of the angiome. We analyzed the functional enrichment of angiogenesis-annotated and associated proteins. We also constructed an extended angiome with 1,233 proteins and 5,726 interactions to derive a more complete map of protein-protein interactions in angiogenesis. Finally, the extended angiome was used to identify growth factor signaling networks that drive angiogenesis, and anti-angiogenic signaling networks. The results of this analysis can be used to identify genes and proteins in different disease conditions and putative targets for therapeutic interventions as high-ranked candidates for experimental validation.

PMID: 22911453 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2012 Aug 20. [Epub ahead of print]

The relationship between vascular endothelial growth factor -2578C/A polymorphism and age-related macular degeneration.

Lucotte G, Change N.

Center of Molecular Neurogenetics , Paris , France.

PMID: 22906062 [PubMed - as supplied by publisher]

PLoS One. 2012;7(8):e42464. Epub 2012 Aug 14.

Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis.

Chen H, Yu KD, Xu GZ.

Department of Ophthalmology, Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, People's Republic of China.

PURPOSE: To investigate the association between polymorphism rs1061170 (T1277C, Y402H) in age-related macular degeneration (AMD) susceptibility gene Complement Factor H (CFH) and treatment response of neovascular AMD.

METHODS: We performed a literature-based meta-analysis including 10 published association studies involving 1,510 patients. Treatments included anti-VEGF (bevacizumab and ranibizumab) or photodynamic therapy. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using fixed- and random-effects models. Q-statistic test was used to assess heterogeneity.

RESULTS: Polymorphism rs1061170 showed a significant summary OR of 1.68 (95% CI, 1.09 to 2.60; P= 0.020; CC versus TT; random-effects) for treatment response of neovascular AMD with heterogeneity of 0.09. In subgroup analysis, rs1061170 was more likely to be a predictor of response to anti-VEGF therapy (P=0.011). However, heterozygous TC genotype was not associated with altered treatment response (OR= 1.18, 95% CI, 0.95 to 1.47; P=0.145; fixed-effects). Influence analysis indicated the robustness of our

findings.

CONCLUSIONS: rs1061170 might be associated with treatment response of neovascular AMD, especially for the anti-VEGF agents. It might be the first meta-analytically confirmed genetic marker predictive for AMD treatment response though a further validation in larger studies is needed.

PMID: 22905135 [PubMed - in process] PMCID: PMC3419212

ScientificWorldJournal. 2012;2012:420190. Epub 2012 Aug 1.

The rs2071559 AA VEGFR-2 Genotype Frequency Is Significantly Lower in Neovascular Age-Related Macular Degeneration Patients.

Lazzeri S, Orlandi P, Figus M, Fioravanti A, Cascio E, Di Desidero T, Agosta E, Canu B, Sartini MS, Danesi R, Nardi M, Bocci G.

Ophthalmology Unit, University Hospital, Via Paradisa, 2-56124 Pisa, Italy.

Abstract

In this prospective, case-control genetic study, 120 consecutive neovascular age-related macular degeneration (AMD) cases and 78 controls were enrolled. Two SNPs (rs2071559 and rs1870377) of VEGF -A receptor-2 (VEGFR-2) gene were analyzed with the technique of Real-Time PCR to investigate a genetic link between AMD and VEGFR-2 gene polymorphisms in Italian patients. The frequency of the VEGFR-2 genotype rs2071559 AA was significantly lower (18.33%) in patients with AMD than in the control subjects (34.62%; P = 0.0095, chi-square test; P(corr) = 0.038; OR = 0.42, 95% CI 0.22 to 0.82). In conclusion, although with the limitations of a small sample size and the few SNPs studied, this study demonstrates a lower frequency of VEGFR-2 rs2071559 AA genotype in an AMD patient population, suggesting future studies on the role VEGFR-2 SNPs.

PMID: 22919317 [PubMed - in process] PMCID: PMC3415178

Invest Ophthalmol Vis Sci. 2012 Aug 23. [Epub ahead of print]

Complement Factor H deficiency results in decreased neuroretinal expression of Cd59a in aged mice.

Faber C, Williams J, Juel HB, Greenwood J, Nissen MH, Moss SE.

Faculty of Health Sciences, University of Copenhagen, ISIM, Copenhagen, DK-2200, Denmark.

Purpose: The complement system is closely linked to the pathogenesis of age-related macular degeneration (AMD). Several complement genes are expressed in retinal pigment epithelium (RPE), and complement proteins accumulate in drusen. Further, a common variant of complement factor H (CFH) confers increased risk of developing AMD. Because the mechanisms by which changes in the function of CFH influence development of AMD are unclear, we examined ocular complement expression as a consequence of age in control and CFH null mutant mice.

Methods: Gene expression in neuroretinas and RPE/choroid from young and aged WT and Cfh-/- C57BL/6J mice was analysed by microarrays. Expression of a wide range of complement genes was compared to expression in liver.

Results: An age-associated increased expression of complement, particularly C1q, C3 and Factor B, in the RPE/choroid coincided with increased expression of the negative regulators Cfh and Cd59a in the neuroretina. Young mice deficient in CFH expressed Cd59a similar to WT, but failed to upregulate Cd59a

expression with age. Hepatic expression of Cd59a increased with age regardless of Cfh genotype.

Conclusions: While the connection between CFH deficiency and failure to up-regulate CD59a remains unknown, these results suggest that expression of CD59 is tissue-specific and that neuroretinal regulation depends on CFH. This could contribute to the visual functional deficits and morphological changes in the Cfh-/- mouse retina that occur with age.

PMID: 22918646 [PubMed - as supplied by publisher]

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

Identification of an RP1 Prevalent Founder Mutation and Related Phenotype in Spanish Patients with Early-Onset Autosomal Recessive Retinitis.

Avila-Fernandez A, Corton M, Nishiguchi KM, Muñoz-Sanz N, Benavides-Mori B, Blanco-Kelly F, Riveiro-Alvarez R, Garcia-Sandoval B, Rivolta C, Ayuso C.

Genetics Department, IIS-Fundación Jiménez Díaz-CIBERER, Madrid, Spain.

OBJECTIVE: To identify the genetic causes underlying early-onset autosomal recessive retinitis pigmentosa (arRP) in the Spanish population and describe the associated phenotype.

DESIGN: Case series.

PARTICIPANTS: A total of 244 unrelated families affected by early-onset arRP.

METHODS: Homozygosity mapping or exome sequencing analysis was performed in 3 families segregating arRP. A mutational screening was performed in 241 additional unrelated families for the p.Ser452Stop mutation. Haplotype analysis also was conducted. Individuals who were homozygotes, double heterozygotes, or carriers of mutations in RP1 underwent an ophthalmic evaluation to establish a genotype-phenotype correlation.

MAIN OUTCOME MEASURES: DNA sequence variants, homozygous regions, haplotypes, best-corrected visual acuity, visual field assessments, electroretinogram responses, and optical coherence tomography images.

RESULTS: Four novel mutations in RP1 were identified. The new mutation p.Ser542Stop was present in 11 of 244 (4.5%) of the studied families. All chromosomes harboring this mutation shared the same haplotype. All patients presented a common phenotype with an early age of onset and a prompt macular degeneration, whereas the heterozygote carriers did not show any signs of retinitis pigmentosa (RP).

CONCLUSIONS: p.Ser542Stop is a single founder mutation and the most prevalent described mutation in the Spanish population. It causes early-onset RP with a rapid macular degeneration and is responsible for 4.5% of all cases. Our data suggest that the implication of RP1 in arRP may be underestimated.

PMID: 22917891 [PubMed - as supplied by publisher]

Diet

Autophagy. 2012 Sep 1;8(9). [Epub ahead of print]

Mechanistically linking age-related diseases and dietary carbohydrate via autophagy and the ubiquitin proteolytic systems.

Taylor A.

Laboratory for Nutrition and Vision Research; JM USDA Human Nutrition Research Center on Aging; Tufts University; Boston, MA USA.

Abstract

Epidemiological data indicate that consuming diets that deliver sugar to the blood rapidly (called high glycemic index, GI) is associated with enhanced risk for age-related diseases such as cardiovascular disease, type 2 diabetes, cataract and age-related macular degeneration (AMD). These debilities are associated with accumulation of toxic protein aggregates as observed in other protein precipitation or amyloid diseases including Alzheimer, Parkinson and Huntington diseases and encephalopathies. Barriers to recommending lower-GI diets to promote health include the absence of established intracellular biochemical mechanisms that link high-GI diets to compromised homeostasis. The data herein corroborate the epidemiological findings and provide platforms to elucidate additional mechanistic aspects of salutary effects of consuming diets of different GIs. They are also useful for testing drugs, including autophagy enhancers, glycemia regulators, or nutraceuticals, which can be exploited to extend health.

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