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MD Research News

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Drug treatment

Retina. 2013 Jun 25. [Epub ahead of print]

INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR FOR RETINAL ANGIOMATOUS PROLIFERATION IN TREATMENT-NAIVE EYES: Long-term Functional and Anatomical Results Using A Modified PrONTO-Style Regimen.

Gharbiya M, Parisi F, Cruciani F, Bozzoni-Pantaleoni F, Pranno F, Abdolrahimzadeh S.

*Department of Ophthalmology, Sapienza University, Policlinico Umberto I, Rome, Italy; and †Department of Ophthalmology, San Filippo Neri Hospital, Rome, Italy.

PURPOSE: To evaluate long-term outcome of intravitreal anti-vascular endothelial growth factor monotherapy in retinal angiomatous proliferation.

METHODS: Twenty-one treatment-naive eyes were included in this prospective, interventional case series. Treatment was three monthly injections of bevacizumab and/or ranibizumab with a modified PrONTO-style regimen. Best-corrected visual acuity (BCVA) was evaluated. The influence of baseline BCVA and pretreatment pigment epithelial detachment on BCVA outcome or retreatment were assessed by Pearson correlation analysis.

RESULTS: Results were evaluated at 2 years and 3 years for 21 and 13 eyes, respectively. Mean baseline BCVA improved significantly from 44.5 (±11.0) (20/32) to 51.1 (±9.7) (20/24) and 50.8 (±10.4) letters (20/24) at 2 and 3 years, respectively (P = 0.02 and P = 0.049). Pigment epithelial detachment correlated negatively with BCVA outcome (r = -0.65, P = 0.002 and r = -0.67, P = 0.01 at 2 years and 3 years, respectively) and was significantly associated with retreatment (r = 0.62, P = 0.003 and r = 0.87, P < 0.0001 at 2 years and 3 years, respectively). Complete occlusion of the lesion was obtained in 71% and 69% of eyes at 2 years and 3 years, respectively, with a mean of 9.4 injections at 3 years.

CONCLUSION: Intravitreal anti-vascular endothelial growth factor monotherapy was a valid option for retinal angiomatous proliferation. Stable or improved visual acuity was obtained in 95% and 100% of eyes at 2 years and 3 years, respectively.

PMID: 23807188 [PubMed - as supplied

JAMA Ophthalmol. 2013 Jun 27:1-8. doi: 10.1001/jamaophthalmol.2013.4154. [Epub ahead of print]

Exploratory Analysis of the Effect of Intravitreal Ranibizumab or Triamcinolone on Worsening of Diabetic Retinopathy in a Randomized Clinical Trial.

Bressler SB, Qin H, Melia M, Bressler NM, Beck RW, Chan CK, Grover S, Miller DG; for the Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: The standard care for proliferative diabetic retinopathy (PDR) usually is panretinal photocoagulation, an inherently destructive treatment that can cause iatrogenic vision loss. Therefore, evaluating the effects of therapies for diabetic macular edema on development or worsening of PDR might lead to new therapies for PDR.

OBJECTIVE: To evaluate the effects of intravitreal ranibizumab or triamcinolone acetonide, administered to treat diabetic macular edema, on worsening of diabetic retinopathy.

DESIGN: Exploratory analysis was performed on worsening of retinopathy, defined as 1 or more of the following: (1) worsening from no PDR to PDR, (2) worsening of 2 or more severity levels on reading center assessment of fundus photographs in eyes without PDR at baseline, (3) having panretinal photocoagulation, (4) experiencing vitreous hemorrhage, or (5) undergoing vitrectomy for the treatment of PDR.

SETTING: Community- and university-based ophthalmology practices.

PARTICIPANTS: Individuals with central-involved diabetic macular edema causing visual acuity impairment.

INTERVENTIONS: Eyes were assigned randomly to sham with prompt focal/grid laser, 0.5 mg of intravitreal ranibizumab with prompt or deferred (≥24 weeks) laser, or 4 mg of intravitreal triamcinolone acetonide with prompt laser.

MAIN OUTCOMES AND MEASURES: Three-year cumulative probabilities for retinopathy worsening.

RESULTS For eyes without PDR at baseline, the 3-year cumulative probabilities for retinopathy worsening (P value comparison with sham with prompt laser) were 23% using sham with prompt laser, 18% with ranibizumab with prompt laser (P = .25), 7% with ranibizumab with deferred laser (P = .001), and 37% with triamcinolone with prompt laser (P = .10). For eyes with PDR at baseline, the 3-year cumulative probabilities for retinopathy worsening were 40%, 21% (P = .05), 18% (P = .02), and 12% (P < .001), respectively.

CONCLUSIONS AND RELEVANCE: Intravitreal ranibizumab appears to be associated with a reduced risk of diabetic retinopathy worsening in eyes with or without PDR. Intravitreal triamcinolone also appears to be associated with a reduced risk of PDR worsening. These findings suggest that use of these drugs to prevent worsening of diabetic retinopathy may be feasible. Given the exploratory nature of these analyses, the risk of endophthalmitis following intravitreal injections, and the fact that intravitreal triamcinolone can cause cataract or glaucoma, use of these treatments to reduce the rates of worsening of retinopathy, with or without PDR, does not seem warranted at this time.

PMID: 23807371 [PubMed - as supplied by publisher]

by publisher]

Retina. 2013 Jun 25. [Epub ahead of print]

EFFECT OF COMBINED CATARACT SURGERY AND RANIBIZUMAB INJECTION IN POSTOPERATIVE MACULAR EDEMA IN NONPROLIFERATIVE DIABETIC RETINOPATHY.

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Ulsan, Gangneung, Korea.

PURPOSE: To evaluate whether intravitreal ranibizumab injection at cataract surgery prevents postoperative diabetic macular edema (PME) in patients with stable diabetic retinopathy without significant macular edema.

METHODS: Eighty patients with cataract, stable diabetic retinopathy, and no significant macular edema were randomized to a sham group (cataract surgery only) or a group undergoing cataract surgery plus intraoperative ranibizumab injection. Best-corrected visual acuities, central subfield thickness, and total macular volume were assessed at baseline and 1 week, 1, 3, and 6 months postoperatively by spectral domain optical coherence tomography. Clinically meaningful PME (central subfield thickness increase >60 μm relative to baseline) was computed.

RESULTS: The groups did not differ in baseline best-corrected visual acuity, central subfield thickness, and total macular volume. Compared with the ranibizumab injection group, the sham group had significantly larger central subfield thickness increases relative to baseline at 1 week and 1 month; larger total macular volume increases at all time points ($P = 0.012$, $P = 0.005$, $P < 0.001$, $P < 0.001$, $P = 0.005$, $P = 0.017$, respectively); higher PME frequency at 1 month ($P = 0.019$); and poorer best-corrected visual acuity improvement from baseline to 6 months after surgery ($P = 0.046$).

CONCLUSION: In patients with stable diabetic retinopathy without significant macular edema, intravitreal ranibizumab injection at cataract surgery may prevent the postoperative worsening of macular edema and may improve the final visual outcome without affecting safety.

PMID: 23807186 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jun 21. pii: S0002-9394(13)00292-4. doi: 10.1016/j.ajo.2013.04.026. [Epub ahead of print]

A Prospective Randomized Trial of Intravitreal Bevacizumab Versus Ranibizumab for the Management of Diabetic Macular Edema.

Nepomuceno AB, Takaki E, Paes De Almeida FP, Peroni R, Cardillo JA, Siqueira RC, Scott IU, Messias A, Jorge R.

School of Medicine of Ribeirão Preto, University of São Paulo, Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, Ribeirão Preto, Brazil.

PURPOSE: To compare visual acuity and spectral-domain optical coherence tomography (SDOCT) outcomes associated with intravitreal (IV) bevacizumab vs IV ranibizumab for the management of diabetic macular edema (DME).

DESIGN: Prospective randomized trial.

METHODS: Forty-eight patients (63 eyes) with center-involved DME were randomly assigned to receive 1.5 mg (0.06 cc) IV bevacizumab or 0.5 mg (0.05 cc) IV ranibizumab at baseline and monthly if central subfield thickness was greater than 275 μm.

RESULTS: Forty-five patients (60 eyes) completed 48 weeks of follow-up. At baseline, mean ± standard error best-corrected visual acuity (BCVA) (logMAR) was 0.60 (20/80) ± 0.05 in the IV bevacizumab group and 0.63 (20/85) ± 0.05 in the IV ranibizumab group. A significant improvement in mean BCVA was observed in both groups at all study visits ($P < .05$); this improvement was significantly greater in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($P = .032$) and 32 ($P = .042$). A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($P < .05$), with no significant difference in the magnitude of macular thickness reduction between groups. The mean number of injections was significantly higher ($P = .005$) in the IV

bevacizumab group (9.84) than in the IV ranibizumab group (7.67).

CONCLUSIONS: IV bevacizumab and IV ranibizumab are associated with similar effects on central subfield thickness in patients with DME through 1 year of follow-up. IV ranibizumab is associated with greater improvement in BCVA at some study visits, and the mean number of injections is higher in the IV bevacizumab group.

PMID: 23795985 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jul;156(1):1-2.e1. doi: 10.1016/j.ajo.2013.04.009.

Switching anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration.

Schachat AP.

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PMID: 23791369 [PubMed - in process]

Other treatment & diagnosis

Retina. 2013 Jun 20. [Epub ahead of print]

GREEN OR YELLOW LASER TREATMENT FOR DIABETIC MACULAR EDEMA: Exploratory Assessment Within the Diabetic Retinopathy Clinical Research Network.

Bressler SB, Almukhtar T, Aiello LP, Bressler NM, Ferris FL 3rd, Glassman AR, Greven CM; for the Diabetic Retinopathy Clinical Research Network.

*Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland; †Jaeb Center for Health Research, Tampa, Florida; ‡Department of Ophthalmology, Beetham Eye Institute, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts; §Division of Epidemiology and Clinical Applications, National Eye Institute and the National Institutes of Health, Bethesda, Maryland; and ¶Department of Ophthalmology, Wake Forest University Eye Center, Winston-Salem, North Carolina.

PURPOSE: Explore differences in green compared with yellow focal/grid laser treatment on functional and anatomical endpoints in eyes with diabetic macular edema.

METHODS: Data from two randomized clinical trials were evaluated for differences in visual acuity and optical coherence tomography parameters for eyes assigned to sham injection + prompt laser, ranibizumab + prompt laser, or prompt laser only: among subgroups of eyes treated exclusively and electively with either green or yellow laser.

RESULTS: In the sham injection + prompt laser group, the mean visual acuity letter score change for eyes receiving green and yellow laser treatment, respectively, was +2.4 ± 14 and +5.1 ± 13 at the 52-week visit (P = 0.06) and +2.4 ± 15 and +6.0 ± 13 at the 104-week visit (P = 0.13), with no corresponding evidence of differences in optical coherence tomography thickness. When comparing wavelength groups in the ranibizumab + prompt laser and prompt laser-only groups, meaningful differences in visual acuity and optical coherence tomography thickness were not detected at 1 year or 2 years.

CONCLUSION: A trend toward improved vision outcome with yellow laser observed in one trial was not corroborated by anatomical outcomes or by the other trial. In this study, without random assignment to

different wavelengths controlling for bias and confounding, it is not possible to determine whether one wavelength is better than the other.

PMID: 23792486 [PubMed - as supplied by publisher]

Pathogenesis

Elife. 2013 Jun 18;2:e00324. doi: 10.7554/eLife.00324. Print 2013.

Photoreceptor avascular privilege is shielded by soluble VEGF receptor-1.

Luo L, Uehara H, Zhang X, Das SK, Olsen T, Holt D, Simonis JM, Jackman K, Singh N, Miya TR, Huang W, Ahmed F, Bastos-Carvalho A, Le YZ, Mamalis C, Chiodo VA, Hauswirth WW, Baffi J, Lacal PM, Orecchia A, Ferrara N, Gao G, Young-Hee K, Fu Y, Owen L, Albuquerque R, Baehr W, Thomas K, Li DY, Chalam KV, Shibuya M, Grisanti S, Wilson DJ, Ambati J, Ambati BK.

Moran Eye Center , University of Utah , Salt Lake City , United States ; Department of Ophthalmology , The 306th Hospital of PLA , Beijing , China.

Abstract: Optimal phototransduction requires separation of the avascular photoreceptor layer from the adjacent vascularized inner retina and choroid. Breakdown of peri-photoreceptor vascular demarcation leads to retinal angiomatous proliferation or choroidal neovascularization, two variants of vascular invasion of the photoreceptor layer in age-related macular degeneration (AMD), the leading cause of irreversible blindness in industrialized nations. Here we show that sFLT-1, an endogenous inhibitor of vascular endothelial growth factor A (VEGF-A), is synthesized by photoreceptors and retinal pigment epithelium (RPE), and is decreased in human AMD. Suppression of sFLT-1 by antibodies, adeno-associated virus-mediated RNA interference, or Cre/lox-mediated gene ablation either in the photoreceptor layer or RPE frees VEGF-A and abolishes photoreceptor avascularity. These findings help explain the vascular zoning of the retina, which is critical for vision, and advance two transgenic murine models of AMD with spontaneous vascular invasion early in life. DOI:http://dx.doi.org/10.7554/eLife.00324.001.

PMID: 23795287 [PubMed] PMCID: PMC3687373

Protein Cell. 2013 Jun 20. [Epub ahead of print]

Direct conversion of human fibroblasts into retinal pigment epithelium-like cells by defined factors.

Zhang K, Liu GH, Yi F, Montserrat N, Hishida T, Rodriguez Esteban C, Izpisua Belmonte JC.

Gene Expression Laboratory, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA, 92037, USA.

Abstract: The generation of functional retinal pigment epithelium (RPE) is of great therapeutic interest to the field of regenerative medicine and may provide possible cures for retinal degenerative diseases, including age-related macular degeneration (AMD). Although RPE cells can be produced from either embryonic stem cells or induced pluripotent stem cells, direct cell reprogramming driven by lineagedetermining transcription factors provides an immediate route to their generation. By monitoring a human RPE specific Best1::GFP reporter, we report the conversion of human fibroblasts into RPE lineage using defined sets of transcription factors. We found that Best1::GFP positive cells formed colonies and exhibited morphological and molecular features of early stage RPE cells. Moreover, they were able to obtain pigmentation upon activation of Retinoic acid (RA) and Sonic Hedgehog (SHH) signaling pathways. Our study not only established an ideal platform to investigate the transcriptional network regulating the RPE cell fate determination, but also provided an alternative strategy to generate functional RPE cells that complement the use of pluripotent stem cells for disease modeling, drug screening, and cell therapy of retinal

degeneration.

PMID: 23793999 [PubMed - as supplied by publisher]

PLoS One. 2013 Jun 14;8(6):e65518. doi: 10.1371/journal.pone.0065518. Print 2013.

Systemic Administration of Abeta mAb Reduces Retinal Deposition of Abeta and Activated Complement C3 in Age-Related Macular Degeneration Mouse Model.

Catchpole I, Germaschewski V, Hoh Kam J, Lundh von Leithner P, Ford S, Gough G, Adamson P, Overend P, Hilpert J, López FJ, Ng YS, Coffey P, Jeffery G.

Topical BioPharm Discovery Research and Development Unit, King of Prussia, Philadelphia, Pennsylvania, United States of America ; GSK Ophthalmology, King of Prussia, Philadelphia, Pennsylvania, United States of America.

Abstract: Age-related macular degeneration (AMD) is a leading cause of legal blindness in the Western world. There are effective treatments for the vascular complications of neo-vascular AMD, but no effective therapies are available for the dry/atrophic form of the disease. A previously described transgenic CFH-gene deficient mouse model, (cfh-/-), shows hallmarks of early AMD. The ocular phenotype has been further analysed to demonstrate amyloid beta (Aβ) rich basement membrane deposits associated with activated complement C3. Cfh-/- mice were treated systemically in both prophylactic and therapeutic regimes with an anti-Aβ monoclonal antibody (mAb), 6F6, to determine the effect on the cfh-/- retinal phenotype. Prophylactic treatment with 6F6 demonstrated a dose dependent reduction in the accumulation of both Aβ and activated C3 deposition. A similar reduction in the retinal endpoints could be seen after therapeutic treatment. Serum Aβ levels after systemic administration of 6F6 show accumulation of Aβ in the periphery suggestive of a peripheral sink mechanism. In summary, anti-Aβ mAb treatment can partially prevent or reverse ocular phenotypes of the cfh-/- mouse. The data support this therapeutic approach in humans potentially modulating two key elements in the pathogenesis of AMD - Aβ and activated, complement C3.

PMID: 23799019 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Jun 21;54(6):4321-9. doi: 10.1167/iovs.13-11611.

Laser-Induced Choroidal Neovascularization in Mice Attenuated by Deficiency in the Apelin-APJ System.

Hara C, Kasai A, Gomi F, Satooka T, Sakimoto S, Nakai K, Yoshioka Y, Yamamuro A, Maeda S, Nishida K.

Department of Ophthalmology, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan.

PURPOSE: To investigate the role of the apelin-APJ system in the development of choroidal neovascularization (CNV).

METHODS: Experimental CNV was induced by laser photocoagulation in wild-type (WT), apelin-deficient (apelin-KO), and apelin receptor (APJ)-deficient (APJ-KO) mice. The gene expression levels of angiogenic or inflammatory factors were determined by quantitative real-time reverse transcription-polymerase chain reaction. APJ expression in CNV lesions was examined by immunohistochemistry. The sizes of the CNV lesions in the three mouse models were measured and compared histologically using isolectin B4 staining. Macrophage recruitment was measured by flow cytometric analysis. Proliferation of endothelial cells was determined using the alamar Blue assay.

RESULTS: Laser photocoagulation significantly increased expression of apelin and APJ in the retina-retinal pigment epithelium (RPE) complex. APJ immunoreactive cells were found in the CNV lesions and

colocalized with platelet endothelial cell adhesion molecule-1, an endothelial cell marker. The sizes of the CNV lesions in apelin-KO or APJ-KO mice decreased significantly compared with those in the WT mice. Macrophages in the RPE complex of the apelin-KO mice, in which gene expression of the inflammatory factors was almost equal to that in WT mice, were recruited as a result of laser photocoagulation to the same degree as in WT mice. In addition, apelin small and interfering RNA (siRNA) suppressed proliferation of endothelial cells independently of vascular endothelial growth factor (VEGF) receptor 2 signaling, while VEGF increased expression of apelin and APJ in human umbilical vein endothelial cells.

CONCLUSIONS: The results suggested that the apelin-APJ system contributes to CNV development partially independent of the VEGF pathway.

PMID: 23722395 [PubMed - in process]

Epidemiology

Am J Prev Med. 2013 Jul;45(1):29-35. doi: 10.1016/j.amepre.2013.02.018.

Age-related eye diseases and visual impairment among U.S. Adults.

Chou CF, Frances Cotch M, Vitale S, Zhang X, Klein R, Friedman DS, Klein BE, Saaddine JB.

Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, Georgia. Electronic address: CChou@cdc.gov.

BACKGROUND: Visual impairment is a common health-related disability in the U.S. The association between clinical measurements of age-related eye diseases and visual impairment in data from a national survey has not been reported.

PURPOSE: To examine common eye conditions and other correlates associated with visual impairment in the U.S.

METHODS: Data from the 2005-2008 National Health and Nutrition Examination Survey of 5222 Americans aged ≥40 years were analyzed in 2012 for visual impairment (presenting distance visual acuity worse than 20/40 in the better-seeing eye), and visual impairment not due to refractive error (distance visual acuity worse than 20/40 after refraction). Diabetic retinopathy (DR) and age-related macular degeneration (AMD) were assessed from retinal fundus images; glaucoma was assessed from two successive frequency-doubling tests and a cup-to-disc ratio measurement.

RESULTS: Prevalence of visual impairment and of visual impairment not due to refractive error was 7.5% (95% CI=6.9%, 8.1%) and 2.0% (1.7%, 2.3%), respectively. The prevalence of visual impairment not due to refractive error was significantly higher among people with AMD (2.2%) compared to those without AMD (0.8%), or with DR (3.5%) compared to those without DR (1.2%). Independent predictive factors of visual impairment not due to refractive error were AMD (OR=4.52, 95% CI=2.50, 8.17); increasing age (OR=1.09 per year, 95% CI=1.06, 1.13); and less than a high school education (OR=2.99, 95% CI=1.18, 7.55).

CONCLUSIONS: Visual impairment is a public health problem in the U.S. Visual impairment in two thirds of adults could be eliminated with refractive correction. Screening of the older population may identify adults at increased risk of visual impairment due to eye diseases.

PMID: 23790986 [PubMed - in process]

Genetics

Gene Ther. 2013 Jun 27. doi: 10.1038/gt.2013.36. [Epub ahead of print]

Long-term efficacy of ciliary muscle gene transfer of three sFlt-1 variants in a rat model of laser-induced choroidal neovascularization.

El Sanharawi M, Touchard E, Benard R, Bigey P, Escriou V, Mehanna C, Naud MC, Berdugo M, Jeanny JC, Behar-Cohen F.

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Abstract: Inhibition of vascular endothelial growth factor (VEGF) has become the standard of care for patients presenting with wet age-related macular degeneration. However, monthly intravitreal injections are required for optimal efficacy. We have previously shown that electroporation enabled ciliary muscle gene transfer results in sustained protein secretion into the vitreous for up to 9 months. Here, we evaluated the long-term efficacy of ciliary muscle gene transfer of three soluble VEGF receptor-1 (sFlt-1) variants in a rat model of laser-induced choroidal neovascularization (CNV). All three sFlt-1 variants significantly diminished vascular leakage and neovascularization as measured by fluorescein angiography (FA) and flatmount choroid at 3 weeks. FA and infracyanine angiography demonstrated that inhibition of CNV was maintained for up to 6 months after gene transfer of the two shortest sFlt-1 variants. Throughout, clinical efficacy was correlated with sustained VEGF neutralization in the ocular media. Interestingly, treatment with sFlt-1 induced a 50% downregulation of VEGF messenger RNA levels in the retinal pigment epithelium and the choroid. We demonstrate for the first time that non-viral gene transfer can achieve a long-term reduction of VEGF levels and efficacy in the treatment of CNV.Gene Therapy advance online publication, 27 June 2013; doi:10.1038/gt.2013.36.

PMID: 23804076 [PubMed - as supplied by publisher]

Genet Med. 2013 Jun 27. doi: 10.1038/gim.2013.80. [Epub ahead of print]

Variations in predicted risks in personal genome testing for common complex diseases.

Kalf RR, Mihaescu R, Kundu S, de Knijff P, Green RC, Janssens AC.

Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.

Purpose: The promise of personalized genomics for common complex diseases depends, in part, on the ability to predict genetic risks on the basis of single nucleotide polymorphisms. We examined and compared the methods of three companies (23andMe, deCODEme, and Navigenics) that have offered direct-to-consumer personal genome testing.

Methods: We simulated genotype data for 100,000 individuals on the basis of published genotype frequencies and predicted disease risks using the methods of the companies. Predictive ability for six diseases was assessed by the AUC.

Results: AUC values differed among the diseases and among the companies. The highest values of the AUC were observed for age-related macular degeneration, celiac disease, and Crohn disease. The largest difference among the companies was found for celiac disease: the AUC was 0.73 for 23andMe and 0.82 for deCODEme. Predicted risks differed substantially among the companies as a result of differences in the sets of single nucleotide polymorphisms selected and the average population risks selected by the companies, and in the formulas used for the calculation of risks.

Conclusion: Future efforts to design predictive models for the genomics of common complex diseases may

benefit from understanding the strengths and limitations of the predictive algorithms designed by these early companies.Genet Med advance online publication 27 June 2013Genetics in Medicine (2013); doi:10.1038/gim.2013.80.

PMID: 23807614 [PubMed - as supplied by publisher]

Diet

Exp Eye Res. 2013 Jun 18. pii: S0014-4835(13)00138-3. doi: 10.1016/j.exer.2013.05.019. [Epub ahead of print]

Specific roles for Group V secretory PLA2 in retinal iron-induced oxidative stress. Implications for age-related macular degeneration.

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Abstract: Iron accumulation and oxidative stress are hallmarks of retinas from patients with age-related macular degeneration (AMD). We have previously demonstrated that iron-overloaded retinas are a good in vitro model for the study of retinal degeneration during iron-induced oxidative stress. In this model we have previously characterized the role of cytosolic phospholipase A2 (cPLA2) and calcium-independent isoform (iPLA2). The aim of the present study was to analyze the implications of Group V secretory PLA2 (sPLA2), another member of PLA2 family, in cyclooxygenase (COX)-2 and nuclear factor kappa B (NF-κB) regulation. We found that sPLA2 is localized in cytosolic fraction in an iron concentration-dependent manner. By immunoprecipitation (IP) assays we also demonstrated an increased association between Group V sPLA2 and COX-2 in retinas exposed to iron overload. However, COX-2 activity in IP assays was observed to decrease in spite of the increased protein levels observed. p65 (RelA) NF-κB levels were increased in nuclear fractions from retinas exposed to iron. In the presence of ATK (cPLA2 inhibitor) and YM 26734 (sPLA2 inhibitor), the nuclear localization of both p65 and p50 NF-κB subunits was restored to control levels in retinas exposed to iron-induced oxidative stress. Membrane repair mechanisms were also analyzed by studying the participation of acyltransferases in phospholipid remodeling during retinal oxidation stress. Acidic phospholipids, such as phosphatidylinositol (PI) and phosphatidylserine (PS), were observed to show an inhibited acylation profile in retinas exposed to iron while phosphatidylethanolamine (PE) showed the opposite. The use of PLA2 inhibitors demonstrated that PS is actively deacylated during iron-induced oxidative stress. Results from the present study suggest that Group V sPLA2 has multiple intracellular targets during iron-induced retinal degeneration and that the specific role of sPLA2 could be related to inflammatory responses by its participation in NF-κB and COX-2 regulation.

PMID: 23791636 [PubMed - as supplied by publisher]

Med Lett Drugs Ther. 2013 Jun 24;55(1416):50-1.

Nutritional supplements for age-related macular degeneration revisited.

[No authors listed]

PMID: 23797797 [PubMed - in process]