Drug treatment


Does Ranibizumab (Lucentis®) Change Retrobulbar Blood Flow in Patients with Neovascular Age-Related Macular Degeneration?

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Department of Radiology, School of Medicine, Gaziantep University, Gaziantep, Turkey.

Purpose: To investigate the effects of intravitreal ranibizumab on retrobulbar blood flow in patients with neovascular age-related macular degeneration (AMD).

Methods: Thirty-one eyes of 30 patients with neovascular AMD were examined prospectively by both color Doppler imaging and fundus fluorescein angiography. Color Doppler imaging was used to measure the maximum and minimum velocities of the central retinal vein, peak systolic/end-diastolic velocities of blood flows, and pulsatility index and resistivity index values in the central retinal artery, nasal/temporal posterior ciliary arteries (NPCA/TPCA) and ophthalmic artery. The t test for paired samples was used for comparing retrobulbar blood flow values before and after intravitreal ranibizumab (Lucentis®) injection in the study and control groups.

Results: There was a statistically significant (p < 0.05) difference between the pre-injection and post-injection end-diastolic velocities of the NPCA and TPCA and resistivity index values of TPCA. The other parameters showed no statistically significant difference.

Conclusion: Our results show that intravitreal ranibizumab injection increases retrobulbar blood flow.

PMID: 22042133 [PubMed - as supplied by publisher]


Rapid resolution of macular edema associated with central retinal vein occlusion using ranibizumab after failure with multiple bevacizumab injections.

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Medical Retina Service, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles, CA, USA.
Purpose: To report improvement in cystoid macular edema from central retinal vein occlusion with one injection of ranibizumab after failure with seven injections of bevacizumab.

Methods: Case report.

Results: A 74-year-old female developed persistent blurred vision for three months. Ocular examination revealed macular edema secondary to nonischemic central retinal vein occlusion. The patient was treated with intravitreal bevacizumab (1.25 mg in 0.05 mL). She received seven injections (every 5-6 weeks). Vision fluctuated between 20/30 and 20/60 with minimal variation in central foveal thickness (449-574 μm). However, weeks after one injection of ranibizumab the patient's vision improved to 20/20 with near resolution of macular edema (CFT = 343 μm).

Conclusions: Patients with no response to bevacizumab injections can show a rapid and large improvement with ranibizumab. This underscores the important differences between these two medications. Further study is required to determine if these initial effects of ranibizumab can be maintained.

PMID: 22044337 [PubMed - in process]
ated exudative retinal detachment, and the results have been inspiring. Here, we report the case of a 36-year-old man with longstanding CCH who suffered from blurred vision for 3 years. He underwent PDT with intravenous infusions of verteporfin, which was a treatment method based on a modified version of the standard macular degeneration PDT protocol, in addition to subsequent intravitreal administrations of bevacizumab as adjuvant therapy for macular edema. Twelve months after treatment, the CCH tumor remained noticeably shrunken, with the complete absorption of the subretinal fluid and the absence of macular edema. In terms of treating subretinal fluid retention, this combination treatment is a safe, effective, and long-lasting therapy for treating established CCH tumors. However, even though the patient's visual field defects improved, the patient's visual acuity remained stable at 6/60 without further improvement. Long-term CCH with prolonged macular edema might have affected the visual prognosis. Patients with CCH still require long-term follow-up examinations after receiving PDT treatments.

PMID: 22036141 [PubMed - in process]


Reflux of Drug During Intra-vitreal Anti-VEGF Therapies.
Usman Saeed M, Batra R, Qureshi F, Clark D.
Walton Day Care Hospital, Aintree University Hospitals NHS Trust, Liverpool, UK.

Purpose: To report reflux of anti-VEGF drug during intravitreal injections.
Method: Review of electronic case notes of patients undergoing intra-vitreal anti-VEGF treatments. Prospective data collection was performed with a specific emphasis on presence or absence of reflux.

Results: 152 records of 102 eyes were available from an 8-month period. 119 Ranibizumab injections and 33 bevacizumab injections were considered. Reflux was noted in 48 injections (31%). For eyes with first injection of anti-VEGF agent, reflux was noted in 9/23 eyes. Eyes with at least one previous injection were observed to have reflux in 24/79 eyes. Presence of reflux was statistically tested against posterior vitreous detachment and phakic status and was found to be statistically insignificant.

Conclusion: Intra-vitreal anti-VEGF injections with volumes of 0.05 ml appears to produce displacement of the conjunctiva with a transient fluid-filled bleb immediately after the injection in approximately 1/3 of eyes.
PMID: 22044333 [PubMed - in process]

Other treatment & diagnosis


Central retinal function as measured by the multifocal electroretinogram and flicker perimetry in early age-related macular degeneration.
Gin TJ, Luu CD, Guymer RH.

Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Australia.

Purpose: To determine the retinal function in early AMD assessed by the multifocal electroretinogram (mERG) and flicker perimetry and to seek a relationship between local objective mERG parameters and subjective flicker perimetry thresholds.

Methods: mERG and flicker perimetry were performed in 15 patients (15 eyes) with early AMD and 14 con-
trols (14 eyes) of similar age group. The mfERG P1 response amplitude density (RAD, nV/deg(2)) and P1 implicit time of the first-order kernel and the flicker thresholds of each concentric ring were analysed. The relationship between individual mfERG responses and the corresponding individual flicker sensitivity outcomes was determined.

Results: The mfERG response amplitude of the central ring (ring 1) was significantly reduced in early AMD eyes compared to the controls (p=0.009). No significant difference in mfERG amplitude between early AMD and control eyes was detected in the other rings. The mfERG implicit time was significantly increased in the early AMD eyes but only within the central 4 rings of 12 degrees. A significant reduction in flicker sensitivity was also detected in early AMD eyes but only within the central 6 degrees. There was a significant, moderate correlation (r = -0.477, p<0.001) between local mfERG latency and flicker sensitivities from the same tested locations within the central 6 degrees. There was a weak correlation (r=0.200, p=0.014) between mfERG amplitude and flicker sensitivity.

Conclusion: Both mfERG and flicker perimetry show abnormal retinal function, but only in the very central macula, in early AMD. A novel relationship between mfERG and flicker sensitivity should enhance the clinical monitoring of disease progression.

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Validated Automatic Segmentation of AMD Pathology including Drusen and Geographic Atrophy in SDOCT Images.

Chiu SJ, Izatt JA, O'Connell RV, Winter KP, Toth CA, Farsiu S.

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Purpose: To automatically segment retinal spectral domain optical coherence tomography (SDOCT) images of eyes with age-related macular degeneration (AMD) pathology and varying image quality to advance the study of retinal pigment epithelium (RPE) + drusen complex (RPEDC) volume changes indicative of AMD progression.

Methods: We utilized our general segmentation framework based on graph theory and dynamic programming to segment three retinal boundaries in SDOCT images of eyes with drusen and geographic atrophy (GA). We conducted a validation study for eyes with non-neovascular AMD, forming subgroups based on scan quality and presence of GA. To test for accuracy, the layer thickness results from two certified graders were compared against automatic segmentation results for 220 B-scans across 20 patients. For reproducibility, we compared automatic layer volumes generated from 0° versus 90° scans in five volumes with drusen.

Results: The mean differences in the measured thicknesses of the total retina and RPEDC layers were 4.2±2.8 and 3.2±2.6 μm for automatic versus manual segmentation. When comparing the 0° and 90° datasets, the mean differences in the calculated total retina and RPEDC volumes were 0.28±0.28% and 1.60±1.57%, respectively. The average segmentation time per image was 1.7 seconds automatically, versus 3.5 minutes manually.

Conclusions: Our automatic algorithm accurately and reproducibly segmented three retinal boundaries in images containing drusen and GA. This automatic approach can reduce time and labor costs and yield objective measurements that potentially reveal quantitative RPE changes in longitudinal clinical AMD studies.

PMID: 22039246 [PubMed - as supplied by publisher]

A Method to Enhance Cell Survival on Bruch’s Membrane in Eyes Affected by Age and Age-Related Macular Degeneration (AMD).

Sugino IK, Rapista A, Sun Q, Wang J, Nunes CF, Cheewatrakoolpong N, Zarbin MA.

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Purpose: To determine whether conditioned medium (CM) derived from bovine corneal endothelial cells (BCEC) can support transplanted cells on aged and age-related macular degeneration (AMD) Bruch’s membrane (BM).

Methods: RPE derived from human embryonic stem cells (hES-RPE) and cultured fetal and aged adult RPE were seeded onto the inner collagenous layer of submacular BM-choroid-sclera explants generated from aged and AMD human donor eyes. Paired explants were cultured in BCEC-CM or CM vehicle. To assess cell behavior after attachment to BM was established, explants were harvested after 21 days in culture. To assess whether sustained exposure to BCEC-CM was necessary for improved cell survival on BM, short exposure to BCEC-CM (3, 7, 14 days) was compared to 21-day exposure. Explants were harvested and evaluated by scanning electron (SEM) and light microscopy. Extracellular matrix (ECM) deposition after exposure to BCEC-CM was evaluated following RPE removal after day-21 on tissue culture dishes or on BM.

Results: BCEC-CM significantly enhanced hES-RPE, fetal RPE, and aged adult RPE survival on BM, regardless of submacular pathology. While shorter BCEC-CM exposure times showed significant improvement in cell survival compared to culture in CM vehicle, longer BCEC-CM exposure times were more effective. BCEC-CM increased RPE ECM deposition on tissue culture plastic and on BM.

Conclusions: The results of this study indicate that RPE survival is possible on AMD BM and offer a method that could be developed for enhancing transplanted cell survival on AMD BM. Increased ECM deposition may account for improved cell survival following culture in BCEC-CM.

PMID: 22039244 [PubMed - as supplied by publisher]


Objectives of teaching direct ophthalmoscopy to medical students.

Benbassat J, Polak BC, Javitt JC.

Myers-JDC-Brookdale Institute, The Smokler Center for Health Policy Research, Jerusalem, Israel VU University Medical Center, Department of Ophthalmology, Amsterdam, The Netherlands Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland, USA.

Purpose: To propose the objectives of undergraduate training in direct ophthalmoscopy (DO).

Method: Narrative review of the literature on (i) opinions about the expected proficiency from students in DO, and (ii) estimates of its diagnostic value.

Results: (i) Authorities disagree on the proficiency in DO that they expect from students. Textbooks of physical diagnosis differ in their coverage of DO. Surveys have indicated that US physicians expect students to be able to detect optic nerve head abnormalities. The Association of American Medical Colleges expects students to perform ophthalmoscopic examination and describe observations. The International Council of Ophthalmology expects students to recognize also diabetic and hypertensive retinopathies. The Association of University Professors in Ophthalmology requires that students recognize papilloedema, cholesterol emboli, glaucomatous cupping and macular degeneration. (ii) There is evidence that DO, even by
ophthalmologists, is inadequate for screening for glaucoma, diabetic and hypertensive retinopathies. Two studies have suggested a limited value of DO in detecting clinical emergencies.

Conclusions: The evidence that DO, even by ophthalmologists, is sub-optimal in detecting common abnormalities challenges existing the notions of training medical students. On pending the results of additional studies of the value of DO in detecting emergencies, we suggest that undergraduate teaching of DO should impart the following: (i) an ability to identify the red fundus reflex and optic disc; (ii) an ability to recognize signs of clinical emergencies in patients, mannequins or fundus photographs; and (iii) knowledge about, but not an ability to detect, other retinopathies.

PMID: 22040169  [PubMed - as supplied by publisher]


New Grading Criteria Allow for Earlier Detection of Geographic Atrophy in Clinical Trials.

Brader HS, Ying GS, Martin ER, Maguire MG; and the Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group.

Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA.

Purpose: To evaluate new grading criteria for geographic atrophy (GA) as detected by annual stereoscopic color fundus photographs (CFP) and fluorescein angiograms (FA) and to assess whether application of the revised criteria provides earlier identification of GA than previous criteria involving only CFP.

Methods: Annual fundus image sets from 114 CAPT patients who developed GA in the untreated eye during 5-6 years of follow-up were re-assessed for the presence of GA using revised grading criteria, in which geographic atrophy was defined by 1) presence of hyperfluorescence on FA; and 2) at least one other characteristic indicative of involution of the retinal pigment epithelium; i.e., sharp edges, excavation of the retina, or visible choroidal vessels on either color images or FA. Reliability and time of initial detection of GA using the revised criteria were assessed.

Results: The revised criteria are reliable (97.8% intragrader, 93.3% intergrader agreement) and accurate (false-positive rate = 0.8%) for detecting individual early GA lesions. Using this revised method, individual GA lesions were identified 1-year earlier on average than with criteria used in previous CFP studies. Use of 2 imaging modalities is more sensitive in detecting GA and its features than either imaging modality alone (p=<0.0001).

Conclusions: Early GA areas can be reliably identified when defining criteria are based on both color photographs and FAs. These methods can be used to investigate the natural history of GA earlier in the course of disease than previously described and to facilitate design of future clinical trials of therapies for GA.

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Treatment for submacular hemorrhage associated with neovascular age-related macular degeneration.

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Abstract

Submacular hemorrhage associated with neovascular age-related macular degeneration is a complication
known to have potentially devastating effects on visual acuity. Multiple treatment modalities have been suggested including intravitreal anti-vascular endothelial growth factor injections, photodynamic therapy, pneumatic displacement with or without adjuvant intravitreal tissue plasminogen activator, and pars plana vitrectomy with or without adjuvant subretinal tissue plasminogen activator. However, there remains no consensus on optimal treatment, as clinical trials for neovascular age-related macular degeneration have excluded patients with submacular hemorrhage. This manuscript offers guidelines to the management of subretinal hemorrhage based on its size and characteristics, and highlights the need for clinical trials in this area.

PMID: 22044334 [PubMed - in process]


Retinal prostheses: current clinical results and future needs.

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Doheny Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California.

Abstract

Degenerative diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP) primarily affect the photoreceptors, ultimately resulting in significant loss of vision. Retinal prostheses aim to elicit neural activity in the remaining retinal cells by detecting and converting light into electrical stimuli that can then be delivered to the retina. The concept of visual prostheses has existed for more than 50 years and recent progress shows promise, yet much remains to be understood about how the visual system will respond to artificial input after years of blindness that necessitate this type of prosthesis. This review focuses on 3 major areas: the histopathologic features of human retina affected by AMD and RP, current results from clinical trials, and challenges to overcome for continued improvement of retinal prostheses.

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Ocular epithelial transplantation: current uses and future potential.

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Abstract

Visual loss may be caused by a variety of ocular diseases and places a significant burden on society. Replacing or regenerating epithelial structures in the eye has been demonstrated to recover visual loss in a number of such diseases. Several types of cells (e.g., embryonic stem cells, adult stem/progenitor/differentiated epithelial cells and induced pluripotent cells) have generated much interest and research into their potential in restoring vision in a variety of conditions: from ocular surface disease to age-related macular degeneration. While there has been some success in clinical transplantation of conjunctival and particularly corneal epithelium utilizing ocular stem cells, in particular, from the limbus, the replacement of the retinal pigment epithelium by utilizing stem cell sources has yet to reach the clinic. Advances in our understanding of all of these cell types, their differentiation and subsequent optimization of culture conditions and development of suitable substrates for their transplantation will enable us to overcome current clinical obstacles. This article addresses the current status of knowledge concerning the biology of stem cells, their progeny and the use of differentiated epithelial cells to replace ocular epithelial cells. It will highlight the
clinical outcomes to date and their potential for future clinical use.

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Pathogenesis

Biomaterials. 2011 Oct 31. [Epub ahead of print]

Dendrimer-based targeted intravitreal therapy for sustained attenuation of neuroinflammation in retinal degeneration.

Iezzi R, Guru BR, Glybina IV, Mishra MK, Kennedy A, Kannan RM.

Ligon Research Center of Vision, Wayne State University, Detroit, MI, USA; Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA.

Abstract

Retinal neuroinflammation, mediated by activated microglia, plays a key role in the pathogenesis of photoreceptor and retinal pigment epithelial cell loss in age-related macular degeneration and retinitis pigmentosa. Targeted drug therapy for attenuation of neuroinflammation in the retina was explored using hydroxyl-terminated polyamidoamine (PAMAM) dendrimer-drug conjugate nanodevices. We show that, upon intravitreal administration, PAMAM dendrimers selectively localize within activated outer retinal microglia in two rat models of retinal degeneration, but not in the retina of healthy controls. This pathology-dependent biodistribution was exploited for drug delivery, by covalently conjugating fluocinolone acetonide to the dendrimer. The conjugate released the drug in a sustained manner over 90 days. In vivo efficacy was assessed using the Royal College of Surgeons (RCS) rat retinal degeneration model over a four-week period when peak retinal degeneration occurs. One intravitreal injection of 1 μg of FA conjugated to 7 μg of the dendrimer was able to arrest retinal degeneration, preserve photoreceptor outer nuclear cell counts, and attenuate activated microglia, for an entire month. These studies suggest that PAMAM dendrimers (with no targeting ligands) have an intrinsic ability to selectively localize in activated microglia, and can deliver drugs inside these cells for a sustained period for the treatment of retinal neuroinflammation.

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Epidemiology


Age-related macular degeneration in Onitsha, Nigeria.

Nwosu S.

Guinness Eye Center, Onitsha, Nigeria.

Objectives: To determine the incidence, pattern and ocular morbidity associated with age-related macular degeneration (AMD) at the Guinness Eye Center Onitsha Nigeria.

Materials and Methods: The case files of all new patients aged 50 years and above seen between January 1997 and December 2004 were reviewed. The files of patients with AMD were further studied. Information on age, gender, occupation, duration of symptoms, type of maculopathy, visual acuity, ocular and systemic co-morbidities were abstracted into a standard proforma and analyzed using the chi-square test, student t-test and confidence interval estimation.

Results: Two hundred and fifty-six of 7966 (3.2%) new patients had AMD; M:F = 2:3; 60 -79 year age group
constitute 70% of the cases. Non-neovascular AMD occurred in 210 (82%) patients with 182 (71.1%) having early AMD and 28 (10.9%) geographic atrophy. Neovascular AMD occurred in 46 (18%) patients. AMD was bilateral in 221 (86.3%) patients. Most patients presented late. Systemic co-morbidities were hypertension and diabetes; the main ocular co-morbidities were cataract and glaucoma. Thirty-four (13.3%) patients were bilaterally blind and 130 (50.8%) had bilateral visual impairment. Of the blind patients 13 (38.3%) had neovascular AMD and 6 (17.7%) had geographic atrophy. This makes AMD the cause of blindness in 7.4% of the patients. An affected eye was more likely to have low vision than an unaffected eye (95% CI: 0.07, 0.21; P<0.05); persons aged 70 years and above were more likely to be blind ($\chi^2$ 7.26, df 1; P<0.05); females were also more likely to be blind than males (t 2.857, df 8; P<0.05) and neovascular AMD significantly causes more blindness than the non-neovascular type (95% CI: 0.11, 0.37; P<0.05).

Conclusions: AMD was the main cause of blindness in 7.4% of the patients. Treatment facilities including low vision aids for AMD patients should be provided in eye hospitals in Nigeria. Health education of the public highlighting the risk factors for AMD should be mounted as part of Vision 2020 programme in Nigeria. A community based study is required to fully define the epidemiologic characteristics of AMD in Nigerians.

PMID: 22037079 [PubMed - in process]

**Genetics**


Can genetic risk information for age-related macular degeneration influence motivation to stop smoking? A pilot study.

Rennie CA, Stinge A, King EA, Sothirachagan S, Osmond C, Lotery AJ.

Department of Ophthalmology, Southampton General Hospital, Southampton, UK.

Aims: Smoking can increase the risk of macular degeneration and this is more than additive if a person also has a genetic risk. The purpose of this study was to examine whether knowledge of genetic risk for age-related macular degeneration (AMD) could influence motivation to quit smoking.

Methods: A questionnaire-based study of hypothetical case scenarios given to 49 smokers without AMD. Participants were randomly allocated to a generic risk, high genetic risk, or low genetic risk of developing AMD scenario.

Results: Forty-seven percent knew of the link between smoking and eye disease. In all, 76%, 67%, and 46% for the high risk, generic, and low risk groups, respectively, would rethink quitting (P for trend=0.082). In all, 67%, 40%, and 38.5%, respectively, would be likely, very likely, or would definitely quit in the following month (P for trend=0.023). Few participants (<16% of any group) were very likely to or would definitely attend a quit smoking session with no difference across groups. In all, 75.5% of participants would consider taking a genetic test for AMD.

Conclusion: In this pilot study, a trend was seen for the group given high genetic risk information to be more likely to quit than the generic or low genetic risk groups. Participants were willing to take a genetic test but further work is needed to address the cost benefits of routine genetic testing for risk of AMD. More generic risk information should be given to the public, and health warnings on cigarette packets that ‘smoking causes blindness’ is a good way to achieve this.Eye advance online publication, 28 October 2011; doi:10.1038/eye.2011.256.

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Automated Discovery and Quantification of Image Based Complex Phenotypes: A Twin Study of Drusen Phenotypes in Age-related Macular Degeneration.

Quellec G, Russell SR, Seddon JM, Reynolds R, Scheetz T, Mahajan VB, Stone EM, Abràmoff MD.

Purpose: We hypothesize that image analysis has the potential for formalized discovery of new visible phenotypes, and we tested this in twins affected with age-related macular degeneration (AMD).

Background: Relationships between phenotype and genotype of many disorders can improve clinical diagnoses, implicate disease mechanisms, and enhance therapy. Most genetic disorders result from interaction of many genes that obscure the discovery of such relationships.

Methods: Fundus images from 43 monozygotic (MZ) and 32 dizygotic (DZ) twin pairs with AMD were examined. First, we segmented soft and hard drusen. Then we identified newly defined phenotypes using drusen distribution statistics that significantly separate MZ from DZ twins. Using the ACE model, we attributed the contributions of Additive genetic (A), Common environmental (C) and non-shared Environmental (E) effects to drusen distribution phenotypes.

Results: Four drusen distribution characteristics significantly separated MZ from DZ twin pairs. One encoded the quantity and the remaining three encoded the spatial distribution of drusen; achieving zygosity prediction accuracy of 76%, 74%, 68% and 68%, respectively. Three of the four phenotypes had a 55%-77% genetic effect in an AE model, while the fourth phenotype showed a non-shared environmental effect (E model).

Conclusions: Computational discovery of genetically determined features can reveal quantifiable AMD phenotypes that are genetically determined without explicitly linking them to specific genes. In addition, it can identify phenotypes that appear to result predominantly from environmental exposure. Our approach is rapid and unbiased, suitable for large datasets, and can be utilized to discover unknown phenotype-genotype relationships.

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Shan H, Ji D, Barnard AR, Lipinski DM, You Q, Lee EJ, Kamalden TT, Sun X, Maclaren RE.

Purpose: To determine whether human X-linked inhibitor of apoptosis (XIAP) enhances the survival of cultured human retinal pigment epithelial cells exposed to H(2)O(2).

Methods: ARPE-19 cells were exposed to H(2)O(2) to induce oxidative cell death. Intracellular reactive oxygen species (ROS) were measured using 2',7'-dichlorofluorescein diacetate. MTT assay was performed to quantify mitochondrial stress. Cell apoptosis was determined by TUNEL assay. Human XIAP was delivered with bicistronic expression of green fluorescent protein (GFP), using recombinant adeno-associated virus (AAV-XIAP-GFP). The null vector, containing identical sequences but without XIAP, was used as a control (AAV-NULL-GFP). Transduced cells underwent fluorescence-activated cell sorting. XIAP over-expression was examined by immunostaining and Western blot.
Results: ARPE-19 cells exposed to 0.25mM H(2)O(2) for 1 hour showed increased TUNEL staining compared to non-stressed cells (17±1.4 vs. 1.8±0.4 cells per x20 field, p=0.000006), accompanied by a significant increase in intracellular ROS (207±46% vs. 100±9.5%, p=0.0002). The AAV-XIAP-GFP transduced cells had 11-fold higher XIAP expression than the AAV-NULL-GFP controls (1300±126% vs. 120±10%, p=0.0006). XIAP over-expression significantly reduced the number of apoptotic cells after stress compared with the AAV-NULL-GFP controls (3.2±0.6 vs. 18±1.6 cells per x 20 field, p=0.00003). Mitochondrial stress was reduced by AAV-XIAP-GFP, but did not reach a statistical significance (68±3.5% vs. 74±3.8%, p=0.24).

Conclusions: Over-expression of human XIAP protects ARPE-19 cells against H(2)O(2) induced oxidative cell death by acting downstream on the apoptotic pathway. XIAP gene therapy using AAV may provide a means of reducing the effect of oxidative stress to RPE cells in age-related macular degeneration.
AMD risk allele (rs6982567 A) is associated with decreased expression of GDF6 and increased expression of HTRA1. Similarly, the HTRA1 AMD risk allele (rs10490924 T) is associated with decreased GDF6 and increased HTRA1 expression. We observed decreased vascular development in the retina and significant up-regulation of gdf6 gene in RPE layer, retinal and brain tissues from HTRA1 knockout (htra1/-) mice as compared to the wild-type counterparts. We also showed enhanced SMAD signaling in htra1/- mice. Our data suggests a critical role of HTRA1 in the regulation of angiogenesis via TGF-β signaling and identified GDF6 as a novel disease gene for AMD.

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Bioinformatics. 2011 Nov 3. [Epub ahead of print]

Detecting genome-wide epistases based on the clustering of relatively frequent items.

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Department of Computer Science and Engineering, University of California, Riverside, CA 92521, USA.

MOTIVATION: In genome-wide association studies (GWAS), up to millions of single nucleotide polymorphisms (SNPs) are genotyped for thousands of individuals. However, conventional single-locus based approaches are usually unable to detect gene-gene interactions underlying complex diseases. Due to the huge search space for complicated high-order interactions, many existing multi-locus approaches are slow and may suffer from low detection power for GWAS.

RESULTS: In this paper, we develop a simple, fast and effective algorithm to detect genome-wide multi-locus epistatic interactions based on the clustering of relatively frequent items. Extensive experiments on simulated data show that our algorithm is fast and more powerful in general than some recently proposed methods. On a real genome-wide case-control data set for age-related macular degeneration (AMD), the algorithm has identified genotype combinations that are significantly enriched in the cases.

AVAILABILITY: http://www.cs.ucr.edu/~minzhux/EDCF.zip

CONTACT: minzhux@cs.ucr.edu; jingli@cwru.edu.

PMID: 22053078  [PubMed - as supplied by publisher]


Plasma Biomarkers of Oxidative Stress and Genetic Variants in Age-Related Macular Degeneration.


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PURPOSE: To compare plasma levels of oxidative stress biomarkers in patients with age-related macular degeneration (AMD) and controls and to evaluate a potential relationship between biochemical markers of oxidative stress and AMD susceptibility genotypes.

DESIGN: Prospective case-control study.

METHODS: Plasma levels of oxidative stress biomarkers were determined in 77 AMD patients and 75 controls recruited from a clinical practice. Cysteine, cystine (CySS), glutathione, isoprostane, and isofuran were measured, and participants were genotyped for polymorphisms in the complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genes.

RESULTS: CySS was elevated in cases compared with controls (P = .013). After adjustment for age, sex,
and smoking, this association was not significant. In all participants, CySS levels were associated with the CFH polymorphism rs3753394 (P = .028) as well as an 8-allele CFH haplotype (P = .029) after correction for age, gender, and smoking. None of the other plasma markers was related to AMD status in our cohort.

CONCLUSIONS: Our investigation of the gene-environment interaction involved in AMD revealed a relationship between a plasma biomarker of oxidative stress, CySS, and CFH genotype. These data suggest a potential association between inflammatory regulators and redox status in AMD pathogenesis.

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