Macular Degeneration Foundation™
Our focus is your vision

MD Research News

Issue 41

Tuesday August 9, 2011

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”.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with ‘Subscribe to MD Research News’ in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your ‘unsubscribe’ request.

Drug treatment

Retina. 2011 Jul 30. [Epub ahead of print]

THREE-YEAR SAFETY AND VISUAL ACUITY RESULTS OF EPIMACULAR 90STRONTIUM/90YTTRIUM BRACHYTHERAPY WITH BEVACIZUMAB FOR THE TREATMENT OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Avila MP, Farah ME, Santos A, Carla L, Fuji G, Rossi J, Nau J.

From the *CBCO, Federal University of Goiana, Goiana, Brazil; †Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil; ‡Center for Medical and Surgical Retina, Medical Center Puerta de Hierro, Guadalajara, Jalisco, Mexico; §NeoVista, Inc, Newark, California.

PURPOSE: To evaluate the long-term safety and visual acuity outcomes associated with epimacular strontium 90 brachytherapy combined with intravitreal bevacizumab for the treatment of subfoveal choroidal neovascularization because of age-related macular degeneration.

METHODS: Thirty-four treatment-naive patients with predominantly classic, minimally classic, and occult subfoveal choroidal neovascularization lesions participated in this prospective, 2-year, nonrandomized multicenter study. Subjects from 1 center (n = 19) were reconsented and followed-up for 3 years. Each subject received a single 24-Gy beta irradiation treatment via an intraocular delivery device and 2 planned injections of bevacizumab at treatment and 1 month later. Additional bevacizumab therapy was permitted based on prespecified retreatment criteria. Adverse events were observed, and best-corrected visual acuity was measured using Early Treatment Diabetic Retinopathy Study vision charts. Subjects were evaluated every 3 months during the first year of follow-up and every 6 months during Years 2 and 3 of follow-up.

RESULTS: All 34 subjects were followed-up for 24 months and 19 were followed-up through 36 months. With up to 24 months of follow-up, 12 of 24 phakic patients (50%) exhibited ≥2 grades of progression in Lens Opacification Classification System (LOCS) II lens classification; 5 eyes underwent cataract extraction before the Month 36 visit. There was 1 case of nonproliferative retinopathy identified at 36 months of follow-up that did not have an adverse effect on visual acuity, was stable at 43 months of follow-up, and was isolated to the parafoveal region. Mean best-corrected visual acuity demonstrated an average gain of +15.0 and -4.9 letters at 12 months and 24 months, respectively; the drop in mean gain at Month 24 was largely attributable to cataract formation. At 36 months (n = 19), the mean best-corrected visual acuity was +3.9, 90% (17 of 19) of eyes had lost <15 letters from baseline, 53% (10 of 19) had gained ≥1 letter, and 21% (4 of 19) had gained ≥15 letters. Through 36 months, 11 eyes required additional bevacizumab retreatment therapy and received a mean of 3.0 injections (range, 2-7 injections).

CONCLUSION: Epimacular brachytherapy shows promise as a therapeutic option for subfoveal neovascular age-related macular degeneration. The procedure was safe and well tolerated, with a reasonable risk-benefit profile that warrants further study in larger subject populations. The most common adverse event was cataract progression/formation. Surgical complications are similar to those expected from standard vitrectomy trials. This novel device is currently being evaluated in two prospective, randomized, controlled trials in treatment-naive subjects (CABERNET) and in subjects already treated with anti-vascular endothelial growth factor therapy (MERLOT).

PMID:21817963[PubMed - as supplied by publisher]

Acta Ophthalmol. 2011 Jul 29. doi: 10.1111/j.1755-3768.2011.02209.x. [Epub ahead of print]

Retinal blood flow in response to an intravitreal injection of ranibizumab for neovascular age-related macular degeneration.

Micieli JA, Tsui E, Lam WC, Brent MH, Devenyi RG, Hudson C.

Retina Research Group, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada School of Optometry, University of Waterloo, Waterloo, Ontario, Canada.

Purpose: To assess the hemodynamic response of retinal arterioles and venules following a single intravitreal injection of ranibizumab in neovascular age-related macular degeneration (NV-AMD) patients and to assess the influence of the number of prior injections on this response.

Methods: Fifteen NV-AMD patients were prospectively recruited and grouped according to the dosage of ranibizumab previously received. Group 1 NV-AMD patients (n = 7) had previously received 1.50 mg or less, and group 2 patients (n = 8) had received more than 1.50 mg in the study eye. A group of 12 non-NV AMD patients were also recruited for control comparison. Vessel diameter, centreline blood velocity and blood flow were assessed with the Canon Laser Blood Flowmeter immediately prior to an injection and at a mean follow-up of 37.7 and 36.7 days for group 1 and group 2 patients, respectively.

Results: The NV-AMD patients as a whole and the group 1 cohort had a significantly greater arteriolar diameter at baseline than the non-NV AMD patients. There was a significant reduction in arteriolar diameter, velocity and blood flow in group 1 but not in group 2 NV-AMD patients at follow-up. There was only an insignificant decrease in measured parameters of the retinal venules. At follow-up, there was no difference in the diameter, velocity or flow between AMD patients.

Conclusion: Intravitreal ranibizumab treatment for NV-AMD induces a reduction in arteriolar diameter, velocity, and blood flow in patients who have received <1.50 mg of ranibizumab.

PMID:21801339[PubMed - as supplied by publisher]

Retina. 2011 Jul 30. [Epub ahead of print]

A SYSTEMATIC REVIEW OF THE ADVERSE EVENTS OF INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS.

Van der Reis MI, La Heij EC, Jong-Hesse YD, Ringens PJ, Hendrikse F, Schouten JS.

From the *Department of Ophthalmology, University Eye Clinic Maastricht, Maastricht, the Netherlands; and †Department of Ophthalmology, VU University Medical Centre, Amsterdam, the Netherlands.

BACKGROUND: Intravitreal ranibizumab and pegaptanib are registered for neovascular age-related macular degeneration. No formal safety study has been conducted for intravitreal bevacizumab. These anti-vascular endothelial growth factor (anti-VEGF) drugs are being used on a large scale in daily practice for

different ocular diseases. The objective of the present study was to systematically assess and compare the incidences of adverse events of anti-VEGFs.

METHODS: A systematic search was conducted in April 2009 with no date restrictions in PubMed, Embase, Toxline, and the Cochrane library. We used the terms pegaptanib, bevacizumab, ranibizumab, intravitreal, and specific and general terms for adverse events. Studies describing adverse events after anti-VEGF injections and the official safety data were included.

RESULTS: Two hundred and seventy-eight articles were included, and the incidences of adverse events were calculated separately for effect, safety, and specific side effect studies. The incidences of serious ocular and nonocular adverse events were approximately below 1 per 100 injections for intravitreal bevacizumab, intravitreal ranibizumab, and intravitreal pegaptanib. Most mild ocular adverse events were below 5 per 100 injections.

CONCLUSION: The reported rates of serious adverse events were low after anti-VEGF injections. There is no sufficient evidence to conclude that there is a difference in incidences between the anti-VEGFs.

PMID:21817960[PubMed - as supplied by publisher]

Retina. 2011 Jul 30. [Epub ahead of print]

Intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularization secondary to ocular histoplasmosis syndrome.

Nielsen JS, Fick TA, Saggau DD, Barnes CH.

From the *Wolfe Eye Clinic, West Des Moines, Iowa; and †Wolfe Eye Clinic, Cedar Rapids, Iowa.

BACKGROUND: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is beneficial in treating choroidal neovascularization from age-related macular degeneration, but few long-term studies have shown its efficacy in choroidal neovascularization from ocular histoplasmosis syndrome. Intravitreal anti-VEGF therapy may be effective in cases of choroidal neovascularization because of ocular histoplasmosis syndrome.

METHODS: Retrospective chart review of 54 eyes treated with intravitreal anti-VEGF therapy for choroidal neovascularization in ocular histoplasmosis syndrome with >1 year of follow-up after initiation of anti-VEGF treatment was performed. Previous treatment and demographic information were recorded. Visual acuity was recorded for each injection treatment and at the last follow-up visit. The anti-VEGF agent was recorded for each injection treatment. Visual acuity was recorded at the last follow-up visit.

RESULTS: Mean visual acuity improved from 20/53 to 20/26 over an average of 26.8 months. Either bevacizumab or ranibizumab were administered on an average of 4.5 injections per patient per year of follow-up. Vision loss was seen in only three eyes with loss limited to a single line of vision. Patients experienced no serious complications from treatment.

CONCLUSION: Long-term intravitreal anti-VEGF therapy with bevacizumab or ranibizumab is beneficial in treatment of choroidal neovascularization in ocular histoplasmosis syndrome.

PMID:21817958[PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2011 Aug;27(4):401-5.

Bilateral intravitreal bevacizumab injection for exudative age-related macular degeneration: effect of baseline visual acuity.

Jonas JB, Tao Y, Rensch F.

Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University , Heidelberg, Germany .

Abstract Purpose: To assess side differences in patients undergoing bilateral intravitreal bevacizumab injections as treatment of exudative age-related macular degeneration (AMD).

Methods: The clinical interventional case series study included 48 patients (96 eyes) who consecutively and bilaterally received 3 intravitreal bevacizumab injections. The mean age was 76.5±7.5 years (range: 59-88 years). Follow-up was 6 months. Main outcome parameters were best-corrected visual acuity (BCVA) and measurements by optic coherence tomography. The eyes of the same patient were assigned to a study group 1 for the eye with the higher visual acuity at baseline, and study group 2 for the contralateral eye with the lower visual acuity at baseline.

Results: The increase in BCVA was significantly (P=0.02) greater in group 2 (0.07±0.25 logarithm of the minimum angle of resolution, LogMAR) than in group 1 (0.05±0.29 LogMAR). The height of a detached retinal pigment epithelium, the height of subretinal fluid, and the tissue thickness of the macula decreased significantly (P<0.05) in group 2 during follow-up, whereas these parameters did not markedly change in the eyes of group 1 (P=0.96, P=0.38, and P=0.07, respectively). The reduction in the height of a detached retinal pigment epithelium and in the height of subretinal fluid was significantly more pronounced in group 2 than in group 1 (P=0.03, P=0.04, respectively).

Conclusions: After an initial set of 3 bilateral bevacizumab injections, patients with bilateral exudative AMD have a higher likelihood for an improvement in vision in the worse-seeing eye at baseline than in the better-seeing eye.

PMID:21810019[PubMed - in process]

Ophthalmologica. 2011 Jul 29. [Epub ahead of print]

Evaluation of the Incidence of Endophthalmitis after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor.

Inoue M, Kobayakawa S, Sotozono C, Komori H, Tanaka K, Suda Y, Matsushima H, Kinoshita S, Senoo T, Tochikubo T, Kadonosono K.

Department of Ophthalmology, Yokohama City University Medical Center, Yokohama, Japan.

Aims: To report the incidence of infectious and noninfectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor (VEGF) from a multicenter clinical trial in Japan.

Methods: A retrospective multicenter review of the data of patients who received intravitreal anti-VEGF injections between January 2007 and March 2011 was undertaken. Cases with the clinical diagnosis of endophthalmitis resulting from intravitreal injection were identified and reviewed.

Results: A total of 5,236 intravitreal anti-VEGF injections (1,209 intravitreal injections of bevacizumab, 3,827 injections of ranibizumab, and 200 injections of pegaptanib sodium) had been administered. Five patients (0.095%), all of whom had received bevacizumab, were diagnosed as having endophthalmitis after the intravitreal injection. All patients visited the institutes for re-examination within 1-2 days after the injection. Among the 5 patients, 2 (0.038%) were culture positive for Streptococcus oralis and Enterococcus faecalis, respectively. The remaining 3 eyes (0.057%) developed presumed noninfectious endophthalmitis.

Conclusion: Although endophthalmitis is a rare complication associated with intravitreal injection, in this series intravitreal anti-VEGF injection caused infectious or noninfectious endophthalmitis at a relatively high frequency. Further investigations are needed to consider an appropriate injection protocol for minimizing

the incidence rates of endophthalmitis, and to assess the optimal treatment protocol for intravitreal injection-related endophthalmitis although it was difficult to differentiate these two entities.

PMID:21811052[PubMed - as supplied by publisher]

Hum Gene Ther. 2011 Jul 29. [Epub ahead of print]

Persistent Suppression of Ocular Neovascularization with Intravitreal Administration of AAVrh.10 Coding for Bevacizumab.

Crystal R, Mao Y, Kiss S, Hackett N, Qiu J, Carbone A, Mezey J, Kaminsky S, D'Amico D.

Weill Medical College of Cornell University, Genetic Medicine, 1300York Avenue, Box 96, New York, New York, United States, 10021, (646) 962-4591, (646) 962-0220; geneticmedicine@med.cornell.edu.

Abstract

Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of neovascular age-related macular degeneration (AMD) and diabetic retinopathy (DR). Bevacizumab, an anti-VEGF monoclonal, is efficacious for these disorders, but requires monthly intravitreal administration, with associated discomfort, cost and adverse event risk. We hypothesized that a single intravitreal administration of adeno-associated virus (AAV) vector expressing bevacizumab would result in persistent eye expression of bevacizumab and suppress VEGF-induced retinal neovascularization. We constructed an AAV rhesus serotype rh.10 vector to deliver bevacizumab (AAVrh.10BevMab) and assessed its ability to suppress neovascularization in transgenic mice overexpressing human VEGF165 in photoreceptors. Intravitreal AAVrh.10BevMab directed long-term bevacizumab expression in the retinal pigmented epithelium. Treated homozygous mice had reduced levels of neovascularization, with 90 ± 4% reduction 168 days following treatment. Thus, a single administration of AAVrh.10BevMab provides long term suppression of neovascularization without the costs and risks associated with the multiple administrations required for the current conventional bevacizumab monoclonal drug delivery.

PMID:21801028[PubMed - as supplied by publisher]

N Engl J Med. 2011 Jul 28;365(4):378-9; author reply 379.

Counterfeit bevacizumab and endophthalmitis.

Sun X, Xu X, Zhang X.

Comment on

N Engl J Med. 2011 Feb 10;364(6):582.

PMID:21793759[PubMed - indexed for MEDLINE]

Ophthalmology. 2011 Aug;118(8):1693-4.

Ranibizumab for Age-related Macular Degeneration.

Seider MI, Stewart JM.

San Francisco, California.

PMID:21813100[PubMed - in process]

Publication Types Letter

Other treatment & diagnosis

J Cataract Refract Surg. 2011 Jul 29. [Epub ahead of print]

Atypical case of ocular hemosiderosis: Leopard cataract.

Masket S, Ceran BB.

From a private practice (Masket, Ceran), Century City, and the David Geffen School of Medicine (Masket), University of California, Los Angeles, California, USA.

Abstract

We present an interventional case report of an 83-year-old woman who developed ocular hemosiderosis secondary to massive retinal and intravitreal bleeding associated with a choroidal neovascular membrane as a result of age-related macular degeneration. Anterior segment manifestations included low-grade inflammation, posterior synechiae, reversible hyperchromic heterochromia, and a mature cataract with "leopard spots." The longstanding vitreous hemorrhage was thought to be the etiology of these findings. At the request of the vitreoretinal surgeon, cataract surgery was performed to provide visualization of the posterior segment. However, the patient's visual potential was limited by her underlying retinal pathology.

PMID:21803538[PubMed - as supplied by publisher]

Retina. 2011 Jul 30. [Epub ahead of print]

VITREOUS HEMORRHAGE COMPLICATING INTRAVITREAL TISSUE PLASMINOGEN ACTIVATOR AND PNEUMATIC DISPLACEMENT OF SUBMACULAR HEMORRHAGE.

Wu TT, Kung YH, Hong MC.

From the Department of Ophthalmology, Kaohsiung Veterans General Hospital, Kaohsiung; and National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China.

PURPOSE: To evaluate the clinical factors associated with vitreous hemorrhage (VH) complicating intravitreal tissue plasminogen activator and pneumatic displacement of submacular hemorrhage, and analyze visual outcomes.

METHODS: In this retrospective, comparative study, 120 consecutive eyes underwent intravitreal tissue plasminogen activator (50 μg) and perfluoropropane (0.3 mL) injection for submacular hemorrhage secondary to different causes. We recorded their demographic data, visual acuity, complications, and further treatment after VH. Two groups created according to the occurrence of VH were compared to identify possible risk factors.

RESULTS: Breakthrough VH occurred in 18 eyes (15%). The size of submacular hemorrhage was significantly positively related to the occurrence of VH (P for trend <0.001). Among etiology, idiopathic polypoidal choroidal vasculopathy (IPCV) was associated with a significantly higher incidence of VH (odds ratio, 15.63; 95% confidence interval, 2.30-106.15; P = 0.005). Age-related macular degeneration was much less likely than other causes to result in VH (odds ratio, 0.121; 95% confidence interval, 0.023-0.642; P = 0.013). Best and final visual acuity improved significantly from initial visual acuity in both groups (P < 0.05).

CONCLUSION: A large area of submacular hemorrhage (≥10 disk areas) and IPCV were risk factors for VH after injection. The occurrence of VH did not affect final visual outcome.

PMID:21817964[PubMed - as supplied by publisher]

Can J Ophthalmol. 2011 Aug;46(4):372. Epub 2011 Jul 7.

Utilitarian and lottery theory in age-related macular degeneration.

Ramsey KM.

Kelowna, B.C.

PMID:21816264[PubMed - in process] Related citations

Publication Types Letter

Epidemiology & pathogenesis

Am J Pathol. 2011 Aug;179(2):850-9. Epub 2011 Jun 12.

Advanced Glycation Endproduct Changes to Bruch's Membrane Promotes Lipoprotein Retention by Lipoprotein Lipase.

Cano M, Fijalkowski N, Kondo N, Dike S, Handa J.

Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, Maryland.

Abstract

Lipoprotein particles accumulate in Bruch's membrane before the development of basal deposits and drusen, two histopathologic lesions that define age-related macular degeneration (AMD). We therefore, sought to determine which molecules could participate in lipoprotein retention. Wild-type or lipoprotein lipase-deficient mice were injected with low-dose d-galactose or PBS subcutaneously for 8 weeks to induce advanced glycation endproduct (AGE) formation. Some mice were also injected with the AGE breaker phenacylphiazolium bromide and d-galactose. Rhodamine-labeled low-density lipoproteins were injected into mice, and the fluorescence was measured up to 72 hours later. AGEs, proteoglycans, and other lipid-retaining molecules were evaluated by IHC. Lipoprotein lipase distribution was assessed in AMD samples by IHC. d-galactose-treated mice retained lipoproteins in the retinal pigment epithelial and Bruch's membrane to a greater extent than either PBS- or phenacylphiazolium bromide/d-galactose-treated mice at 24 and 72 hours after injection ($P \leq 0.04$). Immunolabeling for carboxymethyllysine, biglycan, and lipoprotein lipase was found in d-galactose-treated mice only. Mice deficient for lipoprotein lipase treated with d-galactose did not retain lipoproteins to any measureable extent. Human AMD samples had lipoprotein lipase labeling within drusen, basal deposits, and the choroid. Mice treated with d-galactose to induce AGE formation in Bruch's membrane retain intravenously injected lipoproteins. Our results suggest that lipoprotein retention in Bruch's membrane is mediated by lipoprotein lipase.

PMID:21801873[PubMed - in process]

Genetics

Exp Eye Res. 2011 Jul 27. [Epub ahead of print]

The association between macular pigment optical density and CFH, ARMS2, C2/BF, and C3 genotype.

Loane E, Nolan JM, McKay GJ, Beatty S.

Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland; Ophthalmology Department, St. Vincent's University Hospital, Elm Park,

Dublin 4, Ireland.

Abstract

Age-related macular degeneration (AMD) is the most common cause of blindness in older people in developed countries, and risk for this condition may be classified as genetic or environmental, with an interaction between such factors predisposing to this disease. This study investigated the relationship between AMD risk genes, macular pigment optical density (MPOD), which may protect against AMD, and serum concentrations of the macular carotenoids, lutein (L) and zeaxanthin (Z). This was a cross-sectional study of 302 healthy adult subjects. Dietary intake of L and Z was assessed by food frequency questionnaire, and MPOD was measured by customized heterochromatic flicker photometry. We also calculated MPOD Area as the area of MP under the spatial profile curve, to reflect MP across the macula. Serum L and Z were measured by HPLC. Genotyping of tag SNPs in the genes CFH, ARMS2, C3, C2 and BF was undertaken with multiplex polymerase chain reaction (PCR) and primer extension methodology (ABI Snapshot, ABI Warrington UK) on DNA extracted from peripheral blood. The mean ± SD (range) age of the subjects in this study was 48 ± 11 (21-66) years. There was a statistically significant association between CFH genotype and family history of AMD, with subjects having two non-risk CFH haplotypes (n = 35), or one non-risk and one protective CFH haplotype (n = 33), being significantly more likely to have a negative family history of AMD (Pearson Chi square: p = 0.001). There was no significant association between the AMD risk genes investigated and either MPOD (One way ANOVA: p > 0.05) or serum concentrations of L or Z (One way ANOVA: p > 0.05, for both). Subjects who were homozygous for risk alleles of both CFH and ARMS2 (n = 4) had significantly lower MPOD at 0.5° and 1° retinal eccentricity (Independent samples t test: p < 0.05) and lower MPOD Area which approached statistical significance (Independent samples t test: p = 0.058), compared to other subjects (n = 291). In conclusion, this study did not detect an association between individual AMD risk genotypes and the putatively protective MP, or serum concentrations of its constituent carotenoids. However, the combination of homozygous risk alleles at both CFH and ARMS2 loci was associated with significantly lower MPOD centrally, despite comparable serum concentrations of the macular carotenoids. These findings suggest that the maculae of subjects at very high genetic risk of AMD represent a hostile environment for accumulation and/or stabilization of MP.

PMID:21816153 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Aug 2. [Epub ahead of print]

174delG mutation in mouse MFRP causes photoreceptor degeneration and RPE atrophy.

Fogerty J, Besharse JC.

Department of Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, WI 53226.

Purpose: We have identified a recessive mutation causing progressive retinal degeneration, white fundus flecks, and eventual retinal pigment epithelium (RPE) atrophy. The goal of these studies was to characterize the retinal phenotype, to identify the causative locus and to examine possible functions of the affected gene. Methods: We used SNP mapping, DNA sequencing, and genetic complementation to identify the affected locus. Histology, electroretinography, immunohistochemistry, western blotting, fundus photography, electron microscopy, and in-vitro phagocytosis assays were used to characterize the phenotype of the mouse. Results: Gene mapping identified a single bp deletion in Membrane-Type Frizzled Related Protein (MFRP), designated Mfrp(174delG). MFRP is normally expressed in the RPE and ciliary body, but was undetectable by western blot in mutants. CTRP5, a binding partner of MFRP, was upregulated at the mRNA level and at the protein level in most individuals. Assays designed to test the integrity of retinoid cycling and phagocytic pathways showed no deficits in Mfrp(174delG) or rd6 animals. However, the RPE of both Mfrp(174delG) and rd6 mice exhibited a dramatic increase in the number of apical microvilli. Furthermore, evidence of RPE atrophy was evident in Mfrp(174delG) mice by 21 months.

Conclusion: We have identified a novel, null mutation in mouse Mfrp. This mutation causes photoreceptor degeneration and eventual RPE atrophy, which may be related to alterations in the number of RPE microvilli. These mice will be useful to identify a function of MFRP as well as to study the pathogenesis of atrophic macular degeneration.

PMID:21810984[PubMed - as supplied by publisher]

Hum Genomics. 2011 Jul 1;5(5):420-40.

Clinical validation of a genetic model to estimate the risk of developing choroidal neovascular age-related macular degeneration.

Hageman GS, Gehrs K, Lejnine S, Bansal AT, Deangelis MM, Guymer RH, Baird PN, Allikmets R, Deciu C, Oeth P, Perlee LT.

SourceDepartment of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, UT 84132, USA.

Abstract

Predictive tests for estimating the risk of developing late-stage neovascular age-related macular degeneration (AMD) are subject to unique challenges. AMD prevalence increases with age, clinical phenotypes are heterogeneous and control collections are prone to high false-negative rates, as many control subjects are likely to develop disease with advancing age. Risk prediction tests have been presented previously, using up to ten genetic markers and a range of self-reported non-genetic variables such as body mass index (BMI) and smoking history. In order to maximise the accuracy of prediction for mainstream genetic testing, we sought to derive a test comparable in performance to earlier testing models but based purely on genetic markers, which are static through life and not subject to misreporting. We report a multicentre assessment of a larger panel of single nucleotide polymorphisms (SNPs) than previously analysed, to improve further the classification performance of a predictive test to estimate the risk of developing choroidal neovascular (CNV) disease. We developed a predictive model based solely on genetic markers and avoided inclusion of self-reported variables (eg smoking history) or non-static factors (BMI, education status) that might otherwise introduce inaccuracies in calculating individual risk estimates. We describe the performance of a test panel comprising 13 SNPs genotyped across a consolidated collection of four patient cohorts obtained from academic centres deemed appropriate for pooling. We report on predictive effect sizes and their classification performance. By incorporating multiple cohorts of homogeneous ethnic origin, we obtained >80 per cent power to detect differences in genetic variants observed between cases and controls. We focused our study on CNV, a subtype of advanced AMD associated with a severe and potentially treatable form of the disease. Lastly, we followed a two-stage strategy involving both test model development and test model validation to present estimates of classification performance anticipated in the larger clinical setting. The model contained nine SNPs tagging variants in the regulators of complement activation (RCA) locus spanning the complement factor H (CFH), complement factor H-related 4 (CFHR4), complement factor H-related 5 (CFHR5) and coagulation factor XIII B subunit (F13B) genes; the four remaining SNPs targeted polymorphisms in the complement component 2 (C2), complement factor B (CFB), complement component 3 (C3) and age-related maculopathy susceptibility protein 2 (ARMS2) genes. The pooled sample size (1,132 CNV cases, 822 controls) allowed for both model development and model validation to confirm the accuracy of risk prediction. At the validation stage, our test model yielded 82 per cent sensitivity and 63 per cent specificity, comparable with metrics reported with earlier testing models that included environmental risk factors. Our test had an area under the curve of 0.80, reflecting a modest improvement compared with tests reported with fewer SNPs.

PMID:21807600[PubMed - in process] Related citations

J Thromb Haemost. 2011 Jul;9 Suppl 1:258-64. doi: 10.1111/j.1538-7836.2011.04311.x.

Lessons from genome-wide association studies in venous thrombosis.

Morange PE, Tregouet DA.

INSERM, UMR_S 626, Marseille Université de la Méditerranée, Marseille INSERM UMR_S 937, Université Pierre et Marie Curie (UPMC, Paris 6), Paris, France.

Summary. From the first genome wide association studies (GWAS) conducted on age-related macular degeneration back in 2005 until now, hundreds of studies have applied this strategy to identify novel genetic loci associated with hundreds of human diseases and related quantitative risk factors. While the GWAS revolution has just started to shift towards the next generation sequencing's burst, it is important to illustrate how the genetics research in venous thrombosis has benefit from the GWAS paradigm.

PMID:21781262[PubMed - in process]

Med Sci Monit. 2011 Aug 1;17(8):CR449-455.

Lack of association between the c.544G>A polymorphism of the heme oxygenase-2 gene and age-related macular degeneration.

Wysokinski D, Synowiec E, Chmielewska M, Wozniak K, Zaras M, Sklodowska A, Blasiak J, Szaflik J, Szaflik JP.

Department of Molecular Genetics, University of Lodz, Lodz, Poland.

Background: Age-related macular degeneration (AMD) is a primary cause of blindness among the elderly in developed countries. The nature of AMD is complex and includes both environmental and hereditary factors. Oxidative stress is thought to be essential in AMD pathogenesis. Iron is suggested to be implicated in the pathogenesis of AMD through the catalysis of the production of reactive oxygen species, which can damage the retina. Heme oxygenase-2 is capable of degradation of heme producing free iron ions, thus, diversity in heme oxygenase-2 gene may contribute to AMD. In the present work we analyzed the association between the c.544G>A polymorphism of the heme oxygenase-2 gene (HMOX2) (rs1051308) and AMD.

Material/Methods: This study enrolled 276 AMD patients and 105 sex- and age-matched controls. Genotyping of the polymorphism was performed with restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) on DNA isolated from peripheral blood.

Results: We did not find any association between the genotypes of the c.544G>A polymorphism and the occurrence of AMD. This lack of association was independent of potential AMD risk factors: tobacco smoking, sex and age. Moreover, we did not find any association between AMD and smoking in our study population.

Conclusions: The results suggest that the c.544G>A polymorphism of the heme oxygenase-2 gene is not associated with AMD in this Polish subpopulation.

PMID:21804464[PubMed - in process]

Diet

Eye (Lond). 2011 Aug 5. doi: 10.1038/eye.2011.174. [Epub ahead of print]

Reconsidering the connection between vitamin D levels and age-related macular degeneration.

Golan S, Shalev V, Treister G, Chodick G, Loewenstein A.

Department of Ophthalmology Tel Aviv Medical Center, Tel Aviv, Israel [2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Purpose: Recent evidence has suggested a correlation between reduced vitamin D levels and delayed angiogenesis and reduced inflammatory response, which are known to have a major role in the development and progression of age-related macular degeneration (AMD).

Design: Cross-sectional study.

Participants: Members of the Maccabi Healthcare Services (MHS, one of the four largest Israeli Health Maintenance Organization) aged ≥60 years, whose vitamin D levels were taken as part of routine examinations between 2000 and 2008.

Methods: All data for this study were obtained from MHS databases that include medical information on 1.8 million subscribers. Main outcome measuresSerum 25-OH vitamin D levels.

Results: The total study population comprised of 1045 members diagnosed as having AMD, and 8124 as non-AMD, for whom there was information on vitamin D levels. The mean±SD level of 25-OH vitamin D was 24.1±9.41 ng/ml (range 0.8-120) for the AMD patients and 24.13±9.50 ng/ml (range 0.0-120) for the controls (P=ns). One-third (33.6%) of the AMD patients and 32.86% of the controls had a 25-OH vitamin D level <16 ng/ml, and the proportions of tests in which the 25-OH vitamin D level was >74 ng/ml were 0.19 and 0.14%, respectively (P=ns)

Conclusions: No association was detected between vitamin D levels and the presence of AMD in this cross-sectional study. These results raise some doubt about an association between reduced vitamin D levels and the prevalence of AMD.Eye advance online publication, 5 August 2011; doi:10.1038/eye.2011.174.

PMID:21818133[PubMed - as supplied by publisher]