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MD Research News

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Drug treatment

Int J Ophthalmol. 2012;5(4):448-51. Epub 2012 Aug 18.

Comparison of the effects of bevacizumab and ranibizumab injection on corneal angiogenesis in an alkali burn induced model.

Dursun A, Arici MK, Dursun F, Ozec AV, Toker MI, Erdogan H, Topalkara A.

Department of Ophthalmology, School of Medicine, Cumhuriyet University, Sivas, Turkey.

AIM: To investigate the effects of bevacizumab and ranibizumab on corneal neovascularization in an alkali burn-induced model of corneal angiogenesis.

METHODS: Fifteen Wistar albino rats were divided randomly into 3 groups after chemical cauterization of the cornea. The first group received a single dose of 0.1mL saline solution as a control group whereas second and third groups received a single dose of 2.5mg bevacizumab or 1mg ranibizumab by subconjunctival injection, respectively. After three weeks, the rat corneas were evaluated by biomicroscopy and corneal photographs were taken. The percentage of neovascularization area, length of the longest new vessel, corneal edema and corneal opacity scores were assessed.

RESULTS: The analysis of digital photographs showed that the percentage of neovascularization area to the total corneal area, the length of the longest new vessel, corneal edema and opacity scores were significantly lower in both study groups compared to the control group ($P<0.05$). Additionally, the percentage of corneal neovascularization area, the length of the longest new vessel and corneal opacity score were less with bevacizumab than ranibizumab.

CONCLUSION: Subconjunctival bevacizumab and ranibizumab treatments may be effective methods in reducing corneal neovascularization. Furthermore, bevacizumab is more effective than ranibizumab in the inhibition of corneal neovascularization.

PMID: 22937503 [PubMed]

Clin Ophthalmol. 2012;6:1287-91. Epub 2012 Aug 10.

Occult choroidal neovascularization after successful macular hole surgery treated with ranibizumab.

Oh HN, Lee JE, Kim HW, Yang JW, Yun IH.

Department of Ophthalmology, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea.

PURPOSE: To report on a case that developed an atypical form of occult choroidal neovascularization (CNV) after successful macular hole surgery.

METHODS: Visual acuity change, color fundus photographs, fluorescein and indocyanine green angiograms, and optical coherence tomography results were compared throughout the follow-up duration.

PATIENTS: A 64-year-old woman with a macular hole in the right eye and drusen in both eyes underwent pars plana vitrectomy, internal limiting membrane peeling, and gas tamponade. One month after the operation she developed occult CNV, in which pigment epithelial detachment and fine retinal pigment epithelial (RPE) layer wrinkles were observed under the completely sealed macular hole. After 3-monthly intravitreal injections of ranibizumab, the lesion did not change significantly.

CONCLUSION: CNV can develop after otherwise successful macular hole surgery, especially in patients with pre-existing aging changes in the macula, such as drusen. Care should be taken in such patients, to prevent the development of CNV after macular hole surgery.

PMID: 22927741 [PubMed - in process] PMCID: PMC3422150

Clin Ophthalmol. 2012;6:1201-5. Epub 2012 Jul 31.

Anterior uveitis after treatment of age-related macular degeneration with ranibizumab and bevacizumab: uncommon complication.

Damasceno N, Horowitz S, Damasceno E.

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Abstract

The authors describe one case of anterior uveitis after treatment of age-related macular degeneration with both antiangiogenic drugs: ranibizumab and bevacizumab. The case is described as a complication of ranibizumab and bevacizumab due to an inflammatory process. Several reasons are suggested to explain this possibility, and the authors conclude that the main cause remains unknown.

PMID: 22927728 [PubMed - in process] PMCID: PMC3422141 Free PMC Article

Ophthalmology. 2012 Aug 21. [Epub ahead of print]

Vascular Endothelial Growth Factor in Patients with Exudative Age-Related Macular Degeneration Treated with Ranibizumab.

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Department of Vitreoretinal Surgery, Center of Ophthalmology, University of Cologne, Cologne, Germany.

OBJECTIVES: To analyze the temporal correlations of vascular endothelial growth factor (VEGF) suppression, morphologic recurrence of choroidal neovascularization (CNV), and visual acuity loss in eyes with exudative age-related macular degeneration (AMD) treated with ranibizumab.

DESIGN: Nonrandomized, prospective, clinical study.

PARTICIPANTS: Forty-seven eyes of 47 patients with exudative AMD undergoing intravitreal ranibizumab injections.

METHODS: Aqueous humor specimens were taken before each intravitreal ranibizumab injection. Visual acuity testing, spectral domain optical coherence tomography (SD-OCT), and fundoscopy were performed before each injection. Vascular endothelial growth factor A was measured by Luminex multiplex bead analysis (Luminex Inc., Austin, TX).

MAIN OUTCOME MEASURES: Intraocular VEGF concentration, recurrence of CNV activity shown by SD-OCT, and vision loss.

RESULTS: Ranibizumab resulted in complete VEGF suppression within a mean period of 37.8 days (standard deviation [SD] ± 4.8 days; range, 26-49 days). Recurrences of CNV activity as determined by SD-OCT occurred

93.7 days (SD ± 69.9 days; range, 57-368 days) after the last ranibizumab treatment. The VEGF levels were never suppressed when a recurrence occurred. Functional recurrence (visual acuity) occurred 114.3 days (SD ± 81.4 days; range, 57-398 days) after previous treatment. The VEGF levels did not differ significantly between baseline and recurrence (69.3 pg/ml vs. 74.14 pg/ml; 95% confidence interval, -18.87 to 9.12).

CONCLUSIONS: A monthly intravitreal injection of 0.5 mg ranibizumab yields a durable VEGF inhibition. The recurrences of CNV as determined by SD-OCT are always preceded by a loss of intraocular VEGF suppression and usually followed by loss of visual acuity in the further course.

PMID: 22920670 [PubMed - as supplied by publisher]

Retina. 2012 Sep;32(8):1539-46.

Intravitreal ranibizumab versus bevacizumab for treatment of myopic choroidal neovascularization.

Iacono P, Parodi MB, Papayannis A, Kontadakis S, Sheth S, Cascavilla ML, Bandello F.

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University, Milan, Italy ‡Department of Ophthalmology, Ospedale De Gironcoli, Conegliano, Italy.

PURPOSE: To compare intravitreal bevacizumab (IVB) and intravitreal ranibizumab (IVR) in the treatment of subfoveal choroidal neovascularization associated with pathologic myopia.

METHODS: Fifty-five patients fulfilling inclusion and exclusion criteria were randomized either to IVB or to IVR. After the first injection, re-treatments were performed on a pro re nata basis in monthly examinations over an 18-month follow-up. Primary outcome measures were the change in mean best-corrected visual acuity and the proportion of eyes improving in best-corrected visual acuity by >1 and >3 lines at the 18-month examination.

RESULTS: Forty-eight eyes received the treatment and were subsequently included in the analysis. At the 18-month examination, a significant improvement of 1.7 lines and 1.8 lines compared with baseline were noticed in the IVR and IVB subgroups, respectively. The difference in the final mean best-corrected visual acuity between the groups was not significant. A 3-line gain or higher was noted in 30% of eyes in the IVR subgroup and 44% of eyes in the IVB subgroup. Although both groups attained a significant improvement in central macular thickness, the IVR subgroup achieved a faster central macular thickness reduction. A significantly lower number of injections were administered in the IVR subgroup (2.5) compared with the IVB subgroup (4.7; $P < 0.001$).

CONCLUSION: Intravitreal ranibizumab and IVB are effective in the treatment of subfoveal myopic choroidal neovascularization. Intravitreal ranibizumab achieved greater efficacy than IVB in terms of the mean number of injections administered.

PMID: 22922846 [PubMed - in process]

J Fr Ophtalmol. 2012 Aug 24. [Epub ahead of print]

[Role of intravitreal bevacizumab for resistant macular edema due to central retinal vein occlusion after failure of intravitreal triamcinolone acetonide.] [Article in French]

Le Moigne O, Duncombe A, Portmann A, Muraine M, Genevois O.

Service d'ophtalmologie, hôpital Charles-Nicolle, 1, rue de Germont, 76031 Rouen cedex, France.

PURPOSE: To evaluate the efficacy of bevacizumab injection used secondarily in patients with macular edema due to central retinal vein occlusion after failure of intravitreal triamcinolone acetonide injection.

PATIENTS AND METHODS: The present study represents a retrospective review of eight patients presenting with central retinal vein occlusion complicated by macular edema with central foveolar thickness greater than 350µm by Cirrus-OCT, Zeiss. Between 4 and 6 months after the central vein occlusion, all patients initially

underwent intravitreal triamcinolone acetonide injection (4mg/0.1ml). In the case of functional or anatomic failure, three monthly bevacizumab injections (1.25mg/0.05ml) were administered. Prior to each injection, an ophthalmic examination was performed, documenting visual acuity (ETDRS), biomicroscopy, IOP and central foveolar thickness (OCT 3).

RESULTS: After three intravitreal bevacizumab injections, we found no improvement in visual acuity (M0=45.56±13 letters; M3=44.2±8.6 letters), and no decrease in macular thickness (M0=559µm±193; M3=543µm±263). No intraocular pressure spikes or endophthalmitis were observed.

DISCUSSION: The lack of anatomic and functional efficacy observed in our study does not appear to be related to the method, dosage or timing of injection, nor to the presence of subretinal macroaneurysms. It may be due to a cross-resistance to these two drugs. In any event, recent approval of ranibizumab and intraocular dexamethasone implants will likely change our therapeutic approach.

CONCLUSION: In case of recalcitrant macular edema secondary to central vein occlusion after failed intravitreal triamcinolone acetonide injection, secondary intravitreal bevacizumab does not appear beneficial.

PMID: 22925843 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Lasers Surg Med. 2012 Aug 28. doi: 10.1002/lsm.22070. [Epub ahead of print]

In vivo imaging of photoreceptor disruption associated with age-related macular degeneration: A pilot study.

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BACKGROUND AND OBJECTIVE: Age-related macular degeneration is one of the leading causes of vision loss in the developed world. As the disease progresses, the central part of the retina, called the macula, is compromised leading to a disruption of both structure and visual function. In this study, we investigate the disruption of macular photoreceptor cells in vivo as a function of disease stage in patients with the dry form of age-related macular degeneration AMD.

MATERIALS AND METHODS: An investigational confocal Adaptive Optics Scanning Laser Ophthalmoscope (AO-SLO) was used to obtain high resolution images of the macular photoreceptor mosaic in patients previously diagnosed with AMD. Four patients were selected as representative cases, comprising each of the four clinical stages of AMD progression.

RESULTS: AO-SLO imaging revealed slight disruption in the photoreceptor mosaic in early stage AMD due to focal drusen formation and identified several small drusen deposits that were not observed with standard clinical imaging techniques. An increase in photoreceptor disruption was visualized within the macula in direct correlation with the stage of AMD progression leading to a decrease in visual acuity. Large coalescent drusen and areas of geographic atrophy in advanced stage dry AMD exhibited a significant decrease in visible photoreceptor density. Significant decrease in photoreceptor counts (~35-50%) were observed when comparing earlier stages of AMD progression (Categories I and II) to later stages of the disease (Categories III and IV).

CONCLUSIONS: This study demonstrates the capabilities of adaptive optics retinal imaging to monitor disruption of individual photoreceptor cells as a function of disease progression yielding valuable diagnostic findings in early stage AMD beyond what can be learned about the health of photoreceptors using conventional retinal imaging techniques. Lasers Surg.

PMID: 22930575 [PubMed - as supplied by publisher]

Ophthalmic Res. 2012;48 Suppl 1:11-5. Epub 2012 Aug 21.

Use of home device for early detection of neovascular age-related macular degeneration.

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Abstract

Early treatment for choroidal neovascularization (CNV) is an important part of preserving visual function for patients with age-related macular degeneration. Preferential hyperacuity perimetry (PHP) provides high accuracy, sensitivity and specificity for detecting changes in lesions in diagnostic and treatment stages. The ForeseeHome is a PHP device designed for home use by patients. Regular use alerts retina specialists and patients of detected changes and allows patients to come in for visits when CNV begins or recurs. To maximize the benefit of recent breakthroughs in CNV treatment, patients should be better monitored with the ForeseeHome to detect new CNV while their vision is still good, and to promptly manage recurrence after treatment.

PMID: 22907144 [PubMed - in process]

Ophthalmic Res. 2012;48 Suppl 1:6-10. Epub 2012 Aug 21.

Strategies for following dry age-related macular degeneration.

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Abstract

Spectral domain optical coherence tomography (SDOCT) provides a novel strategy for imaging and monitoring progression in patients with age-related macular degeneration (AMD). The advantage of SDOCT over other imaging modalities or functional tests is that one modality can be used to image both drusen and geographic atrophy while obtaining reproducible, quantitative data on both drusen morphology and the area of geographic atrophy. Moreover, this strategy enables the clinician to follow the disease as it progresses from drusen to both geographic atrophy and choroidal neovascularization. No other imaging modality is able to quantitatively assess all forms of AMD. This unique feature of SDOCT makes it the ideal imaging modality for monitoring patients with AMD, providing routine care, and for following patients in clinical trials designed to assess the efficacy of new drugs for the treatment of dry AMD.

PMID: 22907143 [PubMed - in process]

Klin Monbl Augenheilkd. 2012 Aug 28. [Epub ahead of print]

[Chronic Central Serous Chorioretinopathy (cCSC): Differential Diagnosis to Choroidal Neovascularisation (CNV) Secondary to Age-Related Macular Degeneration (AMD).] [Article in German]

Inhoffen W, Ziemssen F, Bartz-Schmidt KU.

Augenklinik, Universitäts-Augenklinik Tübingen.

Abstract

Central neurosensory detachments (NSD) with time-dependent height constitute a disease called central serous chorioretinopathy (CSC), if not arising from uveitis, choroidal neovascularisations (CNV) or leaking retinal vessels. In 10 % of these patients, CSC develops into a chronic disease with recurrent NSD, atrophy of photoreceptors

and severe drop in visual acuity. This review article summarises recent progress in understanding this disease and its appearance in funduscopy, FLA, ICG, OCT, autofluorescence as well as its progress, therapy and possible development into secondary CNV. The provided examples illustrate the progression of acute CSC into chronic CSC and with CNV over years. The different appearance of polypoidal choroidal vasculopathy (PCV) in ICG and some of the signs of atypical chronic CSC are discussed. To distinguish between cCSC and wet AMD - both exhibiting leakage in FLA - typical signs are helpful, e.g., "gravitational tracks", retinal precipitates and missing drusen.

However, in small lesions, it may be difficult or almost impossible to ensure the correct diagnosis of the underlying disease. The same holds for occult and classic secondary CNV in cCSC vs. CNV in AMD, where photodynamic therapy (PDT) can be successful only in cCSC-CNV and in cCSC without CNV. Corticosteroids often lead to further impairment, even in cases of atypical cCSC, when frequently misdiagnosed as uveitis. As a duration of NSD of more than 4 months is suspected to induce an impairment of photoreceptors, regular examinations are necessary not only in chronic CSC but also after acute CSC (as this form can develop into chronic CSC), while effective therapies are available to resolve the NSD (PDT, anti-VEGF).

PMID: 22930236 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Aug 28. [Epub ahead of print]

Visual Search with Image Modification in Age-Related Macular Degeneration.

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PURPOSE: Age-related macular degeneration (AMD) results in loss of central vision and a dependence on low-resolution peripheral vision. While many image enhancement techniques have been proposed, there is a lack of quantitative comparison of the effectiveness of enhancement. We developed a natural visual search task that uses patients' eye movements as a quantitative and functional measure of the efficacy of image modification.

METHODS: Eye movements of seventeen patients (mean age = 77 years) with AMD were recorded while they searched for target objects in natural images. Eight different image modification methods were implemented and included manipulations of local image or edge contrast, color and crowding. In a subsequent task, patients ranked their preference of the image modifications.

RESULTS: Within individual participants, there was no significant difference in search duration or accuracy across eight different image manipulations. When data were collapsed across all image modifications, a multivariate model identified six significant predictors for normalized search duration including scotoma size and acuity as well as interactions among scotoma size, age, acuity and contrast ($p < 0.05$). Additionally, an analysis of image statistics showed no correlation with search performance across all image modifications. Rank ordering of enhancement methods based on participants' preference revealed a trend that participants preferred the least modified images ($p < 0.05$).

CONCLUSIONS: There was no quantitative effect of image modification on search performance. A better understanding of low-and high-level components of visual search in natural scenes is necessary to improve future attempts at image enhancement for low vision patients. Different search tasks may require alternative image modifications to improve patient functioning and performance.

PMID: 22930725 [PubMed - as supplied by publisher]

Expert Opin Ther Targets. 2012 Aug 27. [Epub ahead of print]

Ocular actions of platelet-activating factor: clinical implications.

Nitoda E, Moschos MM, Mavragani CP, Koutsilieris M.

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Introduction: To summarize the currently available evidence of platelet-activating factor (PAF) implication in the pathogenesis of inflammatory ocular diseases. Areas covered: PAF is a potent mediator of inflammation, implicated in the pathogenesis of chronic inflammatory disorders, allergic reactions, oncogenic transformation, wound repair and hypoxia-induced angiogenesis. It seems to be involved in the protection of ocular surface against various harmful agents through inflammatory processes, which can lead to chronic allergic reactions or even corneal neovascularization and haze, if they do not undergo regulation. Pathogenesis of uveitis, which is significant cause for the blurring of the visual system, has also been associated with PAF's activity. The hypoxia and the breakdown of the blood-retina barrier, observed in severe vascular retinal diseases, such as age-related macular degeneration and diabetic retinopathy, are associated with PAF ocular activity. Expert opinion: Understanding the pathophysiology of vision threatening diseases could enhance clinical treatment and encourage experimental studies, which could be based on potential beneficial effects of new agents, such as PAF antagonists.

PMID: 22924390 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2012 Aug 23. [Epub ahead of print]

Five-Year Incidence of Age-Related Macular Degeneration: The Beijing Eye Study.

You QS, Xu L, Yang H, Li YB, Wang S, Wang JD, Zhang JS, Wang YX, Jonas JB.

Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China.

PURPOSE: To examine the incidence of age-related macular degeneration (AMD) and its associated factors in an adult Chinese population.

DESIGN: Population-based study.

PARTICIPANTS: The Beijing Eye Study, which included 4439 subjects (age ≥40 years) in 2001, was repeated in 2006 with 3251 (73.2%) subjects participating.

METHODS: Fundus photographs were graded using the International Age-related Maculopathy Epidemiological Study Group grading system.

MAIN OUTCOME MEASURES: Incidence of AMD.

RESULTS: Gradable slides were available on 3049 (93.9%) subjects who participated in the survey of 2001 and again in 2006. The incidence of early, late, and neovascular AMD per eye was 2.6% (95% confidence interval [CI], 2.2-3.0), 0.1% (95% CI, 0.00-0.2), and 0.1% (95% CI, 0.00-0.2), respectively. The incidence of early, late, and neovascular AMD per person was 4.2±0.4% (95% CI, 3.5-5.0), 0.1±0.1% (95% CI, 0.0-0.2), and 0.1±0.1% (95% CI, 0.0-0.2), respectively. By multivariate analysis, incident early AMD was associated significantly with greater age at baseline (P = 0.01; odds ratio [OR], 1.03; 95% CI, 1.01-1.06), smaller optic disc size (P = 0.007; OR, 0.50; 95% CI, 0.30-0.83), smaller scleral spur distance (P = 0.04; OR, 0.59; 95% CI, 0.36-0.98), and hyperopic refractive error (P = 0.057; OR, 1.15; 95% CI, 1.00-1.33), with the latter being significant only marginally. It was not associated with the systemic parameters of gender, body height, body mass index, region of habitation, level of education, social class as a peasant, smoking, arterial blood pressure, diabetes mellitus, fasting blood concentrations of glucose, triglycerides, high-density or low-density lipoproteins; or the ocular parameters of intraocular pressure, retinal arterial and vein diameters, retinal microvascular abnormalities, amount of nuclear cataract, cortical cataract or subcapsular cataract, pseudophakia, glaucoma, nonglaucomatous optic neuropathy, retinal vein occlusions, size of the beta zone of parapapillary atrophy, or progression of the zone of atrophy during the follow-up from 2001 to 2006.

CONCLUSIONS: Hyperopia, short interscleral spur distance, and small optic disc size were, beside older age, the main factors associated with incident early AMD. This may point to a small globe size, potentially in relation to a firmly attached vitreous, playing a role in early incident AMD.

PMID: 22921389 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2012 Aug 28. [Epub ahead of print]

Activation of the Alternative Complement Pathway in Vitreous is Controlled by Genetics in Age-related Macular Degeneration.

Loyet KM, Deforge LE, Katschke KJ Jr, Diehl L, Graham RR, Pao L, Sturgeon L, Lewin-Koh SC, Hollyfield JG, van Lookeren Campagne M.

Genentech, Inc., South San Francisco, CA, United States.

Purpose: To determine if the progression of age-related macular degeneration (AMD) is associated with complement activation in the eye.

Methods: Immunohistochemistry and enzyme-linked immunosorbent assays were used to determine the distribution, concentration, and activation of the alternative pathway complement proteases factor B (FB) and factor D (FD) and the central complement protein C3 in genotyped human post-mortem donor eyes graded as having no or minimal usen (category 1; controls), large drusen (category 3), and large drusen with advanced AMD (category 4).

Results: C3, FB, and FD were present in vitreous and Bruch's membrane-choroid (BM/C) interface of the macula of eyes in all tested AMD severity categories (n = 100). C3, FB, and FD were predominantly located to the choroidal vasculature and Bruch's membrane and elevated in BM/C extracts of category 4 eyes (n = 23) compared with category 1 eyes (n = 24). A significant increase in FB activation was found in vitreous of category 4 eyes (n=23) compared with category 1 eyes (n=25). Genetic variants of complement factor H (CFH), C3, C2, and FB associated with increased risk of AMD were correlated with alternative pathway complement activation in vitreous, whereas complement levels in BM/C protein extracts were independently associated with disease progression.

Conclusions: Increased activation of the alternative complement pathway in vitreous was correlated with genetic variation in the complement pathway and disease stage, supporting a role for complement activation in AMD disease pathogenesis.

PMID: 22930722 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Aug 28. [Epub ahead of print]

Association of Genetic Variants on 8p21 and 4q12 with Age-related Macular Degeneration in Asian Populations.

Nakata I, Yamashiro K, Akagi-Kurashige Y, Miyake M, Kumagai K, Tsujikawa A, Liu K, Chen LJ, Liu DT, Lai TY, Sakurada Y, Yoneyama S, Cheng CY, Cackett P, Yeo IY, Tay
WT, Cornes BK, Vithana EN, Aung T, Matsuo K, Matsuda F, Wong TY, Iijima H, Pang CP, Yoshimura N.

Department of Ophthalmology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Purpose: To evaluate the association of genetic variants at chromosomes 8p21 and 4q12 with the risk of developing age-related macular degeneration (AMD) and its two main subtypes, choroidal neovascular membrane (CNV) and polypoidal choroidal vasculopathy (PCV), in Asian populations.

Methods: The study population comprised 2,360 patients with neovascular AMD (1,013 typical AMD-CNV and 1,282 PCV) and 3,598 controls from four independent cohorts-two Japanese (n = 4,859) and two Chinese (n = 1,099) ethnicity. We performed a meta-analysis in case-control studies of two reported SNPs (rs13278062 at TNFRSF10A-LOC389641 on 8p21 and rs1713985 at REST-C4orf14-POLR2B-IGFBP7 on 4q12) by using logistic regression analysis adjusted for age and gender. Subgroup analysis by CNV and PCV subtypes were performed to evaluate the significance of these two variants.

Results: The reported association between rs13278062 at 8p21 and neovascular AMD was replicated in this population [P = 1.12 × 10-4, odds ratio (OR) = 0.79, 95% confidence interval (CI) = 0.70-0.89]. However, there was no association of rs1713985 at 4q12 with neovascular AMD, or its two subtypes, typical AMD-CNV and PCV (all P > 0.05). The study sample size had a statistical power of >99% to detect an association of a risk allele with AMD with an OR of 1.30, as reported in the original study of rs1713985 and AMD.

Conclusions: The present results did not replicate the reported association between rs1713985 at 4q12 and neovascular AMD. However, we confirmed the association between rs13278062 at 8p21 and neovascular AMD in Asian populations.

PMID: 22930721 [PubMed - as supplied by publisher]

Hum Mol Genet. 2012 Aug 29. [Epub ahead of print]

Can Genetic Associations Change with Age? CFH and Age-Related Macular Degeneration.

Adams MK, Simpson JA, Richardson AJ, Guymer RH, Williamson E, Cantsilieris S, English DR, Aung KZ, Makeyeva GA, Giles GG, Hopper J, Robman LD, Baird PN.

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

Background: Genetic variation in the gene encoding complement factor H (CFH) on chromosome 1q31 has repeatedly been associated with increased risk of Age Related Macular Degeneration (AMD); however previous studies have had inadequate numbers of participants across a sufficiently wide age range to determine whether the association varies by age.

Methods: We conducted a genetic case-control study using data from 2,294 cases and 2,294 controls selected from the Melbourne Collaborative Cohort Study, matched on age, sex and region-of-origin. Four consistently replicated CFH single nucleotide polymorphisms (SNPs) were genotyped: rs1061170 (Y402H); rs2274700; rs393955 and rs800292; their relationship with AMD prevalence was determined across the age range 48-86 years.

Results: A difference in genotype frequencies was seen across age groups, where the low risk homozygote prevalence rose with each increasing age group. Associations with early AMD were strongly modified by age for three of the four SNPs (interaction P-value 0.01 - 0.00003). An inverse association between the high risk homozygote for each SNP and early AMD was observed in the younger age groups (Odds Ratios (OR) range 0.37 - 0.48 for age < 55 years), reversing to a positive association with increasing age (OR 1.87 - 2.8 for age > 75 years).

Conclusions: The direction of associations for this gene change from inverse to risk with increasing age. These findings have important implications for predictive models for AMD and potentially other age related diseases which extrapolate risks from older cohorts, as they assume homogeneity of association by age, which might not exist.

PMID: 22936692 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:2271-8. Epub 2012 Aug 18.

Association analysis of genetic and environmental risk factors in the cuticular drusen subtype of age-related macular degeneration.

van de Ven JP, Smailhodzic D, Boon CJ, Fauser S, Groenewoud JM, Chong NV, Hoyng CB, Klevering BJ, den Hollander AI.

PURPOSE: To assess the association of gender, cigarette smoking, body-mass index, and nine genetic risk variants with cuticular drusen (CD), a well recognized subtype of age-related macular degeneration (AMD).

METHODS: A total of 757 patients with AMD, including 217 patients with CD, and 553 control individuals were interviewed with a questionnaire and underwent an ophthalmic examination. Venous blood samples were obtained for genomic DNA extraction, and genotyping was performed of single nucleotide polymorphisms previously associated with AMD. Odds ratios were calculated for patients with CD, using unaffected control individuals as a reference. Furthermore, odds ratios in patients with CD were compared to those in patients with "non-CD" AMD.

RESULTS: The CD subtype of AMD was significantly associated with current smoking as well as variants in the complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), complement factor B/complement component 2 (CFB/C2), complement component 3 (C3), and apolipoprotein E (APOE) genes. In patients with CD, the association with the CFH Y402H risk allele was significantly higher ($p=0.022$), whereas the association with current smoking was significantly lower ($p<0.001$) than in the heterogeneous group of patients with "non-CD" AMD.

CONCLUSIONS: The AMD subtype of CD was associated with previously identified genetic AMD risk factors. However, the association with the CFH Y402H risk allele appeared to be stronger, whereas the association with smoking was less pronounced when compared to AMD as a whole. This study suggests a more important role for genetic factors than environmental factors in the development of this well defined subtype of AMD. These findings stress the importance of detailed phenotyping in AMD to identify homogeneous AMD subtypes, which may be associated with different risk factors and disease mechanisms. Such studies will improve the accuracy of predictive models and the effectiveness of preventive and therapeutic options in AMD.

PMID: 22933840 [PubMed - in process]