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MD Research News

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Drug treatment

Am J Ophthalmol. 2012 Jan 13. [Epub ahead of print]

Delay to Treatment and Visual Outcomes in Patients Treated With Anti-Vascular Endothelial Growth Factor for Age-Related Macular Degeneration.

Lim JH, Wickremasinghe SS, Xie J, Chauhan DS, Baird PN, Robman LD, Hageman G, Guymer RH.

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

PURPOSE: To investigate the potential influences that affect visual acuity (VA) outcome in a clinic-based cohort of age-related macular degeneration (AMD) patients undergoing anti-vascular endothelial growth factor (anti-VEGF) treatment for choroidal neovascularization.

DESIGN: Prospective interventional case series.

METHODS: Patients with subfoveal choroidal neovascularization (CNV) secondary to AMD were prospectively recruited. A detailed questionnaire was given to patients at time of enrollment, to collect information relating to demographics, history of visual symptoms, visual acuity (VA), and treatment scheduling. Delay from symptoms to treatment ("Treatment delay") was measured in terms of weeks and analyzed in tertiles. Information pertaining to treatment outcomes was collected over a 6-month period.

RESULTS: One hundred eighty-five eyes of 185 patients were recruited into the study. Longer delay from first symptoms suggestive of CNV to first injection was a significant predictor (P = .015) of poorer treatment outcome, when controlling for age, sex, and baseline VA. Patients with a delay in treatment of 21 weeks or more compared to a delay of 7 weeks or less had an odds ratio of 2.62 (1.20, 5.68) for worsening vision after treatment.

CONCLUSIONS: Patients experiencing a longer delay between their first symptoms of CNV and their first anti-VEGF treatment have a significantly lower chance of improving vision at 6 months following anti-VEGF therapy. It is critical that this information reach those at potential vision loss from AMD, in order that prompt treatment may be instituted, to maximize the benefits of anti-VEGF treatment.

PMID: 22245460 [PubMed - as supplied by publisher]

Retina. 2012 Jan 17. [Epub ahead of print]

CAUSES OF UNSUCCESSFUL RANIBIZUMAB TREATMENT IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION IN CLINICAL SETTINGS.

Cohen SY, Oubraham H, Uzzan J, Dubois L, Tadayoni R.

*Laser and Imaging Ophthalmology Center, Paris, France †Department of Ophthalmology, Lariboisière Hospital, and Paris 7 University, Paris, France ‡Department of Ophthalmology, Hospital, Orleans, France §Ophthalmology Center, Rouen, France.

PURPOSE: To identify the causes of loss of vision after ranibizumab therapy in patients with exudative age -related macular degeneration treated in three clinical settings.

METHODS: A retrospective multicentric analysis of 290 consecutive eyes comprising cohorts from 3 clinical settings showed that 21 eyes lost ≥15 letters on the Early Treatment Diabetic Retinopathy Study chart 1 year after the start of ranibizumab treatment. Fundus images of these eyes were analyzed by two independent readers to investigate the causes of visual loss. The three cohorts were compared. A search was made for factors predisposing to visual loss. A second analysis was performed to compare the baseline characteristics of patients who gained (visual acuity gainers) or lost (visual acuity losers) ≥15 letters.

RESULTS: Among the 290 eyes included, the proportions from each center experiencing visual loss were not significantly different (mean, 7.24%, P = 0.2631). Mean visual loss of affected eyes was 27 letters. There was no significant difference between these eyes and others as regards age and gender of patients, laterality, type of choroidal neovascularization, number of visits, or initial visual acuity. Visual loss was secondary to the progression of atrophy in eight eyes, fibrosis in five eyes, a combination of fibrosis and atrophy in three eyes, severe subretinal hemorrhage in three eyes, and retinal pigment epithelial tear in two eyes. A significant difference between visual acuity gainers and losers was observed for 2 parameters: age of patients, 80.9 ± 5.3 years in visual acuity losers versus 77.5 ± 7.3 years in visual acuity gainers (P = 0.0473) and visual acuity at diagnosis, respectively, 56.2 ± 11.2 versus 49.0 ± 12.0 (P = 0.0288).

CONCLUSION: Although uncommon, visual loss may occur during ranibizumab treatment and is because of the natural course of age-related macular degeneration in most cases.

PMID: 22258164 [PubMed - as supplied by publisher]

Trans Am Ophthalmol Soc. 2011 Dec;109:115-56.

The influence of genetics on response to treatment with ranibizumab (lucentis) for age-related macular degeneration: the lucentis genotype study (an american ophthalmological society thesis).

Francis PJ.

Divisions of Retina and Ophthalmic Genetics, Casey Eye Institute, Oregon Health and Science University, Portland, Oregon.

PURPOSE: Age-related macular degeneration (AMD) has a complex etiology arising from genetic and environmental influences. This past decade have seen several genes associated with the disease. Variants in five genes have been confirmed to play a major role. The objective of this study was to evaluate whether genes influence treatment response to ranibizumab for neovascular AMD. The hypothesis was that an individual's genetic variation will determine treatment response.

METHODS: The study was a two-site prospective open-label observational study of patients newly diagnosed with exudative (neovascular) AMD receiving intravitreal ranibizumab therapy. Treatment-naïve patients were enrolled at presentation and received monthly "as needed" therapy. Clinical data was collected monthly and DNA extracted. Genotyping was performed using the Illumina (San Diego, California) 660-Quad single-nucleotide polymorphism (SNP) chip. Regression analyses were performed to identify SNPs associated with treatment-response end points.

RESULTS: Sixty-five patients were enrolled. No serious adverse events were recorded. The primary outcome measure was change in ETDRS visual acuity at 12 months. A SNP in the CFH gene was found to be associated with less improvement in visual acuity while receiving ranibizumab therapy. The C3 gene,

among others, was associated with reduced thickening and improved retinal architecture. VEGFA, FLT1, and CFH were associated with requiring fewer ranibizumab injections over the 12-month study.

CONCLUSIONS: This study is one of the first prospective pharmacogenetic study of intravitreal ranibizumab. Although preliminary, the results identify a number of putative genetic variants, which will be further examined by replication and functional studies to elucidate the complete pharmacogenetic architecture of therapy for AMD.

PMID: 22253485 [PubMed - in process] PMCID: PMC3259677

Ophthalmic Surg Lasers Imaging. 2012 Jan 1;43(1):20-4. doi: 10.3928/15428877-20111129-01.

24-Gy Low-Voltage X-Ray Irradiation With Ranibizumab Therapy for Neovascular AMD: 6-Month Safety and Functional Outcomes.

Canton VM, Quiroz-Mercado H, Velez-Montoya R, Lopez-Miranda MJ, Moshfeghi AA, Shusterman EM, Kaiser PK, Sanislo SR, Gertner M, Moshfeghi DM.

BACKGROUND AND OBJECTIVE: To describe the 6-month safety and preliminary efficacy outcomes of the use of 24-Gy radiation with intravitreal ranibizumab for patients with neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS: A single treatment of a non-invasive, externally delivered low-voltage x-ray irradiation at a dose of 24 Gy was administered in one session through three locations in the inferior pars plana in a consecutive series of patients with neo-vascular AMD (treatment naïve and previously treated). Optical coherence tomography (OCT) and Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity examinations were performed at 1 week, 1 month, and monthly thereafter with quarterly fluorescein angiography.

RESULTS: Nineteen patients completed 6 months of follow-up. There was no evidence of radiation retinopathy, optic neuropathy, or cataract. The mean baseline ETDRS score was 38.3 ± 19.5 letters. At 6 months, the corresponding ETDRS score was 44.7 ± 16.8 letters. At 6 months, the mean change in visual acuity was 6.4 ± 9.8 ETDRS letters. Patients received an average of 0.4 additional ranibizumab injections following the initial two mandated injections.

CONCLUSION: A single treatment of external 24-Gy low-voltage x-ray therapy in conjunction with ranibizumab demonstrated an overall improvement in visual acuity in patients with neovascular AMD at 6 months, with no radiation-related adverse effects.

PMID: 22251841 [PubMed - in process]

Br J Ophthalmol. 2012 Feb;96(2):179-84.

Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease?

Manousaridis K, Talks J.

Department of Ophthalmology, Royal Victoria Infirmary, NHS Foundation Trust, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK; kleanthis.manousaridis@googlemail.com.

Abstract

Anti-vascular endothelial growth factor (anti-VEGF) therapy has been shown to be effective at improving vision in patients with macular oedema due to diabetic retinopathy and vein occlusions, but blocking VEGF at least in theory could be detrimental to vascular integrity. For this reason, some patients with macular ischaemia were excluded from studies showing the effectiveness of therapy. A considerable number of patients present with mixed pathology of macular oedema and macular ischaemia and it is often impossible

to determine the degree to which ischaemia accounts for decreased vision. In this review, the authors have dealt with the specific question of whether or not there is evidence to support potential worsening of the macular perfusion and visual function after anti-VEGF treatment with bevacizumab or ranibizumab for macular oedema secondary to diabetic retinopathy or retinal vein occlusions, especially if there is coexisting macular ischaemia. The authors conclude that anti-VEGF therapy rarely seems to further compromise the retinal circulation; however, worsening of macular ischaemia in the long term cannot be definitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections. The decision to offer prolonged anti-VEGF treatment in cases of significant coexisting macular ischaemia should not be based only on measurements of macular thickness; instead repeat fluorescein angiograms should be performed.

PMID: 22250209 [PubMed - in process]

Other treatment & diagnosis

J Cataract Refract Surg. 2012 Jan 14. [Epub ahead of print]

Long-term visual outcome after cataract surgery: Comparison of healthy eyes and eyes with age-related macular degeneration.

Mönestam E, Lundqvist B.

From the Department of Clinical Sciences/Ophthalmology, Faculty of Medicine, Norrlands University Hospital, Umeå University, Umeå, Sweden.

PURPOSE: To compare the long-term longitudinal visual acuity outcomes after cataract surgery in eyes with age-related macular degeneration (AMD) at surgery and eyes without comorbidity.

SETTING & DESIGN: University-based eye clinic. Longitudinal cohort study.

METHODS: Patients having cataract surgery were evaluated over 1 year. A clinical eye examination and corrected distance visual acuity (CDVA) measurement were performed preoperatively and postoperatively as well as 5 and 10 years postoperatively for eligible patients. The patients were divided into functional groups depending on postoperative signs of macular degeneration and postoperative CDVA.

RESULTS: The study evaluated 810 patients. The rate of CDVA decline with age was faster in AMD patients than in patients without comorbidity. The slope of the visual acuity decline was similar in the 2 subgroups with AMD (almost normal CDVA and reduced CDVA postoperatively). After adjustment for age, there was a mean loss of 2.3 logMAR letters in patients with no comorbidity and 6.4 letters in patients with AMD at surgery for each decade of increasing age. More than 75% of AMD patients had better CDVA 10 years after surgery than before surgery.

CONCLUSIONS: Patients with signs of AMD at cataract surgery had a longitudinally worse visual outcome than patients without clinical signs of AMD. However, there is no reason to discourage patients with concurrent visually significant cataract and AMD from having surgery because most AMD patients had better CDVA 10 years after surgery than before surgery.

PMID: 22245170 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2012;6:33-9. Epub 2011 Dec 30.

Improving quality of life in patients with end-stage age-related macular degeneration: focus on miniature ocular implants.

Singer MA, Amir N, Herro A, Porbandarwalla SS, Pollard J.

Medical Center Ophthalmology Associates, San Antonio, TX, USA.

Abstract

Low vision devices in the past have been mainly extraocular. There are now four new devices in different stages of development and implementation that are currently available. Three of them, the Implantable Miniature Telescope (IMT, VisionCare Ophthalmic Technologies, Saratoga, CA), Intraocular Lens for Visually Impaired People (IOL-VIP, IOL-VIP System, Soleko, Pontecorvo, Italy), and Lipschitz Mirror Implant (LMI, Optolight Vision Technology, Herzlia, Israel) are implanted into the anterior segment while the Argus II (Second Sight Medical Products, Sylmar, CA) is implanted into the posterior segment. The goal of these devices is to increase the patient quality of life which has been measured by Visual Functioning Questionnaire (VFQ) scales. The IMT is the only device that has been shown to increase the VFQ score by seven points at 6 months compared to baseline. It is the only FDA-approved device in the US while the Argus has been approved in Europe. Each of these prosthetics has potential benefits for patients.

PMID: 22259233 [PubMed - in process]

Eye (Lond). 2012 Jan 20. doi: 10.1038/eye.2011.351. [Epub ahead of print]

Cost analysis comparing adjuvant epimacular brachytherapy with anti-VEGF monotherapy for the management of neovascular age-related macular degeneration.

Jackson TL, Kirkpatrick L, Tang G, Prasad S.

1] School of Medicine, King's College, London, UK [2] Department of Ophthalmology, King's College Hospital, London, UK.

Aims: To consider the cost implication of adopting epimacular brachytherapy (EMB) for the treatment of neovascular (wet) age-related macular degeneration (wAMD), compared with ranibizumab or bevacizumab monotherapy.

Methods: This analysis compared the cumulative 3-year costs of anti-VEGF (vascular endothelial growth factor) monotherapy to EMB combined with anti-VEGF therapy. Two patient groups were considered: newly diagnosed (treatment-naïve) patients; and patients already receiving chronic anti-VEGF therapy.

Results: In the treatment-naïve patients, the highest cumulative treatment costs were associated with ranibizumab monotherapy (£25 658), followed by bevacizumab monotherapy (£16 177), EMB with ranibizumab (£14 002), then EMB with bevacizumab (£10 289). In previously treated patients, the highest treatment costs were ranibizumab monotherapy (£18 355), followed by EMB with ranibizumab (£17 428), bevacizumab monotherapy (£16 177), then EMB with bevacizumab (£12 129).

Conclusion: EMB combined with anti-VEGF treatment has the potential to yield considerable cost savings, compared with anti-VEGF monotherapy. If the ongoing large studies of EMB confirm the published feasibility data, then adjuvant EMB may represent a cost-effective alternative to anti-VEGF monotherapy.

PMID: 22261737 [PubMed - as supplied by publisher]

Conf Proc IEEE Eng Med Biol Soc. 2011 Aug;2011:3962-6.

Automatic screening of age-related macular degeneration and retinal abnormalities.

Burlina P, Freund DE, Dupas B, Bressler N.

Abstract

We describe a novel approach for screening retinal imagery to detect evidence of abnormalities. In this paper, we focus our efforts on age-related macular degeneration (AMD), a pathology that may often go

undetected in the early or intermediate stages, and can lead to a neovascular form often resulting in blindness, if untreated. Our strategy for retinal anomaly detection is to employ a single class classifier applied to fundus imagery. We use a multiresolution locally-adaptive scheme that identifies both normal and anomalous regions within the retina. We do this by using a hybrid parametric/non-parametric characterization of the support of the probability distribution of normal retinal tissue in color and intensity feature space. We apply this approach to screen for evidence of AMD on a dataset of 66 healthy and pathological cases and found a detection sensitivity and specificity of 95% and 96%.

PMID: 22255207 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2011 Aug;2011:3958-61.

Geographic atrophy segmentation in infrared and autofluorescent retina images using supervised learning.

Devisetti K, Karnowski TP, Giancardo L, Li Y, Chaum E.

Abstract

Geographic Atrophy (GA) of the retinal pigment epithelium (RPE) is an advanced form of atrophic age-related macular degeneration (AMD) and is responsible for about 20% of AMD-related legal blindness in the United States. Two different imaging modalities for retinas, infrared imaging and autofluorescence imaging, serve as interesting complimentary technologies for highlighting GA. In this work we explore the use of neural network classifiers in performing segmentation of GA in registered infrared (IR) and autofluorescence (AF) images. Our segmentation achieved a performance level of 82.5% sensitivity and 92.9% specificity on a per-pixel basis using hold-one-out validation testing. The algorithm, feature extraction, data set and experimental results are discussed and shown.

PMID: 22255206 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2011 Aug;2011:2933-6.

Ultra-high photosensitivity silicon nanophotonics for retinal prosthesis: Electrical characteristics.

Khraiche ML, Lo Y, Wang D, Cauwenberghs G, Freeman W, Silva GA.

Abstract

Retinal degenerative diseases such as age related macular degeneration (AMD) and retinitis pigmentosa (RP), lead to the loss of the photoreceptor cells rendering the retina incapable of detecting light. Several engineering approaches have aimed at replacing the function of the photoreceptors by detecting light via an external camera or photodiodes and electrically stimulating the remaining retinal tissue to restore vision. These devices rely heavily on off-device processing to solve the computational challenge of matching the performance of the PRs. In this work, we present a unique ultra-high sensitivity photodetector technology with light sensitivity, signal amplification, light adaptation that shows signal transduction performance approaching those of the rods and cones in the mammalian retina. In addition, the technology offers nanoscale control over photodetectors topography with the potential to reproduce the visual acuity of the natural retina. This technology promises to drastically reduce the foot print, power consumption and computational needs of the current retinal prothesis, while reproducing high resolution vision.

PMID: 22254955 [PubMed - in process]

J Ophthalmol. 2011;2011:459251. Epub 2011 Dec 27.

Inflammatory and angiogenic protein detection in the human vitreous: cytometric bead assay.

Koss MJ, Pfister M, Koch FH.

Section of Vitreo-Retinal Surgery, Department of Ophthalmology, Hospital of the Goethe University, Goethe University, 60590 Frankfurt am Main, Germany.

Introduction: To evaluate clinical feasibility and reproducibility of cytometric bead assay (CBA) in nondiluted vitreous samples of patients with age-related macular degeneration (ARMD), diabetic macular edema (DME), and central retinal vein occlusion (CRVO).

Methods: Twelve patients from a single clinics day qualified for intravitreal injections (ARMD n = 6, DME n = 3, CRVO n = 3) and underwent a combination treatment including a single-site 23 gauge core vitrectomy which yielded a volume of 0.6 mL undiluted vitreous per patient. Interleukin-6 (IL-6), vascular endothelial growth factor isoform A (VEGF-A), and monocyte chemo-attractant protein-1 (MCP-1) were assessed directly from 0.3 mL at the same day (fresh samples). To assess the reproducibility 0.3 ml were frozen for 60 days at -80°, on which the CBA was repeated (frozen samples).

Results: In the fresh samples IL-6 was highest in CRVO (median IL-6 55.8 pg/mL) > DME (50.6) > ARMD (3.1). Highest VEGF was measured in CRVO (447.4) > DME (3.9) > ARMD (2.0). MCP-1 was highest in CRVO (595.7) > AMD (530.8) > DME (178). The CBA reproducibility after frozen storage was examined to be most accurate for MCP1 (P = 0.91) > VEGF (P = 0.68) > IL-6 (P = 0.49).

Conclusions: CBA is an innovative, fast determining, and reliable technology to analyze proteins in fluids, like the undiluted vitreous, which is important to better understand ocular pathophysiology and pharmacology. There is no influence of intermittent storage at -80° for the reproducibility of the CBA.

PMID: 22254128 [PubMed - in process] PMCID: PMC3255300

Pathogenesis

Klin Oczna. 2011;113(7-9):228-32.

[Elevated level of circulating endothelial cells as an exponent of chronic vascular dysfunction in the course of AMD].

[Article in Polish]

Machalińska A, Safranow K, Sylwestrzak Z, Szmatłoch K, Kuprjanowicz L, Karczewicz D.

Z Katedry i Zakładu Histologii i Embriologii Pomorskiego Uniwersytetu Medycznego w Szczecinie. annam@sci.pam.szczecin.pl

PURPOSE: In recent years, emerging data support the concept of endothelial dysfunction in the course of age-related macular degeneration (AMD). Circulating endothelial cells (CECs) are desquamated mature cells that have detached from the intimal monolayer in response to endothelial injury. In this study we sought to explore the potential role of endothelial dysfunction in pathogenesis of AMD by measuring the concentration of CECs in peripheral blood of AMD patients.

MATERIAL AND METHODS: Peripheral blood samples from 31 patients with diagnosed dry AMD and 46 patients with neovascular AMD were collected. Forty six, age- and sex-matched volunteers without AMD were enrolled as a control group. CECs were counted and analyzed by flow cytometry.

RESULTS: Multivariate analyses of patients and controls adjusted for age, gender, presence of ischemic heart disease, hypertension and smoking (current or past) revealed that both wet (beta = +0.45, p = 0.0003) and dry (beta = +0.28, p = 0.027) forms of AMD are independent factors associated with higher number of CECs.

CONCLUSIONS: Our results suggest that there is an endothelial alteration accompanying AMD. Increased numbers of CECs AMD patients reflect a severe vascular disturbance and may contribute to the disease

process. These findings can help expand our knowledge of the pathogenic mechanisms of AMD and may be relevant to the potential treatment of this disease.

PMID: 22256563 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2011 Aug;2011:6236-41.

Statistical characterization and segmentation of drusen in fundus images.

Santos-Villalobos H, Karnowski TP, Aykac D, Giancardo L, Li Y, Nichols T, Tobin KW, Chaum E.

Abstract

Age related Macular Degeneration (AMD) is a disease of the retina associated with aging. AMD progression in patients is characterized by drusen, pigmentation changes, and geographic atrophy, which can be seen using fundus imagery. The level of AMD is characterized by standard scaling methods, which can be somewhat subjective in practice. In this work we propose a statistical image processing approach to segment drusen with the ultimate goal of characterizing the AMD progression in a data set of longitudinal images. The method characterizes retinal structures with a statistical model of the colors in the retina image. When comparing the segmentation results of the method between longitudinal images with known AMD progression and those without, the method detects progression in our longitudinal data set with an area under the receiver operating characteristics curve of 0.99.

PMID: 22255764 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2011 Aug;2011:1081-4.

Physiological response of mouse retinal ganglion cells to electrical stimulation: Effect of soma size.

Cho AK, Sampath AP, Weiland JD.

Abstract

An epiretinal prosthesis aims to restore functional vision by stimulating electrically the retinal ganglion cells (RGCs) in patients affected by photoreceptor degenerative diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). During retinal degeneration, photoreceptor death is followed by pronounced remodeling and rewiring of inner retinal cells. Despite these changes, a considerable population of RGCs remain receptive to prosthetic stimulation. To target selectively a localized subset of RGCs, an improved understanding of the anatomical and physiological properties of these cells is required. Additionally, potential alterations in electrical excitability produced by the retinal degeneration needs to be assessed. This study investigates the effect of RGC soma size on the threshold for action potential (spike) generation and its implications for the rescue of visual function.

PMID: 22254501 [PubMed - in process]

Neurobiol Aging. 2012 Jan 11. [Epub ahead of print]

Lipofuscin can be eliminated from the retinal pigment epithelium of monkeys.

Julien A S, Schraermeyer A U.

Section of Experimental Vitreoretinal Surgery, Centre for Ophthalmology, Tübingen, Germany.

Abstract

Lipofuscin is a cytologic hallmark of aging in metabolically active postmitotic cells including neurons,

cardiac muscle cells, and the retinal pigment epithelium (RPE). High levels of lipofuscin are involved in the pathogenesis of age-related macular degeneration (AMD), the main cause of blindness in the elderly population in the western world. Degradation and exocytosis of lipofuscin by RPE cells have not been observed in vivo until now, and no drug is known to eliminate the intracellular amount of lipofuscin. Here, we show that in monkeys treated with a small molecule belonging to the tetrahydropyridoethers class (n = 36 of 48 monkeys), RPE cells significantly release lipofuscin. In 4 eyes, macrophages were detected which had taken up lipofuscin. They were located between the Bruch's membrane and the RPE, and in the choroid. The quantification of pigment granules was performed by transmission electron microscopy. Our findings open the way to develop therapeutic strategies to remove lipofuscin from RPE cells, which may have implications for the treatment of age-related macular degeneration in which lipofuscin accumulation in cells is a causative factor.

PMID: 22244091 [PubMed - as supplied by publisher]

Epidemiology

Clin Ter. 2011 Nov;162(6):e187-94.

A simulation of cost-benefit analysis of blindness prevention in Italy.

Muscio A, Ciriaci D, Cruciani F.

Department of Economics, Mathematical and Statistics Science (DSEMS), University of Foggia; European Commission, Directorate General JRC, Institute for Prospective Technological Studies (IPTS), Seville, Spain; IAPB - International Agency for Prevention of Blindness, Italian branch,"Sapienza" University of Rome, Head-Neck Department, Ophthalmology, Roma, Italy.

Purpose: The most important purpose is to assess by a trial and error method the financial effects of efficient prevention programmes in our country. The study provides an empiric evidence that Government could reduce public spending thorough investments in projects of prevention about visual care.

Materials and methods: Authors focus on the economic impact of four eye diseases that are the major cause of blindness (90%) and for this reason they were classificated as "diseases of social importance" (DSI from hereforth) according to the WHO: Age - related Macular Degeneration (AMD), Glaucoma, Diabetic Retinopathy (DR), Cataract. Authors use a three-stage approach in order to estimate the impact of blindness prevention on public accounts: 1. Calculation of aggregate costs of the DSI in Italy; 2. Use of the estimated figures in the first stage of the alanysis to estimate the individual average costs; 3. Use of the estimated figures in the second stage of the analysis to run a simulation in capital budgeting comparing the costs associated with taking one of two possible choices: investing or not in a blindness prevention programme.

Discussion: Authors simulate the economic effects of the adoption of a blindness prevention campaign and compare them to the calculated costs of blindness. This comparison was based on the creation of decision trees, which are typically used for the optimisation of investment portfolios, combined with another decision technique: the Net Present Value (NPV).

PMID: 22262339 [PubMed - in process]

Genetics

Invest Ophthalmol Vis Sci. 2012 Jan 12. [Epub ahead of print]

Prospective Assessment of Genetic Effects on Progression to Different Stages of Age-related Macular Degeneration Using Multi-state Markov Models.

Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM.

Ophthalmic Epidemiology and Genetics Service, New England Eye Center, Department of Ophthalmology, Tufts Medical Center, Boston, MA;

Purpose: Understanding the effect of genes on progression to different stages of age-related macular degeneration (AMD) may suggest stage-specific drug targets and more precise prediction for this disease.

Methods: Progression event and time to each stage of AMD were derived from the longitudinal data of 2560 subjects without advanced AMD. SNPs in 12 AMD risk loci were genotyped. A multi-state Markov model for progression from normal to intermediate drusen, then to large drusen, and eventually to neovascular disease (NV) or geographic atrophy (GA) was applied to estimate stage-specific hazard ratios for each SNP. The effects of these genetic factors were also estimated by a multivariate multi-state Markov model adjusted for baseline age, gender, smoking, body mass index (BMI), education, antioxidant treatment, and the status of AMD in the fellow eye.

Results: Controlling for demographic and behavioral factors and other SNPs, the TT genotype of rs10468017 in LIPC was associated with decreased risk of progression from large drusen to NV (HR=0.57, P=0.04) and tended to reduce the risk of progression from normal to intermediate drusen (HR=0.72, P=0.07). Rs1883025 (T allele) in ABCA1 was associated with decreased risk of progression from normal to intermediate drusen (HR per allele = 0.82 per allele, P=9.7x10(-3)) and from intermediate drusen to large drusen (HR per allele =0.77, P=5.2x10(-3)). The genes CFH, C3, CFB, and ARMS2/HTRA1 were associated with progression from intermediate drusen to large drusen, and from large drusen to GA or NV.

Conclusion: Genes in different pathways influence progression to different stages of AMD.

PMID: 22247473 [PubMed - as supplied by publisher]

BMC Med Genomics. 2012 Jan 19;5(1):4. [Epub ahead of print]

The role of disease characteristics in the ethical debate on personal genome testing.

Bunnik EM, Schermer MH, Janssens AC.

BACKGROUND: Companies are currently marketing personal genome tests directly-to-consumer that provide genetic susceptibility testing for a range of multifactorial diseases simultaneously. As these tests comprise multiple risk analyses for multiple diseases, they may be difficult to evaluate. Insight into morally relevant differences between diseases will assist researchers, healthcare professionals, policy-makers and other stakeholders in the ethical evaluation of personal genome tests.

DISCUSSION: In this paper, we identify and discuss four disease characteristics - severity, actionability, age of onset, and the somatic/psychiatric nature of disease - and show how these lead to specific ethical issues. By way of illustration, we apply this framework to genetic susceptibility testing for three diseases: type 2 diabetes, age-related macular degeneration and clinical depression. For these three diseases, we point out the ethical issues that are relevant to the question whether it is morally justifiable to offer genetic susceptibility testing to adults or to children or minors, and on what conditions.

SUMMARY: We conclude that the ethical evaluation of personal genome tests is challenging, for the ethical issues differ with the diseases tested for. An understanding of the ethical significance of disease characteristics will improve the ethical, legal and societal debate on personal genome testing.

PMID: 22260407 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:38-54. Epub 2012 Jan 10.

Regulation of the human tyrosinase gene in retinal pigment epithelium cells: the significance of

transcription factor orthodenticle homeobox 2 and its polymorphic binding site.

Reinisalo M, Putula J, Mannermaa E, Urtti A, Honkakoski P.

PURPOSE: Tyrosinase is the rate-limiting enzyme responsible for melanin biosynthesis in the retinal pigment epithelium (RPE) of the eye. Melanin has an important role in retinal development, function, and protection against light-induced oxidative stress, and melanin levels are associated with age-related macular degeneration (AMD). Because the levels of and protection afforded by melanin seem to decline with increasing age, proper regulation of the human tyrosinase gene (TYR) in the RPE is an important but insufficiently understood process. Our purpose was to obtain detailed information on regulation of the TYR gene promoter in the human RPE and to specify the role of orthodenticle homeobox 2 (OTX2) and microphthalmia-associated transcription factor (MITF).

METHODS: We used luciferase reporter constructs to study regulation of the human TYR gene promoter in cultured human RPE cells. We further studied the role of OTX2 and MITF, their binding sites, and endogenous expression by using mutagenesis, electrophoretic mobility shift assay, yeast two-hybrid assay, RNA interference, and gene expression analyses.

RESULTS: In the RPE, OTX2 activated the human TYR gene promoter via direct trans-activation of novel OTX2 binding elements. In addition, we found that indirect activation by OTX2 via more proximal MITF binding sites, even in the absence of OTX2 sites, took place. These results are consistent with the physical interaction observed between OTX2 and MITF. Overexpression or knockdown of OTX2 in RPE cells resulted in corresponding changes in tyrosinase mRNA expression. Finally, we found that a single nucleotide polymorphism (SNP rs4547091) at the most proximal OTX2 binding site is associated with altered nuclear protein binding and a remarkable decrease in TYR promoter activity in RPE cells. This single nucleotide polymorphism (SNP) is more common in the European population in which AMD is also more prevalent.

CONCLUSIONS: In the RPE, OTX2 activates the human TYR gene promoter by direct DNA binding and by interaction with MITF. Such synergistic interaction highlights the role of OTX2 as a potential coregulator of numerous MITF target genes in the eye. Genetic differences in OTX2 binding sites affect tyrosinase regulation. Collectively, these findings emphasize the role of OTX2 in regulating the human TYR gene, with implications for inter-individual differences in melanin synthesis, retinal development, and function as well as susceptibility to retinal degeneration associated with aging.

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Chlamydia infection status, genotype, and age-related macular degeneration.

Khandhadia S, Foster S, Cree A, Griffiths H, Osmond C, Goverdhan S, Lotery A.

PURPOSE: To evaluate whether Chlamydia (C.) infections are associated with age-related macular degeneration (AMD) and to assess if this association is influenced by the complement factor H (CFH) Y402H or the high temperature requirement A serine peptidase 1 (HTRA1) rs11200638 risk genotypes.

METHODS: One hundred ninety-nine AMD patients with early and late forms of the disease and 100 unaffected controls, at least 50 years old were included in the study. Patients in the AMD and control groups were selected based on known CFH Y402H variant genotype status (one third homozygous CC, one third heterozygous CT, and one third wild-type TT). Plasma from all patients and controls was tested for C. pneumoniae, C. trachomatis, and C. psittaci IgG seropositivity using a micro-immunofluorescent assay to establish previous infection status. Assays were conducted blind to risk genotypes and the results analyzed using univariate and multivariate (logistic regression) analysis.

RESULTS: IgG seropositivity to C. pneumoniae was most prevalent (69.2%, n=207), followed by C. trachomatis (7.4%, n=22) and C. psittaci (3.3%, n=10). No association was found between each of the

three Chlamydia species IgG seropositivity and AMD status or severity (early/late). There was also no significant association between Chlamydia species IgG seropositivity and AMD status or severity, in patients carrying at least one CFH Y402H risk allele (C) or HTRA1 rs11200638 risk allele (A), with univariate or logistic regression analysis.

CONCLUSIONS: Chlamydia infection status does not appear to be associated with AMD status or severity. The presence of CFH Y402H and HTRA1 rs11200638 risk genotypes does not alter this negative association.

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Complement factor H genetic variant and age-related macular degeneration: effect size, modifiers and relationship to disease subtype.

Sofat R, Casas JP, Webster AR, Bird AC, Mann SS, Yates JR, Moore AT, Sepp T, Cipriani V, Bunce C, Khan JC, Shahid H, Swaroop A, Abecasis G, Branham KE, Zareparsi S, Bergen AA, Klaver CC, Baas DC, Zhang K, Chen Y, Gibbs D, Weber BH, Keilhauer CN, Fritsche LG, Lotery A, Cree AJ, Griffiths HL, Bhattacharya SS, Chen LL, Jenkins SA, Peto T, Lathrop M, Leveillard T, Gorin MB, Weeks DE, Ortube MC, Ferrell RE, Jakobsdottir J, Conley YP, Rahu M, Seland JH, Soubrane G, Topouzis F, Vioque J, Tomazzoli L, Young I, Whittaker J, Chakravarthy U, de Jong PT, Smeeth L, Fletcher A, Hingorani AD.

Centre for Clinical Pharmacology, Department of Medicine, University College London, London, UK, Genetic Epidemiology Group, Department of Epidemiology and Public Health, 1-19 Torrington Place, University College London, London, UK, and others

BACKGROUND: Variation in the complement factor H gene (CFH) is associated with risk of late age-related macular degeneration (AMD). Previous studies have been case-control studies in populations of European ancestry with little differentiation in AMD subtype, and insufficient power to confirm or refute effect modification by smoking.

METHODS: To precisely quantify the association of the single nucleotide polymorphism (SNP rs1061170, 'Y402H') with risk of AMD among studies with differing study designs, participant ancestry and AMD grade and to investigate effect modification by smoking, we report two unpublished genetic association studies (n = 2759) combined with data from 24 published studies (26 studies, 26 494 individuals, including 14 174 cases of AMD) of European ancestry, 10 of which provided individual-level data used to test gene-smoking interaction; and 16 published studies from non-European ancestry.

RESULTS: In individuals of European ancestry, there was a significant association between Y402H and late-AMD with a per-allele odds ratio (OR) of 2.27 [95% confidence interval (CI) 2.10-2.45; P = 1.1 x 10(-161)]. There was no evidence of effect modification by smoking (P = 0.75). The frequency of Y402H varied by ancestral origin and the association with AMD in non-Europeans was less clear, limited by paucity of studies.

CONCLUSION: The Y402H variant confers a 2-fold higher risk of late-AMD per copy in individuals of European descent. This was stable to stratification by study design and AMD classification and not modified by smoking. The lack of association in non-Europeans requires further verification. These findings are of direct relevance for disease prediction. New research is needed to ascertain if differences in circulating levels, expression or activity of factor H protein explain the genetic association.

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Relevance of complement factor H-related 1 (CFHR1) genotypes in age-related macular

degeneration (AMD).

Martínez-Barricarte R, Recalde S, Fernández-Robredo P, Millán I, Olavarrieta L, Viñuela A, Pérez-Pérez J, García-Layana A, de Córdoba SR; on behalf of the Spanish Multi-centre Group of AMD.

Department of Cellular and Molecular Medicine, Centro de Investigaciones Biológicas (CSIC) and Ciber de Enfermedades Raras (CIBERER), Ramiro de Maeztu 9, 28040 Madrid, Spain.

Purpose: Age-related Macular Degeneration (AMD) has a strong genetic component with a major locus at 1q31, including the complement factor H gene (CFH). Detailed analyses of this locus have demonstrated the existence of one SNP haplotype block, carrying the CFH-402His allele, which confers increased risk to AMD, and two protective SNP haplotypes, one of them carrying a deletion of the CFHR1 and CFHR3 genes (Δ(CFHR3-CFHR1)). The purpose of these studies was to evaluate the contribution of newly described CFHR1 alleles to the association of the 1q31 locus with AMD.

Methods: 259 patients and 191 age-matched controls of Spanish origin were included in a transversal comparative case-control study using multivariate logistic regression analysis and ROC (Receiver Operating Characteristics) statistics to generate and to test models predictive for developing AMD.

Results: We show for the first time that a particular CFHR1 allotype, CFHR1*A, is strongly associated with AMD (OR, 2.08; 95% CI, 1.59-2.73; P<0.0001) and illustrate a peculiar genotype-phenotype correlation between the CFHR1 alleles and different diseases that may have important implications for understanding the pathophysiology of AMD. We also show that CFHR1*A is in strong linkage disequilibrium with the CFH-402His allele, which provides additional candidate variants within the major risk haplotype at 1q31 for being responsible of its association with AMD. Further, using the Spanish population as a model, we show that analysis of the CFHR1 genotypes provide sufficient information to delineate the individual risk to develop AMD.

Conclusions: Our results support a relevant role of CFHR1 in AMD pathogenesis.

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X-linked juvenile retinoschisis: Clinical diagnosis, genetic analysis, and molecular mechanisms.

Molday RS, Kellner U, Weber BH.

Department of Biochemistry and Molecular Biology, Centre of Macular Research, University of British Columbia, 2350 Health Sciences Mall, Vancouver, B.C. V6T 1Z3, Canada.

Abstract

X-linked juvenile retinoschisis (XLRS, MIM 312700) is a common early onset macular degeneration in males characterized by mild to severe loss in visual acuity, splitting of retinal layers, and a reduction in the b-wave of the electroretinogram (ERG). The RS1 gene (MIM 300839) associated with the disease encodes retinoschisin, a 224 amino acid protein containing a discoidin domain as the major structural unit, an N-terminal cleavable signal sequence, and regions responsible for subunit oligomerization. Retinoschisin is secreted from retinal cells as a disulphide-linked homo-octameric complex which binds to the surface of photoreceptors and bipolar cells to help maintain the integrity of the retina. Over 190 disease-causing mutations in the RS1 gene are known with most mutations occurring as non-synonymous changes in the discoidin domain. Cell expression studies have shown that disease-associated missense mutations in the discoidin domain cause severe protein misfolding and retention in the endoplasmic reticulum, mutations in the signal sequence result in aberrant protein synthesis, and mutations in regions flanking the discoidin domain cause defective disulphide-linked subunit assembly, all of which produce a non-functional protein. Knockout mice deficient in retinoschisin have been generated and shown to display most of the characteristic features found in XLRS patients. Recombinant adeno-associated virus (rAAV) mediated delivery of the normal RS1 gene to the retina of young knockout mice result in long-term retinoschisin

expression and rescue of retinal structure and function providing a 'proof of concept' that gene therapy may be an effective treatment for XLRS.

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Diet

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EFFECTS OF ANTIOXIDANT COMPONENTS OF AREDS VITAMINS AND ZINC IONS ON ENDOTHELIAL CELL ACTIVATION: IMPLICATIONS FOR MACULAR DEGENERATION.

Zeng S, Hernández J, Mullins RF.

Department of Ophthalmology and Visual Sciences, Institute for Vision Research, The University of Iowa, Iowa City, IA.

Purpose: To investigate whether the benefit of AREDS formula multivitamins and zinc in the progression of age-related macular degeneration (AMD) may occur through inhibiting inflammatory events in the choroid.

Methods: Mouse C166 endothelial cells (EC) and, for some experiments, human retinal pigment epithelium (RPE)-choroid organ cultures were treated with AREDS multivitamin solution (MVS) or ZnCl2. Cytotoxicity of MVS was evaluated using a lactate dehydrogenase colorimetric assay. Cell motility was assessed using a scratch assay. Macrophage adhesion to EC monolayers or ICAM-1 protein was determined after MVS and zinc treatment, and with or without lipopolysaccharide (LPS). Quantitative reverse transcription PCR and western blot were used to determine the effects of MVS on expression of pro-inflammatory molecules in treated and untreated cells.

Results: AREDS MVS and zinc did not affect C166 EC viability until the 56th hour post-treatment. Scratch assays showed partial inhibition of MVS and zinc on EC migration. In cell adhesion assays, MVS and zinc decreased the number of macrophages bound to EC and to ICAM-1 protein. Quantitative PCR showed that LPS increased expression of ICAM-1 in both C166 and human RPE-choroid cultures, which was partially offset by MVS and zinc. MVS and zinc also mitigated LPS-induced ICAM-1 protein expression on western blot.

Conclusions: Treatment with AREDS MVS and zinc may affect both angiogenesis and endothelial-macrophage interactions. These results suggest that AREDS vitamins and zinc ions may slow the progression of AMD in part through the attenuation of EC activation.

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