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MD Research News

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

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Drug treatment

Br J Ophthalmol. 2013 Jan 3. [Epub ahead of print]

A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration.

Krebs I, Schmetterer L, Boltz A, Told R, Vécsei-Marlovits V, Egger S, Schönherr U, Haas A, Ansari-Shahrezaei S, Binder S; for the MANTA Research Group.

Vienna, Austria.

AIM: The current accepted standard treatment for neovascular age-related macular degeneration (AMD) consists of antivascular endothelial growth factor agents including ranibizumab and bevacizumab. The aim of the study was to examine whether bevacizumab is inferior to ranibizumab with respect to maintaining/improving visual acuity.

METHODS: In this prospective randomised parallel group multicentre trial patients aged more than 50 years with treatment naive nAMD were included at 10 Austrian centres. Patients were randomised to treatment either with 0.5 mg ranibizumab or 1.25 mg bevacizumab. Both groups received three initial monthly injections and thereafter monthly evaluation of visual acuity and the activity of the lesion. Re-treatment was scheduled as needed. Outcome measures were early treatment of diabetic retinopathy visual acuity, retinal thickness, lesion size and safety evaluation.

RESULTS: A total of 321 patients were recruited of which four had to be excluded due to different reasons. Of the 317 remaining patients 154 were randomised into the bevacizumab group and 163 into the ranibizumab group. At month 12, there was a mean increase of early treatment of diabetic retinopathy visual acuity of 4.9 letters in the bevacizumab and 4.1 letters in the ranibizumab group (p=0.78). Furthermore, there were no significant differences in the decrease of retinal thickness, change of lesion size and number of adverse events between the groups.

CONCLUSIONS: Bevacizumab was equivalent to ranibizumab for visual acuity at all time points over 1 year. There was no significant difference of decrease of retinal thickness or number of adverse events.

PMID: 23292928 [PubMed - as supplied by publisher]

Retina. 2013 Jan 4. [Epub ahead of print]

EFFECTS OF VEGF INHIBITION ON RETINAL MORPHOLOGY, NEOVASCULAR NETWORK SIZE, AND VISUAL ACUITY IN PATIENTS WITH VASCULARIZED PIGMENT EPITHELIUM DETACHMENT BECAUSE OF OCCULT CHOROIDAL NEOVASCULARIZATION.

Veritti D, Macor S, Menchini F, Lanzetta P.

Department of Ophthalmology, University of Udine, Udine, Italy.

PURPOSE: To report the results of vascular endothelial growth factor inhibition for vascularized pigment epithelium detachment associated with choroidal neovascularization secondary to age-related macular degeneration.

METHODS: We performed a retrospective analysis of patients affected by vascularized pigment epithelium detachment treated with intravitreal anti-vascular endothelial growth factor (0.5 mg of ranibizumab or 1 mg of bevacizumab) and a follow-up of 12 months. Retinal angiomatous proliferations were excluded. Treatment was conducted with an initial loading phase followed by a pro re nata phase. Fluorescein angiography and indocyanine green angiography were performed at baseline and every 3 months.

RESULTS: Forty eyes were included in this study. After a follow-up of 12 months and 5.5 treatments on average, best-corrected visual acuity did not vary significantly. Central retinal thickness and pigment epithelium detachment height were significantly reduced, whereas the choroidal neovascularization area remained constant.

CONCLUSION: In vascularized pigment epithelium detachment, anti-vascular endothelial growth factor therapy shows visual stabilization but not best-corrected visual acuity gain. However, it is associated with significant morphologic improvements, and it may offer a benefit over the natural course of the disease.

PMID: 23296046 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2013 Jan 7. pii: S0181-5512(12)00397-X. doi: 10.1016/j.jfo.2012.11.005. [Epub ahead of print]

Intravitreal injection of anti-VEGF and diagnosis of primary intraocular central nervous system lymphoma.

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Abstract: We report a case of primary intraocular central nervous system (CNS) lymphoma in a patient previously treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections for age-related macular degeneration (AMD). An 88-year-old woman, with past medical history significant for bilateral age-related macular degeneration (AMD) treated with intravitreal ranibizumab injections for 1year, was referred to our department for bilateral vitritis diagnosed 10days after the last anti-VEGF injection. A complete uveitis work-up including aqueous humour analysis, brain MRI and vitreous biopsy enabled us to confirm the diagnosis of primary intraocular CNS lymphoma. To the best of our knowledge, this is the first report of the diagnosis of primary intraocular CNS lymphoma in a patient treated with anti-VEGF for AMD. The differential diagnosis of vitritis in elderly patients is relatively broad. Endophthalmitis and uveitis have been described after anti-VEGF injections. In such a situation, there is actually a risk of missing the diagnosis of intraocular lymphoma in the mistaken belief that the observed vitritis may be a reaction to administered anti-VEGFs. If no direct time-relationship with the anti-VEGF injections can be found, a classic vitritis work-up should be performed. Our observation suggests that ranibizumab, at the dosage used for AMD, does not impede the spread of CNS lymphoma in the eye nor interfere with cytological diagnosis.

PMID: 23306179 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2013 Jan 7. pii: S0181-5512(12)00126-X. doi: 10.1016/j.jfo.2012.04.004. [Epub ahead of print]

[Intravitreal ranibizumab for management of choroidal neovascularization secondary to angioid streaks: A case report.] [Article in French]

Wolff B, Sahel JA, Mateo-Montoya A, Mauget-Faÿsse M, Baillif S, Le Mer Y.

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Abstract: Angioid streaks are biomicroscopically observable manifestations that frequently lead to choroidal neovascularization. Traditional treatments used to include laser photocoagulation or photodynamic therapy. Over the past few years, anti-VEGF therapies have been used as an alternative treatment. The case of a 54-year-old patient who received anti-VEGF therapy (ranibizumab) for the treatment of choroidal neovascularization secondary to angioid streaks is reported. The patient received two injections that led to complete resolution of intraretinal fluid and reduction in lesion size. After 1 year of follow-up, the patient has presented no recurrence. This case illustrates the efficacy of intravitreal anti-VEGF therapy for choroidal neovascularization in angioid streaks. Further prospective studies on a larger number of patients should help establish the best treatment and follow-up strategies.

PMID: 23306178 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2012 Oct;48(10):867-9.

[Optimizing the individual treatment of neovascular age-related macular degeneration]. [Article in Chinese]

Sun XD, Wang FH.

Department of Ophthalmology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200080, China. Email: xdsun@sjtu.edu.cn.

Abstract: Neovascular age-related macular degeneration (AMD) is the major cause of visual impairment in elder people. The progress in biomedicine and the launch of new agents provide hope to the patients with AMD. Factors associated with the response of AMD to treatment have been investigated, including the baseline visual acuity, age, the characteristics of the AMD lesions and the genotype of the patients, etc. Preferred Practice Pattern guidelines are developed in different countries based on these evidences, which provided guidance for the pattern of practice, not for the care of a particular individual. To develop an evidence-based individual treatment strategy for the wet AMD patients, accurate and comprehensive evaluation are critical in initial visit and during the follow-up. Individual treatment strategy will not only benefit the patient with better visual outcome and higher quality of life, but also promote the best health economic efficiency for AMD treatment in our aging society.

PMID: 23302237 [PubMed - in process]

Clin Ter. 2012 Nov;163(6):e413-22.

Testing the effectiveness of intravitreal Ranibizumab during 12 months of follow-up in venous occlusion treatment.

Pacella E, Pacella F, La Torre G, Impallara D, Malarska K, Brillante C, Turchetti P, De Giusti M.

Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Department of Public Health and Infectious Diseases, Faculty of Pharmacy and Medicine, Sapienza University of Rome;

National Institute for Health, Migration and Poverty (INMP/NIHMP), Rome, Italy.

Aims: To determine the effectiveness and safety of treatment of intravitreal Ranibizumab for Central Retinal Vein Occlusion.

Patients and Methods: This non-randomized observational clinical study was comprised of a round of therapy with three IVI. Twenty eyes affected by CRVO were recruited. The average age was 65.06 +/- 15 years and criterion for inclusion: age >18 years, best Corrected Visual Acuity (BCVA) from 5 to 40 letters and macular edema with thickness greater than 275 micrometer. The criteria used for reinjection were: CMT> 150 micrometer, ETDRS <10 letters and LogMAR <0.2. The statistical analysis for continuous variables (ETDRS, logMar and CMT) was conducted calculating median and range (min-max), since these variables, due to sample size, were not normally distributed.Time trends of these variables were plotted with boxplot and differences. Events between T0 and T12 were assessed using the analysis of variance (ANOVA) for repeated measurements and the F test (Pillai's trace). The statistical significance was set at p <=0.05.

Results: All of the patients showed improvement. In fact, the ETDRS went from a median of 20.00 to 28.50, LogMAR went from a median of 0.75 to 0.55 and the values for CMT went from a median of 556.00 micrometer to 390.00 micrometer. The drug reaches maximum effectiveness after two months of therapy, with T2 remaining constant from the third injection at T3 until the end of 12 months at T12.

Conclusions: The results produced by our study indicate that Ranibizumab is a valid treatment for CRVO. Clin Ter 2012; 163(6):e413-422.

PMID: 23306756 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2013 Jan 11. doi: 10.1038/eye.2012.292. [Epub ahead of print]

Optimisation of an automated drusen-quantifying software for the analysis of drusen distribution in patients with age-related macular degeneration.

Ong BB, Lee N, Lee WP, Pearce E, Sivaprasad S, Klaver CC, Smith RT, Chong NV.

Oxford Eye Hospital and the University of Oxford, Oxford, UK.

Purpose: The purpose of this study is to optimise the settings of the Retinal Image Analysis Laboratory (RIALAB), a semi-automatic drusen quantification software, in planning for high-throughput quantification of drusen in clinical studies of age-related macular degeneration (AMD).

Patients and methods: A comparison of five different settings in RIALAB was made on 67 images from the Rotterdam eye study (population-based study) and 56 images from the fellow eye of patients with active neovascular AMD in King's College Hospital, London (hospital-based study).ResultsThe 'Few Outer' setting was the best setting, with it being most appropriate for 52 (77.6%) of the Rotterdam cohort and 47 (83.9%) for the London cohort. Pearson's $\chi(2)$-test revealed both results to be statistically significant (P<0.0001).ConclusionsRIALAB is a viable algorithm and software package that can detect, quantify, and analyse drusen efficiently in both population-based and hospital-based studies. We have shown that the 'Few Outer' drusen setting can be employed as the default setting, with fine-tuning only needed in a minority of cases, thus helping to speed up workflow.Eye advance online publication, 11 January 2013; doi:10.1038/eye.2012.292.

PMID: 23306729 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Jan 3. pii: S0161-6420(12)00966-9. doi: 10.1016/j.ophtha.2012.09.054. [Epub ahead of print]

Optical Coherence Tomography Assessment of Apparent Foveal Swelling in Patients with Foveal Sparing Secondary to Geographic Atrophy.

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OBJECTIVE: To determine whether foveal swelling exists in patients with foveal sparing and geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) and to establish the contribution of different foveal layers to this condition by use of spectral-domain optical coherence tomography (SD-OCT).

DESIGN: Prospective comparative case series.

PARTICIPANTS: We assessed patients from a longitudinal study with foveal sparing and GA secondary to AMD. Of an initial sample of 108 patients, 13 eyes of 10 patients complied with the inclusion criteria to study eyes in which apparent swelling would not be questionable. We used a control group of 13 healthy patients to compare the outcome measurements.

METHODS: We acquired high-resolution SD-OCT horizontal and oblique B-scans centered at the umbo. Two retinal specialists (J.M., F.T.) independently classified the SD-OCT images.

MAIN OUTCOME MEASURES: Difference in foveal center thickness, apparent outer nuclear layer (ONL) thickness, ONL thickness without Henle's fiber layer (HFL), sub-ONL thickness, and retinal thickness at 1000 μm and 3500 μm from the foveal center.

RESULTS: The thickness at the foveal center was similar between patients with apparent foveal swelling (cases) and controls without AMD (226 vs. 227 μm; P = 0.56), but the apparent ONL was thicker in cases than in controls (125 vs. 114 μm; P = 0.02). However, when HFL was excluded from the measurements, there was little difference in the results (74 vs. 73 μm; P = 0.82).

CONCLUSIONS: We found neither foveal nor ONL swelling in this study. We observed HFL thickening in foveal sparing secondary to GA, which might be related to swelling of the axons of the photoreceptors, or Müller's cells. We also observed thinning of the retina below the external limiting membrane. The clinical significance of these findings should be addressed by longitudinal studies and may have specific therapeutic implications.

PMID: 23290986 [PubMed - as supplied by publisher]

Clin Ter. 2012 Nov;163(6):e423-8.

Effectiveness of vision rehabilitation treatment through MP-1 microperimeter in patients with visual loss due to macular disease.

Pacella E, Pacella F, Mazzeo F, Turchetti P, Carlesimo SC, Cerutti F, Lenzi T, De Paolis G, Giorgi D.

Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome; National Institute for Health, Migration and Poverty (INMP/NIHMP), Rome, Italy.

Purpose: To evaluate the effectiveness of biofeedback treatment for low-vision rehabilitation in patients affected by macular disease.

Materials and Methods: 171 eyes of 99 patients (42 female and 57 male) between 50 to 75 years old (mean age: 64.6) were included in this study. All patients were suffering from age-related macular degeneration

(AMD) (122 eyes) or macular myopic degeneration (MMD) (49 eyes). All patients underwent an assessment of examinations including visual acuity, reading speed test, slit lamp examination and tonometry, ophthalmoscopic fundus examination, microperimetry, fixation test, retinal sensitivity, fluorangiography (FAG), optical coherence tomography (OCT). The treatment was divided in 16 sessions, the patients underwent other examination assessment at 6 and 12 months, except for FAG and OCT. Statistical analysis was performed using Student's t-test, and p-value <=0.05 was considered statistically significant.

Results: After training 130 eyes of 171 in the study group (76.02%) had a statistically significant improvement of the distant visual acuity (p<0.01): 38 eyes suffering from MMD and 92 eyes suffering from AMD. After 12 months of follow-up a group of 25 eyes of 130 (19.23%) had a loss of benefits that were observed at the end of the treatment sessions: 16 eyes and 9 eyes were suffering from MMD and AMD respectively. Examination assessment during follow-up showed that 4 eyes and 2 eyes of the group that lost benefits had a worsening of MMD and AMD primary disease respectively.

Conclusions: It is not yet understood how biofeedback produces amelioration of visual function. According to the 'Eccentric fixation' theory, with biofeedback rehabilitation patients are trained to use the non-damaged retina areas to develop a new preferred retinal locus. In our study group we found a significant improvement in both visual acuity and fixation.

PMID: 23306757 [PubMed - in process]

Pathogenesis

Br J Ophthalmol. 2013 Jan 3. [Epub ahead of print]

3,4 dihydroxyphenyl ethanol reduces secretion of angiogenin in human retinal pigment epithelial cells.

Granner T, Maloney S, Antecka E, Correa JA, Burnier MN Jr.

McGill University, Montreal, Quebec, Canada.

BACKGROUND: Age-related macular degeneration (AMD) is currently the leading cause of blindness in developed countries. Bevacizumab is a widely used anti-VEGF agent that is a commonly applied therapy for neovascular AMD; however, a consequence of bevacizumab therapy may be the activation of compensatory angiogenic signalling. Combination of bevacizumab with 3,4 dihydroxyphenyl ethanol (DPE) may attenuate this compensatory signalling. The goal of the study was to investigate this therapeutic option in a human retinal pigment epithelial cell line (ARPE-19).

METHODS: ARPE-19 cells were incubated under both normoxic and hypoxic conditions. The cells were treated as follows: control, 100 μM DPE, 0.25 mg/ml bevacizumab, the combination of DPE and bevacizumab. Media was harvested after 24 h for sandwich ELISA-based angiogenesis assays. The secretion of the following 10 pro-angiogenic cytokines was measured: angiogenin, ANG2, EGF, bFGF, HB-EGF, PDGF-BB, Leptin, PIGF, HGF, and VEGF-A.

RESULTS: Treatment of ARPE-19 cells with bevacizumab significantly increased the secretion of angiogenin. Secretion of angiogenin and VEGF-A were significantly reduced following treatment with DPE under both normoxia and hypoxia. In addition, angiogenin secretion was significantly reduced following treatment with the combination of DPE and bevacizumab compared to bevacizumab alone.

CONCLUSIONS: Compensatory angiogenic signalling may occur in neovascular AMD following treatment with bevacizumab. Here we show that DPE, both alone and in combination with bevacizumab, can reduce the secretion of angiogenin, a cytokine that has been upregulated following treatment with bevacizumab in RPE cells. Therefore, DPE may represent a possible therapeutic agent to be used in combination with

bevacizumab for the treatment of neovascular AMD.

PMID: 23292926 [PubMed - as supplied by publisher]

PLoS One. 2013;8(1):e53338. doi: 10.1371/journal.pone.0053338. Epub 2013 Jan 8.

Dynamic Increase in Extracellular ATP Accelerates Photoreceptor Cell Apoptosis via Ligation of P2RX7 in Subretinal Hemorrhage.

Notomi S, Hisatomi T, Murakami Y, Terasaki H, Sonoda S, Asato R, Takeda A, Ikeda Y, Enaida H, Sakamoto T, Ishibashi T.

Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Abstract: Photoreceptor degeneration is the most critical cause of visual impairment in age-related macular degeneration (AMD). In neovascular form of AMD, severe photoreceptor loss develops with subretinal hemorrhage due to choroidal neovascularization (CNV), growth of abnormal blood vessels from choroidal circulation. However, the detailed mechanisms of this process remain elusive. Here we demonstrate that neovascular AMD with subretinal hemorrhage accompanies a significant increase in extracellular ATP, and that extracellular ATP initiates neurodegenerative processes through specific ligation of Purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7; P2X7 receptor). Increased extracellular ATP levels were found in the vitreous samples of AMD patients with subretinal hemorrhage compared to control vitreous samples. Extravascular blood induced a massive release of ATP and photoreceptor cell apoptosis in co-culture with primary retinal cells. Photoreceptor cell apoptosis accompanied mitochondrial apoptotic pathways, namely activation of caspase-9 and translocation of apoptosis-inducing factor (AIF) from mitochondria to nuclei, as well as TUNEL-detectable DNA fragmentation. These hallmarks of photoreceptor cell apoptosis were prevented by brilliant blue G (BBG), a selective P2RX7 antagonist, which is an approved adjuvant in ocular surgery. Finally, in a mouse model of subretinal hemorrhage, photoreceptor cells degenerated through BBG -inhibitable apoptosis, suggesting that ligation of P2RX7 by extracellular ATP may accelerate photoreceptor cell apoptosis in AMD with subretinal hemorrhage. Our results indicate a novel mechanism that could involve neuronal cell death not only in AMD but also in hemorrhagic disorders in the CNS and encourage the potential application of BBG as a neuroprotective therapy.

PMID: 23308196 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2012 Oct;48(10):865-6.

[Development of strategy for study of pathogenesis of age-related macular degeneration]. [Article in Chinese]

Li XX, Huang LZ.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible severe vision loss among people over the age of 50 and a major cause of blindness among people aged over 65 in developed countries. With the improvement of China's economic levels and entering the aging society with an acceleration speed, the growing number of AMD patients has become an increasing concern of the whole society. The etiology and pathogenesis of AMD are still not clear and this is a hot spot for ophthalmic research around the world. Currently thoughts that environment factors and genes, oxidative damage, inflammation, immune reaction, imbalance between angiogenesis factors and anti-angiogenesis factors, etc. are all involved in the occurrence and development of AMD. However, how to explore the pathogenesis of AMD in Chinese population from the complex reported literature deserved attention. The authors

suppose that we should start from analysis of controversy and find a breakthrough in the dispute, to explore the pathogenesis of AMD in Chinese population.

PMID: 23302236 [PubMed - in process]

Epidemiology

Stat Med. 2013 Jan 7. doi: 10.1002/sim.5721. [Epub ahead of print]

Interval-censored parametric regression survival models and the analysis of longitudinal trials.

Mackenzie G, Peng D.

ENSAI, Rennes, France; The Centre for Biostatistics, Department of Mathematics and Statistics, University of Limerick, Limerick, Ireland.

Abstract: This paper develops interval censoring likelihood methods in the context of parametric proportional hazard (PH) and non-PH regression models in the longitudinal study setting to reanalyze the medical research council's randomized controlled trial of teletherapy in age-related macular degeneration. We compare the performance of the interval censoring likelihood with proxy likelihoods that were used to analyze the original data. It is shown, analytically, that the use of such proxy likelihoods in selected PH models leads to biased estimators. Such estimators are artificially precise; further, the magnitude of their percentage bias is quantified in a data-directed simulation study. For non-PH models, we demonstrate that these results obtained from PH models do not hold uniformly and explain the implications of this finding for the reanalysis of proxy likelihood trial data. Our final analysis, of the age-related macular degeneration trial data, based on fitting PH and non-PH models, reassuringly confirms the published findings from the original trial.

PMID: 23297174 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Jan 9. [Epub ahead of print]

[Cost of illness of age-related macular degeneration : Systematic review on the development of a costs diary.] [Article in German]

Gibbert J, Müller D, Fauser S, Stock S.

Institut für Gesundheitsökonomie und klinische Epidemiologie (IGKE), Uniklinik Köln, Gleueler Str. 176-178, 50935, Köln, Deutschland, judith.gibbert@googlemail.com.

Abstract: Due to demographic changes in the German population a significant rise in incident cases of age-related macular degeneration (AMD) is to be expected in the coming years. Also the corresponding increase in costs of the illness requires appropriate survey instruments to allow accurate estimations of costs. The cost diary for patients with AMD developed in this study is based on a previously established systematic review. The seven studies that were included were evaluated regarding their quality in order to then extract the listed cost items. The result is a prospective survey instrument with six different cost sectors of AMD.

PMID: 23297119 [PubMed - as supplied by publisher]

Retina. 2013 Jan 4. [Epub ahead of print]

COSTS OF NEWLY DIAGNOSED NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

AMONG MEDICARE BENEFICIARIES, 2004-2008.

Qualls LG, Hammill BG, Wang F, Lad EM, Schulman KA, Cousins SW, Curtis LH.

*Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina †Global Health Outcomes, GlaxoSmithKline, Inc, Philadelphia, Pennsylvania Departments of‡Ophthalmology §Medicine, Duke University School of Medicine, Durham, North Carolina.

PURPOSE: To examine associations between newly diagnosed neovascular age-related macular degeneration and direct medical costs.

METHODS: This retrospective observational study matched 23,133 Medicare beneficiaries diagnosed with neovascular age-related macular degeneration between 2004 and 2008 with a control group of 92,532 beneficiaries on the basis of age, sex, and race. The index date for each case-control set corresponded to the first diagnosis for the case. Main outcome measures were total costs per patient and age-related macular degeneration-related costs per case 1 year before and after the index date.

RESULTS: Mean cost per case in the year after diagnosis was $12,422, $4,884 higher than the year before diagnosis. Postindex costs were 41% higher for cases than controls after adjustment for preindex costs and comorbid conditions. Age-related macular degeneration-related costs represented 27% of total costs among cases in the postindex period and were 50% higher for patients diagnosed in 2008 than in 2004. This increase was attributable primarily to the introduction of intravitreous injections of vascular endothelial growth factor antagonists. Intravitreous injections averaged $203 for patients diagnosed in 2004 and $2,749 for patients diagnosed in 2008.

CONCLUSION: Newly diagnosed neovascular age-related macular degeneration was associated with a substantial increase in total medical costs. Costs increased over time, reflecting growing use of anti-vascular endothelial growth factor therapies.

PMID: 23296047 [PubMed - as supplied by publisher]

Genetics

Ophthalmic Res. 2013 Jan 10;49(4):177-184. [Epub ahead of print]

Y402H Polymorphism in Complement Factor H and Age-Related Macular Degeneration in the Tunisian Population.

Habibi I, Sfar I, Kort F, Aounallah-Skhiri H, Chebil A, Chouchene I, Bouraoui R, Limaiem R, Largheche L, Jendoubi-Ayed S, Makhlouf M, Ben Abdallah T, Ayed K, El Matri L, Gorgi Y.

Immunology Research Laboratory of Kidney Transplantation and Immunopathology (LR03SP01), University of Tunis El Manar, Charles Nicolle Hospital, Tunis, Tunisia.

Abstract: To evaluate a possible association between the complement factor H (CFH) Y402H polymorphism and susceptibility to age-related macular degeneration (AMD) in the Tunisian population, as well as the impact of the genotype distribution among different phenotypes and the response to treatment with intravitreal bevacizumab, exon 9 of CFH was analyzed for the Y402H polymorphism by direct sequencing in 135 healthy controls and 127 sporadic unrelated AMD patients classified into the following groups: 12 atrophic AMD (group G1), 115 exudative AMD (G2) and 10 AMD patients who had fibrovascular scarring (G3) that did not allow a precise grading of the phenotype. Seventy patients in G2 were treated with 1.25 mg intravitreal bevacizumab at 6-week intervals until choroidal neovascularization (CNV) was no longer active. The frequency of the CFH 402H allele was significantly higher in AMD patients than in controls ($p = 2.62 \times 10(-16)$). However, subgroup analysis does not reveal any association between the variant allele H and phenotypes of AMD or CNV. Also, there was no significant difference in response to bevacizumab treatment according to Y402H CFH genotype ($p = 0.59$). A strong association of the 402H allele with

susceptibility to AMD in the Tunisian population was confirmed; however, this variant does not appear to be involved in the clinical progression of this disease or in the postintravitreal bevacizumab response.

PMID: 23306536 [PubMed - as supplied by publisher]

FASEB J. 2013 Jan 9. [Epub ahead of print]

A rare functional haplotype of the P2RX4 and P2RX7 genes leads to loss of innate phagocytosis and confers increased risk of age-related macular degeneration.

Gu BJ, Baird PN, Vessey KA, Skarratt KK, Fletcher EL, Fuller SJ, Richardson AJ, Guymer RH, Wiley JS.

*Florey Institute of Neuroscience and Mental Health and †Department of Anatomy and Neuroscience, University of Melbourne, Parkville, Victoria, Australia;

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in Western countries and is diagnosed by the clinical appearance of yellow subretinal deposits called drusen. Genetic changes in immune components are clearly implicated in the pathology of this disease. We have previously shown that the purinergic receptor P2X7 can act as a scavenger receptor, mediating phagocytosis of apoptotic cells and insoluble debris. We performed a genetic association study of functional polymorphisms in the P2RX7 and P2RX4 genes in a cohort of 744 patients with AMD and 557 age-matched Caucasian control subjects. The P2X4 Tyr315Cys variant was 2-fold more frequent in patients with AMD compared to control subjects, with the minor allele predicting susceptibility to disease. Pairwise linkage disequilibrium was observed between Tyr315Cys in the P2RX4 gene and Gly150Arg in the P2RX7 gene, and these two minor alleles formed a rare haplotype that was overrepresented in patients with AMD (n=17) compared with control subjects (n=3) (odds ratio 4.05, P=0.026). Expression of P2X7 (wild type or variant 150Arg) in HEK293 cells conferred robust phagocytosis toward latex beads, whereas coexpression of the P2X7 150Arg with P2X4 315Cys variants almost completely inhibited phagocytic capacity. Fresh human monocytes harboring this heterozygous 150Arg-315Cys haplotype showed 40% reduction in bead phagocytosis. In the primate eye, immunohistochemistry indicated that P2X7 and P2X4 receptors were coexpressed on microglia and macrophages, but neither receptor was seen on retinal pigment epithelial cells. These results demonstrate that a haplotype including two rare variants in P2RX7 and P2RX4 confers a functional interaction between these two variant receptors that impairs the normal scavenger function of macrophages and microglia. Failure of this P2X7-mediated phagocytic pathway may impair removal of subretinal deposits and predispose individuals toward AMD.-Gu, B. J., Baird, P. N., Vessey, K. A., Skarratt, K. K., Fletcher, E. L., Fuller, S. J., Richardson, A. J., Guymer, R. H., Wiley, J. S. A rare functional haplotype of the P2RX4 and P2RX7 genes leads to loss of innate phagocytosis and confers increased risk of age related macular degeneration.

PMID: 23303206 [PubMed - as supplied by publisher]

BMC Med Genet. 2013 Jan 9;14(1):4. [Epub ahead of print]

Mitochondrial DNA haplogroups confer differences in risk for age-related macular degeneration: a case control study.

Kenney MC, Hertzog D, Chak G, Atilano SR, Khatibi N, Soe K, Nobe A, Yang E, Chwa M, Zhu F, Memarzadeh M, King J, Langberg J, Small K, Nesburn AB, Boyer DS, Udar N.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of vision loss in elderly, Caucasian populations. There is strong evidence that mitochondrial dysfunction and oxidative stress play a role in the cell death found in AMD retinas. The purpose of this study was to examine the association of the Caucasian mitochondrial JTU haplogroup cluster with AMD. We also assessed for gender bias and additive risk with known high risk nuclear gene SNPs, ARMS2/LOC387715 (G > T; Ala69Ser, rs10490924) and CFH

(T > C; Try402His, rs1061170).

METHODS: Total DNA was isolated from 162 AMD subjects and 164 age-matched control subjects located in Los Angeles, California, USA. Polymerase chain reaction (PCR) and restriction enzyme digestion were used to identify the J, U, T, and H mitochondrial haplogroups and the ARMS2-rs10490924 and CFH-rs1061170 SNPs. PCR amplified products were sequenced to verify the nucleotide substitutions for the haplogroups and ARMS2 gene.

RESULTS: The JTU haplogroup cluster occurred in 34% (55/162) of AMD subjects versus 15% (24/164) of normal (OR = 2.99; p = 0.0001). This association was slightly greater in males (OR = 3.98, p = 0.005) than the female population (OR = 3.02, p = 0.001). Assuming a dominant effect, the risk alleles for the ARMS2 (rs10490924; p = 0.00001) and CFH (rs1061170; p = 0.027) SNPs were significantly associated with total AMD populations. We found there was no additive risk for the ARMS2 (rs10490924) or CFH (rs1061170) SNPs on the JTU haplogroup background.

CONCLUSIONS: There is a strong association of the JTU haplogroup cluster with AMD. In our Southern California population, the ARMS2 (rs10490924) and CFH (rs1061170) genes were significantly but independently associated with AMD. SNPs defining the JTU mitochondrial haplogroup cluster may change the retinal bioenergetics and play a significant role in the pathogenesis of AMD.

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Gene-Gene Interactions of CFH and LOC387715/ARMS2 with Korean Exudative Age-related Macular Degeneration Patients.

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Abstract Purpose: To evaluate the association and interaction of single nucleotide polymorphisms in CFH and LOC387715/ARMS2 with age-related macular degeneration (AMD) in a Korean population.

Methods: A total of 114 exudative AMD patients and 240 normal subjects participated in the study. PCR and direct sequencing were used to screen SNPs in the CFH and in the LOC387715/ARMS2. Genotype and haplotype analyses were performed. Two-locus gene-gene interactions were evaluated by the data mining approach multifactor-dimensionality reduction method.

Results: The *C/*T genotype frequency of rs1061170 in CFH showed a significant difference (OR = 1.79). Genotype and allele frequencies of rs551397 (*C/*C, OR = 2.84; *C, OR = 1.67) and rs800292 (*G/*G, OR = 2.198; *G, OR = 1.676) in CFH, and rs10490924 (T/*T, OR = 12.45; *T, OR = 4.45) and rs2736911 (*C/*C, OR = 3.21; *C, OR = 2.71) in LOC387715/ARMS2 were significantly higher in patients. In the haplotype analysis, C-T of rs2736911-rs10490924 in LOC387715/ARMS2 (OR = 4.85) and C-G of rs551397-rs800292 in CFH (OR = 2.22) predisposed significantly to AMD. After cross-validation consistency (CVC) and permutation tests, we identified the 1 marker model (rs10490924), which has a prediction accuracy of 73.5%, and the two locus model, rs10490924_ rs800292, with 75.3% balanced accuracy in predicting AMD disease risk.

Conclusions: Korean individuals with the LOC387715/ARMS2 rs10490924, and to a lesser extent, CFH rs800292 variants might be at a greater risk for the development of exudative AMD. Furthermore, the risk of exudative AMD may increase significantly if these variants are both present in the two genes.

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Genetic studies of complex human diseases: Characterizing SNP-disease associations using Bayesian networks.

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BACKGROUND: Detecting epistatic interactions plays a significant role in improving pathogenesis, prevention, diagnosis, and treatment of complex human diseases. Applying machine learning or statistical methods to epistatic interaction detection will encounter some common problems, e.g., very limited number of samples, an extremely high search space, a large number of false positives, and ways to measure the association between disease markers and the phenotype.

RESULTS: To address the problems of computational methods in epistatic interaction detection, we propose a score-based Bayesian network structure learning method, EpiBN, to detect epistatic interactions. We apply the proposed method to both simulated datasets and three real disease datasets. Experimental results on simulation data show that our method outperforms some other commonly-used methods in terms of power and sample-efficiency, and is especially suitable for detecting epistatic interactions with weak or no marginal effects. Furthermore, our method is scalable to real disease data.

CONCLUSIONS: We propose a Bayesian network-based method, EpiBN, to detect epistatic interactions. In EpiBN, we develop a new scoring function, which can reflect higher-order epistatic interactions by estimating the model complexity from data, and apply a fast Branch-and-Bound algorithm to learn the structure of a two-layer Bayesian network containing only one target node. To make our method scalable to real data, we propose the use of a Markov chain Monte Carlo (MCMC) method to perform the screening process. Applications of the proposed method to some real GWAS (genome-wide association studies) datasets may provide helpful insights into understanding the genetic basis of Age-related Macular Degeneration, late-onset Alzheimer's disease, and autism.

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