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MD Research News

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Drug treatment

Ophthalmic Surg Lasers Imaging Retina. 2013 Sep 1;44(5):455-9. doi: 10.3928/23258160-20130909-06.

Association Between Systemic Anticoagulation and Rate of Intraocular Hemorrhage Following Intravitreal Anti-VEGF Therapy for Age-Related Macular Degeneration.

Olson JM, Scott IU, Kerchner DL, Kunselman AR.

BACKGROUND AND OBJECTIVE: To investigate the association between systemic anticoagulant medication usage at the time of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection with post-injection intraocular hemorrhage among patients with age-related macular degeneration (AMD).

PATIENTS AND METHODS: Retrospective, consecutive case series of all patients treated with anti-VEGF injection for neovascular AMD at the Penn State Hershey Eye Center between 2004 and 2010: 1,710 anti-VEGF injections performed in 228 eyes of 191 patients. Each injection was analyzed according to whether the patient was taking systemic anticoagulant medication at the time of injection.

RESULTS: Intraocular hemorrhage occurred after intravitreal anti-VEGF injection in four eyes (0.25%). Vitreous hemorrhage occurred in three patients taking systemic anticoagulation. Subretinal hemorrhage occurred in one patient not on anticoagulant therapy. In a bivariate analysis, the odds of intraocular hemorrhage are 1.9 times higher for injections performed in patients on systemic anticoagulation versus those not on systemic anticoagulation; this difference is not statistically significant.

CONCLUSION: The rate of intraocular hemorrhage after intravitreal injection of anti-VEGF therapy among patients with AMD is low, and there is no significant difference between patients taking systemic anticoagulant medications at the time of injection and patients not on anticoagulation. [Ophthalmic Surg Lasers Imaging Retina. 2013;44:455-459.].

PMID: 24044707 [PubMed - in process]

Ophthalmologe. 2013 Sep 19. [Epub ahead of print]

[Tear in retinal pigment epithelium under anti-VEGF therapy for exudative age-related macular degeneration : Function recovery under intensive therapy.] [Article in German]

Bartels S, Barrelmann A, Book B, Heimes B, Gutfleisch M, Spital G, Pauleikhoff D, Lommatzsch A.

Augenabteilung am St. Franziskus Hospital, Hohenzollernring 74, 48145, Münster, Deutschland.

Abstract: This article reports the case of a 72-year-old woman with pigment epithelial detachment with occult choroidal neovascularization (CNV) in exudative age-related macular degeneration (AMD) which developed under anti-vascular endothelial growth factor (VEGF) therapy of a tear in the retinal pigment epithelium (RPE). In the area of free RPE autofluorescence was completely absent and the microperimetry in this area showed an absolute scotoma. The visual acuity was 0.1. After continuation of anti-VEGF therapy because of persistent subretinal and intraretinal fluid over 3 years an increased autofluorescence was observed and the microperimetry showed an increase in central retinal sensitivity. The central visual acuity improved to 0.5 and in this area a whitish subretinal tissue formed morphologically. In the spectral domain optical coherence tomography (SD-OCT) image this structure was hyperreflective which might suggest a certain regeneration process of the RPE under anti-VEGF-therapy.

PMID: 24046170 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Sep 19. [Epub ahead of print]

[VEGF inhibitors in vitreoretinal interventions.] [Article in German]

Feltgen N, Stahl A.

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Abstract: Vascular endothelial growth factor (VEGF) inhibitors are being used for an increasing number of indications. Beyond the classical use in exudative macular degeneration and macular edema, they are being used, for example off-label as additive treatment together with panretinal laser photocoagulation or in preparation for vitrectomy for ischemic retinopathy. In preparation for vitreoretinal surgery VEGF inhibitors are usually given prior to surgery. When given as an adjunct to laser treatment, VEGF inhibitors can be given either consecutively or parallel to laser photocoagulation. In most cases, however, anti-VEGF treatment does not render laser coagulation dispensable. The greatest danger with anti-VEGF treatment in the context of ischemic retinopathies lies in the fact that proliferative membranes are misjudged or overlooked. In these cases, anti-VEGF treatment can induce contraction of these membranes with induction of consecutive tractional retinal detachment. This review summarizes the current knowledge on VEGF inhibition as an adjunct to vitreoretinal surgery and also points out the gaps in the current knowledge and the need for further research.

PMID: 24046167 [PubMed - as supplied by publisher]

JRSM Short Rep. 2013 Jul 30;4(9):2042533313484146. doi: 10.1177/2042533313484146.

Avastin and Lucentis: what do patients know? A prospective questionnaire survey.

Manna A, Oyede O, Ning B, Yang Y, Narendran N.

Wolverhampton Eye Infirmary, The Royal Wolverhampton Hospitals NHS Trust, Wolverhampton WV10 0QP, UK.

OBJECTIVES: To assess patients' knowledge of their drug therapy for neovascular macular degeneration and to identify which aspects of the drug they considered most important if given the option of switching to an alternative drug.

DESIGN: Prospective questionnaire survey.

SETTING: Wolverhampton, England.

PARTICIPANTS: A total of 126 patients attending our hospital service for intravitreal ranibizumab therapy

for neovascular macular degeneration.

MAIN OUTCOME MEASURES: Using a questionnaire, patients were asked questions pertaining to aspects of drug therapy in neovascular macular degeneration. Fields covered included drug names, knowledge of alternative drugs, cost of drugs and their views on switching to another drug.

RESULTS: Eighty (63.5%) had heard of Lucentis (ranibizumab) and 31 (24.6%) were aware of Avastin (bevacizumab). Of the latter 31 patients, 20 did not have a preference between Avastin and Lucentis. These patients felt that the factors they would consider important for them to consider switching were effectiveness (10, 50%), specialist recommendation (8, 40%), safety (2, 10%) and cost (0).

CONCLUSIONS: Introducing a cheaper, off-label alternative in the therapy of macular degeneration in the presence of a licensed option has been extensively debated. Many patients have no knowledge of this controversial issue but it is likely that efficacy and recommendation by clinicians are more important than cost to patients who may consider switching to the off-label Avastin.

PMID: 24040500 [PubMed] PMCID: PMC3767069

Br J Ophthalmol. 2013 Sep 13. doi: 10.1136/bjophthalmol-2013-303978. [Epub ahead of print]

Higher incidence of retinal pigment epithelium tears after ranibizumab in neovascular age-related macular degeneration with increasing pigment epithelium detachment height.

Guber J, Praveen A, Saeed MU.

Sutton Eye Unit, Epsom and St Helier University Hospital, London, UK.

PMID: 24037605 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2013 Sep 14. [Epub ahead of print]

RETINAL VASCULAR ABNORMALITIES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Jackson TL, Danis RP, Goldbaum M, Slakter JS, Shusterman EM, O'shaughnessy DJ, Moshfeghi DM.

*Department of Ophthalmology, School of Medicine, King's College London, London, United Kingdom; †Fundus Photograph Reading Center, University of Wisconsin, Madison, Wisconsin; ‡Department of Ophthalmology, Hospital das Clinicas, University of São Paulo, São Paulo, Brazil; §Digital Angiography Reading Center, New York, New York; ¶Oraya Therapeutics, Inc, Newark, California; and **Department of Ophthalmology, Byers Eye Institute, Horngren Family Vitreoretinal Center, Stanford University School of Medicine, Palo Alto, California.

PURPOSE: To determine the prevalence of retinal vascular abnormalities (RVA) in neovascular age-related macular degeneration (AMD).

METHODS: A post hoc subanalysis of images acquired during a Phase III randomized controlled trial was undertaken, selecting images from participants with untreated, neovascular AMD in at least one eye. Protocol mandated fundus photographs and fluorescein angiograms were acquired at baseline and Year 2, from 107 sham-treated study eyes with neovascular AMD and 107 untreated fellow eyes. Images were reanalyzed by an independent reading center for the presence of RVA, defined as at least one of the following: microaneurysms, vessel staining or leakage, dilated or tortuous vessels, intraretinal hemorrhage, vessel sheathing or narrowing, capillary nonperfusion, or capillary infarcts.

RESULTS: The baseline prevalence of RVA in the sham-treated study eyes was 14.4% (15 of 104 gradable images) versus 8.3% (5 of 60) in the fellow eyes with dry AMD. The baseline prevalence of individual RVAs in study eyes was: microaneurysms (6.7%), vessel staining or leakage (6.7%), dilated or tortuous vessels (4.8%), intraretinal hemorrhage (4.8%), vessel sheathing or narrowing (2.9%), capillary nonperfusion (0%), and capillary infarcts (0%). Results were similar at 24 months.

CONCLUSION: Compared with several studies that relied solely on fundus photographs, this study included fluorescein angiography and found a higher prevalence of RVAs occurring in eyes with neovascular AMD.

PMID: 24045343 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2013 Sep 1;44(5):508-12. doi: 10.3928/23258160-20130909-19.

Epiretinal macular edema associated with thick epiretinal membranes.

Doshi RR, Lowrance MD, Kim BT, Davis JL, Rosenfeld PJ.

Abstract: High-resolution imaging with spectral-domain optical coherence tomography has identified an unusual group of epiretinal membranes (ERMs) in the presence of lamellar macular holes. These ERMs are unusually thick. The authors present the case of a patient with age-related macular degeneration who developed edema within a thickened ERM in both eyes after cataract surgery. The edema resolved with anti-vascular endothelial growth factor (VEGF) therapy. The authors propose that the VEGF-responsive fluid within these thick ERMs arose from fibrovascular tissue derived from the retina. Further studies with histopathology will be required to determine whether neovascular tissue is present in all cases of thickened ERMs with epiretinal edema. PMID: 24044720 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2013 Sep 1;44(5):471-6. doi: 10.3928/23258160-20130909-09.

Hemorrhagic age-related macular degeneration managed with vitrectomy, subretinal injection of tissue plasminogen activator, gas tamponade, and upright positioning.

Kapran Z, Ozkaya A, Uyar OM.

BACKGROUND AND OBJECTIVE:To investigate the outcomes of vitrectomy, subretinal tissue plasminogen (tPA) injection, gas tamponade, and upright positioning in patients with hemorrhagic neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS:Retrospective, noncomparative case series. Records of patients who were diagnosed with submacular hemorrhage secondary to neovascular AMD and underwent treatment with the combined method between 2004 and 2010 were reviewed. The main outcome measure was the difference between preoperative and post-operative best corrected visual acuity (BCVA).

RESULTS:In 10 eyes of 10 patients, mean preoperative and postoperative BCVA values were 1.75 and 1.23 logMAR, respectively (P = .011), after a mean follow-up time of 38.7 ± 26.5 months (range: 10 to 71 months). Eight of 10 patients (80%) gained at least three lines.

CONCLUSION:In patients with hemorrhagic neovascular AMD, treatment with vitrectomy, subretinal tPA injection, gas tamponade, and upright positioning was associated with better visual outcomes than those reported for patients with untreated disease. [Ophthalmic Surg Lasers Imaging Retina. 2013;44:471-476.].

PMID: 24044710 [PubMed - in process]

Clin Ophthalmol. 2013;7:1703-11. doi: 10.2147/OPTH.S48723. Epub 2013 Aug 28.

Two siblings with late-onset cone-rod dystrophy and no visible macular degeneration.

Sakuramoto H, Kuniyoshi K, Tsunoda K, Akahori M, Iwata T, Shimomura Y.

Department of Ophthalmology, Kinki University Faculty of Medicine, Osaka-Sayama City, Osaka, Japan.

BACKGROUND: We report our findings in two siblings with late-onset cone-rod dystrophy (CRD) with no visible macular degeneration.

CASES AND METHODS: Case 1 was an 82-year-old man who first noticed a decrease in vision and color blindness in his early seventies. His mother and younger sister also had visual disturbances. His decimal visual acuity was 0.3 in the right eye and 0.2 in the left eye. Ophthalmoscopy showed normal fundi, and fluorescein angiography was also normal in both eyes. The photopic single flash and flicker eletroretinograms (ERGs) were severely attenuated and the scotopic ERGs were slightly reduced in both eyes. Case 2 was the 80-year-old younger sister of Case 1. She first noticed a decline in vision and photophobia in both eyes in her early seventies. Her decimal visual acuity was 0.4 in the right eye and 0.2 in the left eye. Ophthalmoscopy showed mottling of the retinal pigment epithelium in the midperiphery with no visible macular degeneration. The photopic single flash and flicker ERGs were severely attenuated, and the scotopic ERGs were slightly reduced in both eyes.

CONCLUSION: These siblings are the oldest reported cases of CRD with no visible macular degeneration. Thus, CRD should be considered in patients with reduced visual acuity, color blindness, and photophobia even if they are older than 70 years.

PMID: 24039390 [PubMed] PMCID: PMC3770715

J Ocul Pharmacol Ther. 2013 Sep 19. [Epub ahead of print]

Cell-Based Therapies for Ocular Disease.

Eveleth DD.

E&B Technologies, LLC, San Diego, California.

Abstract: Cell therapy for ocular disease has made significant progress within the last decade. Stem and progenitor populations for many ocular cell types have been identified, and their behavior is now understood well enough to enable clinical application. Corneal epithelial progenitor cell therapy has benefited many patients and is now transitioning from a research technique to established clinical therapy. The application of embryonic stem cell-based therapy is in clinical development for Stargardt's macular dystrophy and dry age-related macular degeneration. These advances have been made possible, in part, by the inherent advantages of the eye as a place to develop and apply cell therapies and the foundation built on transplantation studies. Despite these advances, there are still areas of high unmet need that could benefit from cell therapy when further research identifies methods to identify, generate, and manipulate the progenitor populations. This review discusses, in practical terms, the application of cell therapies to the eye, progress that has been made and progress which remains to be made in the application of cell therapy to ocular disease.

PMID: 24050306 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2013 Sep 10;8(9):e73070. doi: 10.1371/journal.pone.0073070.

Rap1 GTPase Activation and Barrier Enhancement in RPE Inhibits Choroidal Neovascularization In Vivo.

Wittchen ES, Nishimura E, McCloskey M, Wang H, Quilliam LA, Chrzanowska-Wodnicka M, Hartnett ME.

Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, North Carolina, United States of America.

Abstract: Loss of barrier integrity precedes the development of pathologies such as metastasis, inflammatory disorders, and blood-retinal barrier breakdown present in neovascular age-related macular degeneration. Rap1 GTPase is involved in regulating both endothelial and epithelial cell junctions; the specific role of Rap1A vs. Rap1B isoforms is less clear. Compromise of retinal pigment epithelium barrier function is a contributing factor to the development of AMD. We utilized shRNA of Rap1 isoforms in cultured human retinal pigment epithelial cells, along with knockout mouse models to test the role of Rap1 on promoting RPE barrier properties, with emphasis on the dynamic junctional regulation that is triggered when the adhesion between cells is challenged. In vitro, Rap1A shRNA reduced steady-state barrier integrity, whereas Rap1B shRNA affected dynamic junctional responses. In a laser-induced choroidal neovascularization (CNV) model of macular degeneration, Rap1b(-/-) mice exhibited larger CNV volumes compared to wild-type or Rap1a(-/-) . In vivo, intravitreal injection of a cAMP analog (8CPT-2'-O-Me-cAMP) that is a known Rap1 activator significantly reduced laser-induced CNV volume, which correlated with the inhibition of CEC transmigration across 8CPT-2'O-Me-cAMP-treated RPE monolayers in vitro. Rap1 activation by 8CPT-2'-O-Me-cAMP treatment increased recruitment of junctional proteins and F-actin to cell -cell contacts, increasing both the linearity of junctions in vitro and in cells surrounding laser-induced lesions in vivo. We conclude that in vitro, Rap1A may be important for steady state barrier integrity, while Rap1B is involved more in dynamic junctional responses such as resistance to junctional disassembly induced by EGTA and reassembly of cell junctions following disruption. Furthermore, activation of Rap1 in vivo inhibited development of choroidal neovascular lesions in a laser-injury model. Our data suggest that targeting Rap1 isoforms in vivo with 8CPT-2'-O-Me-cAMP may be a viable pharmacological means to strengthen the RPE barrier against the pathological choroidal endothelial cell invasion that occurs in macular degeneration.

PMID: 24039860 [PubMed - in process] PMCID: PMC3769400

Braz J Med Biol Res. 2013 Aug;46(8):659-69. doi: 10.1590/1414-431X20132903. Epub 2013 Aug 30.

SIRT1 negatively regulates amyloid-beta-induced inflammation via the NF-κB pathway.

Cao L, Liu C, Wang F, Wang H.

Tenth People's Hospital, School of Medicine, Affiliate of Tongji University, Department of Ophthalmology, Shanghai, China.

Abstract: Chronic inflammation induced by amyloid-beta (Aβ) plays a key role in the development of age-related macular degeneration (AMD), and matrix metalloproteinase-9 (MMP-9), interleukin (IL)-6, and IL-8 may be associated with chronic inflammation in AMD. Sirtuin 1 (SIRT1) regulates inflammation via inhibition of nuclear factor-kappa B (NF-κB) signaling, and resveratrol has been reported to prevent Aβ-induced retinal degeneration; therefore, we investigated whether this action was mediated via activation of SIRT1 signaling. Human adult retinal pigment epithelial (RPE) cells were exposed to Aβ, and overactivation and knockdown of SIRT1 were performed to investigate whether SIRT1 is required for abrogating Aβ-induced inflammation. We found that Aβ-induced RPE barrier disruption and expression of IL-6, IL-8, and MMP-9 were abrogated by the SIRT1 activator SRT1720, whereas alterations induced by Aβ in SIRT1-silenced

RPE cells were not attenuated by SRT1720. In addition, SRT1720 inhibited Aβ-mediated NF-κB activation and decrease of the NF-κB inhibitor, IκBα. Our findings suggest a protective role for SIRT1 signaling in Aβ-dependent retinal degeneration and inflammation in AMD.

PMID: 24036938 [PubMed - in process]

Eur J Neurosci. 2013 Aug 23. doi: 10.1111/ejn.12349. [Epub ahead of print]

Visual cortex organisation in a macaque monkey with macular degeneration.

Shao Y, Keliris GA, Papanikolaou A, Fischer MD, Zobor D, Jägle H, Logothetis NK, Smirnakis SM.

Max-Planck Institute for Biological Cybernetics, 72076, Tübingen, Germany.

Abstract: The visual field is retinotopically represented in early visual areas. It has been suggested that when adult primary visual cortex (V1) is deprived of normal retinal input it is capable of large-scale reorganisation, with neurons inside the lesion projection zone (LPZ) being visually driven by inputs from intact retinal regions. Early functional magnetic resonance imaging (fMRI) studies in humans with macular degeneration (MD) report > 1 cm spread of activity inside the LPZ border, whereas recent results report no shift of the LPZ border. Here, we used fMRI population receptive field measurements to study, for the first time, the visual cortex organisation of one macaque monkey with MD and to compare it with normal controls. Our results showed that the border of the V1 LPZ remained stable, suggesting that the deafferented area V1 zone of the MD animal has limited capacity for reorganisation. Interestingly, the pRF size of non-deafferented V1 voxels increased slightly (~20% on average), although this effect appears weaker than that in previous single-unit recording reports. Area V2 also showed limited reorganisation. Remarkably, area V5/MT of the MD animal showed extensive activation compared to controls stimulated over the part of the visual field that was spared in the MD animal. Furthermore, population receptive field size distributions differed markedly in area V5/MT of the MD animal. Taken together, these results suggest that V5/MT has a higher potential for reorganisation after MD than earlier visual cortex.

PMID: 24033706 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmic Epidemiol. 2013 Sep 18. [Epub ahead of print]

The Chinese American Eye Study: Design and Methods.

Varma R, Hsu C, Wang D, Torres M, Azen SP; the Chinese American Eye Study Group.

Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago , Chicago, IL , USA and.

Abstract Purpose: To summarize the study design, operational strategies and procedures of the Chinese American Eye Study (CHES), a population-based assessment of the prevalence of visual impairment, ocular disease, and visual functioning in Chinese Americans.

Methods: This population-based, cross-sectional study included 4570 Chinese participants aged 50 years and older, residing in the city of Monterey Park, California. Each eligible participant completed a detailed interview and eye examination. The interview included an assessment of demographic, behavioral and ocular risk factors and health-related and vision-related quality of life. The eye examination included measurements of visual acuity, intraocular pressure, visual fields, fundus and optic disc photography, a detailed anterior and posterior segment examination, and measurements of blood pressure, glycosylated hemoglobin levels, and blood glucose levels.

Results: The objectives of the CHES are to obtain prevalence estimates of visual impairment, refractive error, diabetic retinopathy, open-angle and angle-closure glaucoma, lens opacities, and age-related macular degeneration in Chinese Americans. In addition, outcomes include effect estimates for risk factors associated with eye diseases. Lastly, CHES will investigate the genetic determinants of myopia and glaucoma.

Conclusion: The CHES will provide information about the prevalence and risk factors of ocular diseases in one of the fastest growing minority groups in the United States.

PMID: 24044409 [PubMed - as supplied by publisher]

Genetics

Nat Genet. 2013 Sep 15. doi: 10.1038/ng.2741. [Epub ahead of print]

Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration.

Seddon JM, Yu Y, Miller EC, Reynolds R, Tan PL, Gowrisankar S, Goldstein JI, Triebwasser M, Anderson HE, Zerbib J, Kavanagh D, Souied E, Katsanis N, Daly MJ, Atkinson JP, Raychaudhuri S.

1] Ophthalmic Epidemiology and Genetics Service, New England Eye Center, Tufts Medical Center, Boston, Massachusetts, USA. [2] Department of Ophthalmology, Tufts University School of Medicine, Boston, Massachusetts, USA. [3] Sackler School of Graduate Biomedical Sciences, Tufts University, Boston, Massachusetts, USA.

Abstract: To define the role of rare variants in advanced age-related macular degeneration (AMD) risk, we sequenced the exons of 681 genes within all reported AMD loci and related pathways in 2,493 cases and controls. We first tested each gene for increased or decreased burden of rare variants in cases compared to controls. We found that 7.8% of AMD cases compared to 2.3% of controls are carriers of rare missense CFI variants (odds ratio (OR) = 3.6; P = 2 × 10-8). There was a predominance of dysfunctional variants in cases compared to controls. We then tested individual variants for association with disease. We observed significant association with rare missense alleles in genes other than CFI. Genotyping in 5,115 independent samples confirmed associations with AMD of an allele in C3 encoding p.Lys155Gln (replication P = 3.5 × 10 -5, OR = 2.8; joint P = 5.2 × 10-9, OR = 3.8) and an allele in C9 encoding p.Pro167Ser (replication P = 2.4 × 10-5, OR = 2.2; joint P = 6.5 × 10-7, OR = 2.2). Finally, we show that the allele of C3 encoding Gln155 results in resistance to proteolytic inactivation by CFH and CFI. These results implicate loss of C3 protein regulation and excessive alternative complement activation in AMD pathogenesis, thus informing both the direction of effect and mechanistic underpinnings of this disorder.

PMID: 24036952 [PubMed - as supplied by publisher]

Nat Genet. 2013 Sep 15. doi: 10.1038/ng.2740. [Epub ahead of print]

A rare nonsynonymous sequence variant in C3 is associated with high risk of age-related macular degeneration.

Helgason H, Sulem P, Duvvari MR, Luo H, Thorleifsson G, Stefansson H, Jonsdottir I, Masson G, Gudbjartsson DF, Walters GB, Magnusson OT, Kong A, Rafnar T, Kiemeney LA, Schoenmaker-Koller FE, Zhao L, Boon CJ, Song Y, Fauser S, Pei M, Ristau T, Patel S, Liakopoulos S, van de Ven JP, Hoyng CB, Ferreyra H, Duan Y, Bernstein PS, Geirsdottir A, Helgadottir G, Stefansson E, den Hollander AI, Zhang K, Jonasson F, Sigurdsson H, Thorsteinsdottir U, Stefansson K.

1] deCODE Genetics/Amgen, Reykjavik, Iceland. [2] School of Engineering and Natural Sciences,

University of Iceland, Reykjavik, Iceland. [3].

Abstract: Through whole-genome sequencing of 2,230 Icelanders, we detected a rare nonsynonymous SNP (minor allele frequency = 0.55%) in the C3 gene encoding a p.Lys155Gln substitution in complement factor 3, which, following imputation into a set of Icelandic cases with age-related macular degeneration (AMD) and controls, associated with disease (odds ratio (OR) = 3.45; P = 1.1 × 10-7). This signal is independent of the previously reported common SNPs in C3 encoding p.Pro314Leu and p.Arg102Gly that associate with AMD. The association of p.Lys155Gln was replicated in AMD case-control samples of European ancestry with OR = 4.22 and P = 1.6 × 10-10, resulting in OR = 3.65 and P = 8.8 × 10-16 for all studies combined. In vitro studies have suggested that the p.Lys155Gln substitution reduces C3b binding to complement factor H, potentially creating resistance to inhibition by this factor. This resistance to inhibition in turn is predicted to result in enhanced complement activation.

PMID: 24036950 [PubMed - as supplied by publisher]

Nat Genet. 2013 Sep 15. doi: 10.1038/ng.2758. [Epub ahead of print]

Identification of a rare coding variant in complement 3 associated with age-related macular degeneration.

Zhan X, Larson DE, Wang C, Koboldt DC, Sergeev YV, Fulton RS, Fulton LL, Fronick CC, Branham KE, Bragg-Gresham J, Jun G, Hu Y, Kang HM, Liu D, Othman M, Brooks M, Ratnapriya R, Boleda A, Grassmann F, von Strachwitz C, Olson LM, Buitendijk GH, Hofman A, van Duijn CM, Cipriani V, Moore AT, Shahid H, Jiang Y, Conley YP, Morgan DJ, Kim IK, Johnson MP, Cantsilieris S, Richardson AJ, Guymer RH, Luo H, Ouyang H, Licht C, Pluthero FG, Zhang MM, Zhang K, Baird PN, Blangero J, Klein ML, Farrer LA, Deangelis MM, Weeks DE, Gorin MB, Yates JR, Klaver CC, Pericak-Vance MA, Haines JL, Weber BH, Wilson RK, Heckenlively JR, Chew EY, Stambolian D, Mardis ER, Swaroop A, Abecasis GR.

1] Department of Biostatistics, Center for Statistical Genetics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA. [2].

Abstract: Macular degeneration is a common cause of blindness in the elderly. To identify rare coding variants associated with a large increase in risk of age-related macular degeneration (AMD), we sequenced 2,335 cases and 789 controls in 10 candidate loci (57 genes). To increase power, we augmented our control set with ancestry-matched exome-sequenced controls. An analysis of coding variation in 2,268 AMD cases and 2,268 ancestry-matched controls identified 2 large-effect rare variants: previously described p.Arg1210Cys encoded in the CFH gene (case frequency (fcase) = 0.51%; control frequency (fcontrol) = 0.02%; odds ratio (OR) = 23.11) and newly identified p.Lys155Gln encoded in the C3 gene (fcase = 1.06%; fcontrol = 0.39%; OR = 2.68). The variants suggest decreased inhibition of C3 by complement factor H, resulting in increased activation of the alternative complement pathway, as a key component of disease biology.

PMID: 24036949 [PubMed - as supplied by publisher]