FEATURED ARTICLE

Transcriptomic and proteomic retinal pigment epithelium signatures of age-related macular degeneration.

Nature Communications. 2022 Jul 26

Senabouth A, Daniszewski M, Lidgerwood GE, Liang HH, Hernández D, Mirzaei M, Keenan SN, Zhang R, Han X, Neavin D, Rooney L, Lopez Sanchez MIG, Gulluyan L, Paulo JA, Clarke L, Kearns LS, Gnanasambandapillai V, Chan CL, Nguyen U, Steinmann AM, McCloy RA, Farbehi N, Gupta VK, Mackey DA, Bylsma G, Verma N, MacGregor S, Watt MJ, Guymer RH, Powell JE, Hewitt AW, Pébay A.

There are currently no treatments for geographic atrophy, the advanced form of age-related macular degeneration. Hence, innovative studies are needed to model this condition and prevent or delay its progression. Induced pluripotent stem cells generated from patients with geographic atrophy and healthy individuals were differentiated to retinal pigment epithelium. Integrating transcriptional profiles of 127,659 retinal pigment epithelium cells generated from 43 individuals with geographic atrophy and 36 controls with genotype data, we identify 445 expression quantitative trait loci in cis that are associated with disease status and specific to retinal pigment epithelium subpopulations. Transcriptomics and proteomics approaches identify molecular pathways significantly upregulated in geographic atrophy, including in mitochondrial functions, metabolic pathways and extracellular cellular matrix reorganization. Five significant protein quantitative trait loci that regulate protein expression in the retinal pigment epithelium and in geographic atrophy are identified - two of which share variants with cis- expression quantitative trait loci, including proteins involved in mitochondrial biology and neurodegeneration. Investigation of mitochondrial metabolism confirms mitochondrial dysfunction as a core constitutive difference of the retinal pigment epithelium from patients with geographic atrophy. This study uncovers important differences in retinal pigment epithelium homeostasis associated with geographic atrophy.

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DRUG TREATMENT AND COMPLICATIONS

Risk, Prevalence, and Progression of Glaucoma in Eyes with Age-Related Macular Degeneration Treated with Intravitreal Anti-VEGF Injections.

American Journal of Ophthalmology. 2022 Aug 3

Shah SM, Boopathiraj N, Starr MR, Dalvin LA, AbouChehade J, Damento G, Garcia MD, Hodge DO, Bakri SJ, Sit AJ, Iezzi R.

Purpose: To examine the risk, prevalence, and progression of glaucoma development in age-related macular degeneration (AMD) eyes receiving intravitreal anti-VEGF injections compared to controls.

Design: Retrospective clinical cohort study.

Methods: : Retrospective review of eyes receiving intravitreal anti-VEGF injections from 1/1/2004-12/31/2013 for exudative AMD. Age- and sex-matched control groups of eyes included: eyes with non-exudative AMD (NEAMD) and no AMD. Eyes with a diagnosis of glaucoma or glaucoma suspect were reviewed for injection details, type and date of glaucoma diagnosis, glaucoma treatments, standard automated perimetry (SAP), and SD-OCT. Qualitative progression was determined by indication of glaucoma progression in provider notes. Quantitative progression was assessed based

on change in mean deviation (MD) on SAP, RNFL thickness on SD-OCT, and intraocular pressure (IOP).

Results: There were 707 eyes of 504 patients treated with anti-VEGF injections and 1008 eyes in the NEAMD and no AMD cohorts. There was no difference in glaucoma or suspect prevalence at initial presentation between eyes treated with injections and NEAMD (6.9% vs. 9.7%, p=0.22) or no AMD controls (vs. 8.5%, p=0.55). There was no difference in cumulative five-year probability of new glaucoma diagnosis after anti-VEGF injections compared to NEAMD (1.9% vs. 1.0%, p=0.69) or no AMD controls (vs. 1.6%, p=0.88). There was no difference in qualitative progression of glaucoma in the injection cohort vs. NEAMD (p=0.19) or no AMD controls (p=0.61). The rate of MD change in injection eyes was similar to NEAMD eyes (p=0.74) but greater than no AMD eyes (p=0.02). Eyes receiving injections required more topical glaucoma medications compared to NEAMD (p=0.03) and more glaucoma laser treatments compared to no AMD controls (p=0.009). Eyes receiving injections did not require more frequent incisional glaucoma surgery compared to NEAMD (21.0% vs. 15.0%, p=0.95) or no AMD controls (vs.10.0%, p=0.10).

Discussion/Conclusion: Eyes treated with intravitreal anti-VEGF injections for exudative AMD did not have increased risk of developing glaucoma compared to controls. Of those with a glaucoma diagnosis, exudative AMD eyes receiving injections required a greater number of topical glaucoma medications compared with NEAMD eyes and had a greater rate of MD loss than no AMD controls.

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DRUG TREATMENT

Incidence, predictors and re-treatment outcomes of recurrent myopic choroidal neo-vascularization.

PLoS One. 2022 Jul 21

Jain M, Narayanan R, Jana P, Mohamed A, Raman R, Verkicharla P, Padhy SK, Das AV, Chhablani J.

Objectives: To evaluate incidence, predictors, and re-treatment outcome of recurrent myopic choroidal neovascularization (m-CNV).

Methods: Retrospective consecutive observational series. From year 2014 to 2019, 167 eyes of 167 patients of treatment naïve m-CNV were enrolled. 59 and 108 eyes were treated with intra-vitreal ranibizumab and bevacizumab mono-therapy, respectively. Recurrence was defined as re-appearance of CNV activity, confirmed on optical coherence tomography (OCT) after at least 3 months of cessation of anti-VEGF therapy. Incidence of recurrence, predictors and re-treatment outcomes were studied.

Results: Overall, mean age and spherical equivalence (SE) was 47.95 ± 14.72 years and -12.19 ± 4.93 D respectively. Males constituted 50.9%. 44 eyes (26.4%) had a recurrence during a mean follow up of 16.5 ± 12.86 months. Kaplan-Meier survival analysis showed the risk of recurrence was 8, 26 and, 33.6% at 6, 12 and 18 months, respectively. Age (p = 0.511), gender (p = 0.218), SE (p = 0.092), anti-VEGF (p = 0.629) and baseline BCVA (p = 0.519) did not influence recurrence. Number of injections administered to control the disease in the first episode was the only significant predictor of recurrence (Cox Proportional Hazard Ratio 2.89-3.07, 95% Confidence Interval: 1.28-7.45; p = 0.005). At 12 months, eyes requiring one injection in first episode had a recurrence rate of 12% versus 45% in eyes requiring 3 or more injections in the first episode. A mean number of 1.9 additional injections

per eye was needed during re-treatment. Final BCVA in the recurrence group was similar to that of non-recurrence group (0.53 ± 0.40 versus 0.55 ± 0.36 LogMAR; p = 0.755). Baseline BCVA (p = 0.0001) was the only predictor of final visual outcome irrespective of anti-VEGF drug (p = 0.38).

Conclusion: Eyes requiring greater number of injections for disease control in first episode are "at risk" of early m-CNV recurrence. However, recurrence does not adversely affect visual outcome, if treated adequately.

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DIAGNOSIS AND IMAGING

Analysis of microvascular abnormalities in obesity: a comparative study with healthy subjects using swept source optical coherence tomography angiography and adaptive optics.

Ophthalmologica 2022 Jul 25.

Rolland M, Mohammedi K, Korobelnik JF, Cadart O, Delyfer MN, Cherifi B, Rougier MB.

Purpose: To analyze retinal microvasculature in obese subjects as compared to a normal-weight population.

Methods: In this case-control observational study, swept-source optical coherence tomography angiography (SS-OCTA) and adaptive optics (AO) were performed in eyes of non-diabetic, non-hypertensive, obese patients and in healthy controls. AO was used to calculate the wall-to-lumen ratio (WLR). The foveal avascular zone (FAZ), the macular vessel density (VD) and the macular perfusion density of the superficial and deep capillary plexuses were analyzed in 6x6mm macular OCTA cubes. SS-OCTA was also used to measure the choroidal thickness, the retinal nerve fiber layer (RNFL) and the VD of the retinal peripapillary capillary plexus (RPCP).

Results: The obese group included 45 eyes (24 patients), and the control group included 46 eyes (23 subjects). The central macular density and perfusion density were significantly lower in obese patients compared to controls, in the deep retinal layer (0.28 [0.01-0.69] versus 1.24 [0.82-1.66], p=0.006 and 0.006 [0.001-0.015] versus 0.025 [0.016-0.034], p=0.01), respectively, after adjustment for systolic blood pressure. No differences were found in macular vascular density in other areas, FAZ (circularity, area, perimeter), choroidal thickness, RNFL. WLR was increased in obese patients (0.252 [0.246-0.259] versus 0.239 [0.231-0.245] in controls, p=0.016).

Conclusion: Obesity was associated with retinal microvascular changes regardless of the presence of diabetes and hypertension. Our findings suggest the presence of infraclinical microvascular changes directly associated with obesity, which can be identified noninvasively through retinal imaging.

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ADVERSE EVENTS

Risk of Ocular Adverse Events With Taxane-Based Chemotherapy.

JAMA Ophthalmology 2022 Aug 11.

Sodhi M, Yeung SN, Maberley D, Mikelberg F, Etminan M.

Importance: Taxane-based chemotherapy agents, such as docetaxel and paclitaxel, are used for treating a wide range of cancers. Although much has been published on adverse events related to taxanes, data on ocular outcomes with these very important drugs are scant.

Objective: To quantify the risk of 3 mutually exclusive ocular adverse events of epiphora, cystoid macular edema (CME), and optic neuropathy with taxane-based chemotherapy agents by undertaking a large pharmacoepidemiologic study.

Design, Setting, and Participants: This retrospective cohort study design used a private health-claims database from the US that captures health information of more than 150 million enrollees. The study team created a cohort of new users of women with cancer who were taking taxane-based chemotherapy (docetaxel or paclitaxel) and new users of tamoxifen as controls. Study members were observed to the first incidence of each of the 3 mutually exclusive outcomes. An analysis of taxane-only users was also undertaken.

Exposure: Tamoxifen (unexposed) and taxanes (ie, paclitaxel and docetaxel) as the exposed. MAIN

Outcomes And Measures: First diagnosis of (1) epiphora, (2) cystoid macular edema (CME), or (3) optic neuropathy ascertained using International Statistical Classification of Diseases and Related Health Problems, Ninth Revision or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

Results: Among the 18 219 users in the epiphora analysis and optic neuropathy analysis, there were 1824 taxane users (paclitaxel and docetaxel) (age, mean [SD], 62.1 [12.7] years) and 16 395 tamoxifen users (age, mean [SD], 54.6 [12.8] years), respectively. The crude hazard ratio (HR) for epiphora was 5.55 (95% CI, 2.99-10.29) and adjusted HR was 5.15 (95% CI, 2.79-9.54). For optic neuropathy, the crude HR was 4.43 (95% CI, 1.10-17.82) and the adjusted HR was 4.44 (95% CI, 1.04-18.87). Among the 18 433 users in the CME analysis, there were 1909 taxane users (paclitaxel and docetaxel) (age, mean [SD], 62.5 years) and 16 524 tamoxifen users (age, mean [SD], 54.6 years). The crude HR for CME comparing taxane users with tamoxifen users was 1.37 (95% CI, 0.72-2.60) and adjusted HR was 1.33 (95% CI, 0.70-2.53). The HRs for epiphora and CME in the taxane cohort during the time of exposure compared with the period prior to use of the drugs were 2.86 (95% CI, 1.11-7.39) and 2.27 (95% CI, 0.68-7.54), respectively.

Conclusions and Relevance: In a cohort of women who were using taxane chemotherapy agents, there was an association with elevated risk for epiphora, CME, and optic neuropathy. Ophthalmologists and oncologists should be aware of these adverse events in women with breast cancer who receive these drugs.

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GENETICS

Heritability and risk factors of incident small and large drusen in the Copenhagen Twin Cohort Eye Study: a 20-year follow-up.

Ophthalmologica 2022 Jul 25

Belmouhand M, Rothenbuehler SP, Bjerager J, Dabbah S, Hjelmborg JB, Munch IC, Dalgård C, Larsen M.

Introduction: The transition from a normal fundus to one with early drusen (≥ 20 small hard drusen) to age-related macular degeneration (AMD) in the form of drusen ≥ 63 µm in diameter is of interest, because small hard drusen may be precursors of large drusen. Study of AMD precursors lesions may provide valuable insight into factors that initiate AMD. Here, the progression of drusen was studied over an interval of 20 years in a population-based twin cohort.

Methods: Single-center, 20-year follow-up of 138 twins, including biometry, fundus optical coherence tomography, and fundus photography. Macular characteristics were hierarchically classified as (per eye) 1) < 20 small hard drusen, 2) ≥ 20 small hard drusen, 3) drusen ≥ 63 µm, or 4) ≥ 20 small hard drusen combined with drusen ≥ 63 µm. Additive and dominant genetic effects as well as shared and non-shared environmental effects were analyzed in a bivariate biprobit model with a classic liability-threshold approach and polygenic modeling with random effects.

Results: Median participant age was 59 (range 41 - 66) years. Of 25 (18%) cases of incident macular drusen, 7 had ≥ 20 small hard drusen, and 18 had drusen ≥ 63 µm at follow-up, whereas no participant had developed both traits simultaneously. Smoking was associated with incident ≥ 20 small hard drusen ($p = 0.04$) and incident drusen ≥ 63 µm ($p = 0.003$). Having ≥ 20 small hard drusen at baseline was associated with incident drusen ≥ 63 µm at follow-up ($p = 0.02$). Development of drusen ≥ 63 µm was attributable to 49% genetic effects and 51% environmental effects.

Conclusion: The risk of progressing from 0-19 small hard macular drusen per eye to having ≥ 20 small hard drusen or drusen ≥ 63 µm at follow-up was associated with smoking and genetic predisposition. Having ≥ 20 small hard drusen in the absence of drusen ≥ 63 µm at baseline was associated with incident drusen ≥ 63 µm when examined 20 years later. The study confirms that small hard macular drusen is a forewarning of AMD and that progression to AMD may be hindered by avoidance of smoking.

DOI: 10.1159/000525652

RISK OF DISEASE

Systemic disease associations with angioid streaks in a large healthcare claims database.

Eye (London). 2022 Aug 1.

Nadelmann JB, Li Y, McGeehan B, Yu Y, VanderBeek BL.

Background/Objectives: To assess systemic associations of angioid streaks (AS) using a large US healthcare database.

Subjects/Methods: A retrospective cross-sectional study was conducted of patients diagnosed with AS in a large, national US insurer from 2000-2019. Cases were matched 1:5 to controls. The prevalence rates of established associated disease states and other systemic diseases were calculated and compared using logistic regression. Additionally, the rate of anti-VEGF treatment was assessed as a proxy for the incidence of choroidal neovascularization (CNV).

Results: One thousand eight hundred fifty-two cases of AS and 9028 matched controls were included. The rates of association between AS and the well-characterized conditions included: Pseudoxanthoma elasticum (PXE)-228 patients (12.3%), Ehlers-Danlos syndrome-18 patients (1.0%), Paget's disease-6 patients (0.3%), hemoglobinopathies-30 patients (1.6%), and idiopathic-1573 patients (84.9%). There was a statistically higher prevalence of the following less classically

associated diseases among patients with AS compared to controls: hereditary spherocytosis (1.7% vs. 0.6%, p < 0.001), connective tissue disease (1.0% vs 0.3%, p < 0.001) and non-exudative age-related macular degeneration (33.9% vs 10.6%, p < 0.001). Among 1442 eligible cases analyzed, 427 (29.6%) received at least 1 anti-VEGF injection with 338 (23.4%) patients having the injection after their AS diagnosis.

Conclusions: In the largest collection of AS patients to date, the classical teaching of systemic disease associations occur at rates far, far lower than previously reported. The association of AS with other less reported diseases highlights new potential associations and may contribute to the understanding of AS formation.

DOI: 10.1038/s41433-022-02189

PATHOGENESIS

Extramacular Drusen and Progression of Age-related Macular Degeneration (AMD); Age-related Eye Disease Study 2 Report 30.

Ophthalmology Retina. 2022 Aug 5

Domalpally A, Xing B, Pak JW, Agron E, Ferris FL 3rd, Clemons TE, Chew EY.

Purpose: To identify the prevalence of drusen outside the macula and their role in progression of age-related macular degeneration (AMD).

Design: Retrospective analysis of a prospective cohort study

Participants: 4168 eyes (2998 participants) with intermediate AMD in one or both eyes enrolled in the Age-Related Eye Disease Study 2 (AREDS2), a 5-year multicenter study of nutritional supplements were included.

Method: Baseline 3 field 30-degree color photographs were evaluated for drusen characteristics outside the macular grid including size, area and location. The characteristics of extramacular drusen were compared to drusen within the macula.

Main Outcome Measures: Progression rates to late AMD

Results: Extramacular drusen were seen in 3624 (86.9% eyes) but represented a small area (< 0.5mm2) in 50.3% of eyes with only 17.5% having an area > 1 disc area (DA). Eyes with extramacular drusen had larger macular drusen size and larger macular drusen area compared to eyes without (p < 0.001). Extramacular drusen were not associated with progression to late AMD; hazard ratio adjusted for baseline age, gender, smoking, AMD severity level and reticular pseudodrusen for 4043 eyes at risk of developing late AMD over 5 years was 1.17 (95% confidence interval [CI], 0.88,1.54; P = 0.27) for geographic atrophy and 0.96 (95% CI, 0.76,1.2; P = 0.7) for neovascular AMD.

Conclusion: Drusen outside the macula are commonly seen in eyes with AMD and are more frequent with increasing drusen burden within the macula. In eyes with intermediate AMD, extramacular drusen do not confer additional risk to previously identified risk factors in progression to late AMD.

DOI: 10.1016/j.oret.2022.08.001

REVIEW

Retinitis Pigmentosa: Burden of Disease and Current Unmet Needs.

Clinical Ophthalmology. 2022 Jun 20

Cross N, van Steen C, Zegaoui Y, Satherley A, Angelillo L.

Retinitis Pigmentosa (RP), a group of inherited retinal dystrophies characterised by progressive vision loss, is the leading cause of visual disability and blindness in subjects less than 60 years old. Currently incurable, therapy is aimed at restricting degeneration of vision, treating complications, and helping patients to cope with the psychosocial impact of their disease. Hence, RP is associated with a high burden of disease. This paper describes the current therapeutic landscape for RP and the disease burden for patients, caregivers, and society. A review of available data was conducted in three stages: (1) a literature search of publicly available information on all domains of RP; (2) a systematic literature review using Medline, Embase, the Cochrane Library and grey literature (GlobalData) on epidemiology and cost of RP; and (3) qualitative research with senior physicians treating RP patients in the EU4 and the UK to validate research findings from secondary sources. RP severely impacts the daily lives of over a million people worldwide. Progressive vision loss significantly affects the ability to perform basic daily tasks, to maintain employment, and maintain independence. Consequently, most patients will experience reduced quality of life, with a greater emotional and psychological impact than other conditions related to vision loss such as diabetic retinopathy or age-related macular degeneration. RP is also associated with a high level of carer burden, arising from psychological and financial stress. The therapeutic landscape for RP is limited, with few treatment options and minimal guidance for the diagnosis, treatment, and care of patients. A curative intervention, voretigene neparvovec (Luxturna®), only exists for 1-6% of patients. Although disease management can be successful in developing coping strategies, most patients live with this chronic, progressive condition without interventions to change the disease course. Innovative new therapies can transform the therapeutic landscape, provided appropriate clinical guidance is forthcoming.

DOI: 10.2147/OPTH.S365486

Prevalence of diabetic retinopathy in Indigenous and non-Indigenous Australians: a systematic review and meta-analysis.

Ophthalmology. 2022 Aug 2

Chia MA, Taylor JR, Stuart KV, Khawaja AP, Foster PJ, Keane PA, Turner AW.

Topic: This systematic review and meta-analysis summarises evidence relating to the prevalence of diabetic retinopathy (DR) among Indigenous and non-Indigenous Australians.

Clinical Relevance: Indigenous Australians suffer disproportionately from diabetes-related complications. Exploring ethnic variation in disease is important for equitable distribution of resources and may lead to identification of ethnic-specific modifiable risk factors. Existing DR prevalence studies comparing Indigenous and non-Indigenous Australians have shown conflicting results.

Methods: This study was conducted following Joanna Briggs Institute guidance on systematic reviews of prevalence studies (PROSPERO ID: CRD42022259048). We performed searches of Medline

(Ovid), EMBASE, and Web of Science until October 2021, using a strategy designed by an information specialist. We included studies reporting DR prevalence among diabetic patients in Indigenous and non-Indigenous Australian populations. Two independent reviewers performed quality assessments using a 9-item appraisal tool. Meta-analysis and meta-regression were performed using double arcsine transformation and a random-effects model comparing Indigenous and non-Indigenous subgroups.

Results: Fifteen studies with 8219 participants met criteria for inclusion. The Indigenous subgroup scored lower on the appraisal tool compared to the non-Indigenous subgroup (mean score 50% vs 72%, p=0.04). In the unadjusted meta-analysis, DR prevalence in the Indigenous subgroup (30.2% [95%CI: 24.9-25.7]) did not differ significantly (p=0.17) from the non-Indigenous subgroup (23.7% (95%CI: 16.8-31.4]). After adjusting for age and for quality, DR prevalence was higher in the Indigenous subgroup (p-values<0.01), with prevalence ratio point estimates ranging between 1.72-2.58, depending on the meta-regression model. For the secondary outcomes, prevalence estimates were higher in the Indigenous subgroup for diabetic macular oedema (8.7% vs 2.7%, p=0.02) and vision-threatening DR (8.6% vs 3.0%, p=0.03), but not for proliferative DR (2.5% vs 0.8%, p=0.07).

Conclusion: Indigenous studies scored lower for methodological quality, raising the possibility that systematic differences in research practices may be leading to underestimation of disease burden. After adjusting for age and for quality, we found a higher DR prevalence in the Indigenous subgroup. This contrasts with a previous review which reported the opposite finding of lower DR prevalence using unadjusted pooled estimates. Future epidemiological work exploring DR burden in Indigenous communities should aim to address methodological weaknesses identified by this review.

DOI: 10.1016/j.ophtha.2022.07.024

PATIENT EXPERIENCE

Anxiety in Patients with Neovascular Age-related Macular Degeneration.

Ophthalmic Epidemiology 2022 Jul 11

Weinstein O, Cohen AD, Levy J, Zloto O, Freud T, Krieger I, Comaneshter D, Shemesh R.

Purpose: The main objective of the study is to investigate the prevalence of anxiety in patients with neovascular age-related macular degeneration (nAMD).

Methods: A retrospective cross-sectional study of 3 304 nAMD patients and 16 515 age- and gender-matched controls. The proportions of patients with anxiety were compared between the groups using univariate analyses and a multivariate logistic regression model. Proportion of anxiety in patients with nAMD was compared with the proportion of anxiety in controls, matched for age and gender. Data was obtained from the largest health maintenance organization in Israel (Clalit Health Services) with 4 200 000 members.

Results: The mean age of patients was 79.7 years; 54.8% were females; Anxiety was more common in patients with nAMD (13.2%) compared to the control group (10.2%) (OR 1.3; 95%CI 1.2-1.5). Multivariate logistic regression analysis revealed a significant association between anxiety and nAMD (OR 1.3; 95% CI: 1.2-1.5), adjusted for age, gender, and socio-economic status.

Conclusion: Our study demonstrated that anxiety is more common in patients with nAMD compared to a control group. Physicians treating patients with nAMD should be aware of this association, in order to provide appropriate care for the anxiety associated with nAMD.

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