

FEATURED ARTICLE

Genome-wide association meta-analysis of 88,250 individuals highlights pleiotropic mechanisms of five ocular diseases in UK Biobank.

EBioMedicine 2022 Jul 13

Xue Z, Yuan J, Chen F, Yao Y, Xing S, Yu X, Li K, Wang C, Bao J, Qu J, Su J, Chen H.

Background: Ocular diseases may exhibit common clinical symptoms and epidemiological comorbidity. However, the extent of pleiotropic mechanisms across ocular diseases remains unclear. We aim to examine shared genetic etiology in age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, retinal detachment (RD), and myopia.

Methods: We analyzed genome-wide association analyses for the five ocular diseases in 43,877 cases and 44,373 controls of European ancestry from UK Biobank, estimated their genetic relationships (LDSC, GNOVA, and Genomic SEM), and identified pleiotropic loci (ASSET and METASOFT).

Findings: The genetic correlation of common SNPs revealed a meaningful genetic structure within these diseases, identifying genetic correlations between AMD, DR, and glaucoma. Cross-trait meta-analysis identified 23 pleiotropic loci associated with at least two ocular diseases and 14 loci unique to individual disorders (non-pleiotropic). We found that the genes associated with these shared genetic loci are involved in neuron differentiation ($P = 8.80 \times 10^{-6}$) and eye development systems ($P = 3.86 \times 10^{-5}$), and single cell RNA sequencing data reveals their heightened gene expression from multipotent progenitors to other differentiated retinal cells during retina developmental process.

Interpretation: These results highlighted the potential common genetic architectures among these ocular diseases and can deepen the understanding of the molecular mechanisms underlying the related diseases.

DOI: [10.1016/j.ebiom.2022.104161](https://doi.org/10.1016/j.ebiom.2022.104161)

DRUG TREATMENT

Topical treatment of diabetic macular edema using dexamethasone ophthalmic suspension: A randomized, double-masked, vehicle-controlled study.

Acta Ophthalmologica. 2022 Jul 18.

Stefansson E, Loftsson T, Larsen M, Papp A, Kaarniranta K, Munk MR, Dugel P, Tadayoni R; DX-211 study group.

Purpose: To evaluate topical dexamethasone ophthalmic suspension OCS-01 (Oculus SA, Lausanne, Switzerland) in diabetic macular edema (DME).

Methods: This was a multicenter, double-masked, parallel-group, randomized, Phase 2 study. Patients aged 18-85 years with DME of <3 years duration, ETDRS central subfield thickness $\geq 310 \mu\text{m}$ by SD-OCT, and ETDRS letter score ≤ 73 and ≥ 24 in the study eye were randomized 2:1 to OCS-01 or matching vehicle, 1 drop 3 times/day for 12 weeks. Efficacy was evaluated as change from baseline to Week 12 of ETDRS letter score and central macular thickness (CMT). The primary analysis used a

linear model with baseline ETDRS letters as a covariate, and missing data imputed using multiple imputation pattern mixture model techniques. Active treatment was considered superior to vehicle if the one-sided p-value was <0.15 and the difference in mean change from baseline in ETDRS letters was >0 .

Results: Mean CMT showed a greater decrease from baseline with OCS-01 (N = 99) than vehicle (N = 45) at Week 12 (-53.6 vs -16.8 μm , $p = 0.0115$), with significant differences favouring OCS-01 from Weeks 2 to 12. OCS-01 was well-tolerated, and increased intraocular pressure was the most common adverse event. Mean change in ETDRS letter score from baseline to Week 12 met the p was $+2.6$ letters with topical OCS-01 and 1 letter with vehicle ($p = 0.125$). In a post-hoc analysis, there was a greater difference in patients with baseline BCVA ≤ 65 letters, the OCS-01 group improved 3.8 letters compared with 0.9 letters with vehicle.

Conclusion: Topical OCS-01 was significantly more effective than vehicle in improving central macular thickness in patients with DME. Visual improvement was better in eyes with lower baseline vision.

DOI: [10.1111/aos.15215](https://doi.org/10.1111/aos.15215)

RISK OF DISEASE

The risk of retinal vein occlusion among patients with neovascular age related macular degeneration: a large-scale cohort study.

Eye (London) 2022 July 1

Weinstein O, Kridin M, Kridin K, Mann O, Cohen AD, Zloto O.

Purpose: To examine the risk for retinal-vein-occlusion (RVO) in patients with neovascular age-related-macular-degeneration (AMD) as compared to age- and sex-matched controls.

Method: This is a population-based, cohort study. The study encompassed 24,578 consecutive patients with neovascular AMD and 66,129 control subjects. Multivariate cox regression analysis was utilized to detect the risk of RVO among patients with neovascular AMD. Predictors of RVO in patients with neovascular AMD were identified using multivariate logistic regression analysis. Mortality of patients was assessed using Kaplan-Meier method.

Results: The incidence rate of RVO was estimated at 1.25 (95% CI, 1.06-1.45) per 1000 person-years among patients with neovascular AMD and 0.25 (95% CI, 0.20-0.31) per 1000 person-years among controls. Patients with neovascular AMD were associated with an increased risk of RVO (adjusted HR, 4.35; 95% CI, 3.34-5.66; $P < 0.001$). Among patients with neovascular AMD, older age (≥ 79.0 years) was associated with a decreased risk of RVO (adjusted OR, 0.50; 95% CI, 0.37-0.70; $P < 0.001$), whilst a history of glaucoma increased the likelihood of RVO (adjusted OR, 2.66; 95% CI, 1.94-3.65; $P < 0.001$). Patients with neovascular AMD and comorbid RVO had a comparable risk of all-cause mortality relative to other patients with neovascular AMD (HR, 0.90; 95% CI, 0.67-1.22; $P = 0.500$)

Conclusions: An increased risk of RVO was found among patients with neovascular AMD. Younger age and glaucoma predicted the development of RVO in patients with neovascular AMD. Awareness of this comorbidity is of benefit for clinicians as patients with neovascular AMD might be carefully examined for RVO signs and complications.

DOI: [10.1038/s41433-022-02163-7](https://doi.org/10.1038/s41433-022-02163-7)

CASE STUDY

Unusual Presentation of Acute Hydroxychloroquine Retinopathy.

Ocular Immunology and Inflammation 2022 Jul 8

Lian YY, Ma YC, Cheng CK.

Purpose: To report a rare case of cystoid macular edema (CME) as a presentation of acute hydroxychloroquine-related retinal toxicity.

Observations: A 37-year-old female patient visited our ophthalmology department in October 2019 complaining of bilateral blurred vision and metamorphopsia for 3 days. Best-corrected visual acuity (BCVA) was 6/6 in the right eye and 6/7.5 in the left eye under the Snellen E chart. Before presentation, she had taken hydroxychloroquine as a "reproduction-facilitating medication" prior to the in vitro fertilization (IVF) procedures with the daily dose of 200 mg for 1 week in March 2019 and 400 mg for 1 month in September 2019. She also took a combination of several herbal medicine including "Angelica sinensis" for 6 months in this period. On examination, typical signs of hydroxychloroquine maculopathy such as bilateral paracentral retinal pigment epithelium (RPE) change in blue autofluorescence and loss of the paracentral ellipsoid zone in optical coherence tomography ("flying saucer sign") were noted. CME was also found in fluorescein angiography. Her symptoms improved gradually after cessation of hydroxychloroquine and herb medicine without any further treatment. Resolution of bilateral CME was revealed at 16 weeks with final bilateral BCVA 6/6.

Conclusions and Importance: Although rare, acute hydroxychloroquine maculopathy could occur in patients with concomitant usage of medications that could interfere with P450 enzymes system. Careful acquisition of drug history and serial ophthalmological examinations are advised in using hydroxychloroquine for disease management even for a short period of time.

DOI: [10.1080/09273948.2022.2088563](https://doi.org/10.1080/09273948.2022.2088563)

EARLY RESEARCH

Transcranial direct current stimulation in the treatment of visual hallucinations in Charles Bonnet syndrome: A randomized placebo-controlled crossover trial.

Ophthalmology. 2022 Jul 8

DaSilva Morgan K, Schumacher J, Collerton D, Colloby S, Elder GJ, Olsen K, Ffytche DH, Taylor JP.

Objective: To investigate the potential therapeutic benefits and tolerability of inhibitory transcranial direct current stimulation (tDCS) on the remediation of visual hallucinations in Charles Bonnet Syndrome (CBS).

Design: Randomized, double-masked(blind), placebo-controlled crossover trial.

Participants: Sixteen individuals diagnosed with CBS secondary to visual impairment caused by eye disease experiencing recurrent visual hallucinations.

Intervention: All participants received four consecutive days of active and placebo cathodal stimulation (current density: 0.29mA/cm²) to the visual cortex (Oz) over two defined treatment weeks, separated by a four-week wash-out period.

Main Outcome Measures: Ratings of visual hallucination frequency and duration following active and placebo stimulation, accounting for treatment order, using a 2x2 repeated measures model. Secondary outcomes included impact ratings of visual hallucinations and electrophysiological measures.

Results: When compared to placebo treatment, active inhibitory stimulation of visual cortex resulted in a significant reduction in the frequency of visual hallucinations measured by the North East Visual Hallucinations Interview, with a moderate-to-large effect size. Impact measures of visual hallucinations improved in both placebo and active conditions suggesting support and education for CBS may have therapeutic benefits. Participants who demonstrated greater occipital excitability on electroencephalography assessment at the start of treatment were more likely to report a positive treatment response. Stimulation was found to be tolerable in all participants with no significant adverse effects reported, including no deterioration in pre-existing visual impairment.

Conclusions: Findings indicate that inhibitory tDCS of visual cortex may reduce the frequency of visual hallucinations in people with CBS, particularly individuals who demonstrate greater occipital excitability prior to stimulation. tDCS may offer a feasible, novel intervention option for CBS with no significant side effects, warranting larger scale clinical trials to further characterize its efficacy.

DOI: [10.1016/j.ophtha.2022.06.041](https://doi.org/10.1016/j.ophtha.2022.06.041)

EPIDEMIOLOGY

Long-term incidence and risk factors of macular fibrosis, macular atrophy, and macular hole in eyes with myopic neovascularization.

Ophthalmology Retina. 2022 Jun 27.

Cicinelli MV, La Franca L, De Felice E, Rabiolo A, Marchese A, Battaglia Parodi M, Introini U, Bandello F.

Purpose: To identify the risk factors associated with myopic macular neovascularization (mMNV)-related complications in patients treated with intravitreal anti-vascular endothelial growth factor (VEGF) agents.

Design: Longitudinal cohort study.

Participants: Myopic eyes (n=313) with active mMNV and median[interquartile range, IQR] follow-up of 42[18-68] months after initiation of anti-VEGF treatment.

Methods: Patients' clinical and mMNV characteristics were collected at baseline. Subsequent optical coherence tomography (OCT) scans were inspected for mMNV-related complications. Best-measured visual acuity (BMVA) values were retrieved from each visit.

Main Outcome Measures: Incidence rate and hazard ratio (HR)(95% confidence interval, CI) of risk factors for fibrosis and macular atrophy calculated with Kaplan-Meier curves and Cox regression models. Crude incidence of macular hole (MH). Longitudinal BMVA changes.

Results: Five-year incidence of fibrosis, atrophy, and macular hole were 34%, 26%, and 8%, respectively. Rate of fibrosis[95% CI] was 10.3[8.25-12.6] for 100 person-year. Risk factors were subfoveal mMNv location (HR[95% CI]=12.7[2.70-56.7] vs. extrafoveal, $p=0.001$) and intraretinal fluid at baseline (HR[95% CI]=1.75[1.05-2.98], $p=0.03$). Rate of macular atrophy[95% CI] was 6.5 [5-8.3] for 100 person-year. Risk factors were diffuse (HR[95% CI]=2.20[1.13-5.45] vs. tessellated fundus, $p=0.02$) or patchy chorioretinal atrophy (HR[95% CI]=3.17[1.32-7.64] vs. tessellated fundus, $p=0.01$) at baseline, and more numerous anti-VEGF injections before baseline (HR[95% CI]=1.21[1.06-1.38] for each treatment, $p=0.005$). Eyes with fibrosis and macular atrophy had faster BMVA decay over follow-up. Twenty eyes (6%) developed MH. Two subtypes of MH were identified: "atrophic" and "tractional".

Conclusion: mMNv-related complications are common in the long term despite initially successful treatment and have detrimental effects on visual acuity. Insights on their incidence and risk factors may help for future treatments to mitigate sight-threatening outcomes.

DOI: [10.1016/j.oret.2022.06.009](https://doi.org/10.1016/j.oret.2022.06.009)

PATIENT OUTCOMES

Anti-VEGF treatment discontinuation and interval in neovascular age-related macular degeneration in the US.

American Journal of Ophthalmology 2022 Jun 20

Bakri SJ, Karcher H, Andersen S, Souied EH.

Purpose: To assess the association between treatment interval and likelihood of anti-vascular endothelial growth factor (anti-VEGF) discontinuation among patients with neovascular age-related macular degeneration (nAMD) in a real-world setting US.

Design: Retrospective clinical cohort study.

Methods: Health insurance claims data from the IBM MarketScan® Commercial and Medicare Supplemental databases were retrospectively reviewed to identify adults with nAMD who received anti-VEGF for the first time between 1 January 2011 and 30 June 2020. The proportion of discontinued patients was analyzed using Kaplan-Meier curves. Cox proportional hazards models were used to examine the association between treatment intervals at 24 months and anti-VEGF discontinuation.

Results: The analysis included 8,167 patients on continuous, unilateral anti-VEGF treatment for at least 24 months. Baseline demographics and clinical characteristics were well balanced between treatment interval groups. The overall rate of discontinuation from 24 months until 60 months after treatment initiation was 30.4%. At 60 months, patients on shorter treatment intervals were more likely to remain on treatment than those on longer intervals, ranging from 76.8% (4-week interval group) to 60.6% (>12-week interval group) and corresponding to a 28% lower likelihood (HR [SE] 0.72 [0.12], $p<0.01$) and 55% higher likelihood of discontinuing treatment (HR [SE] 1.55 [0.07], $p<0.01$), respectively, compared with the 8-week group.

Conclusions: nAMD patients on longer anti-VEGF treatment intervals at 24 months had consistently higher discontinuation rates than patients on shorter intervals in the following years. This highlights the need to support and educate patients on long treatment intervals to continue with their treatment.

DOI: [10.1016/j.ajo.2022.06.005](https://doi.org/10.1016/j.ajo.2022.06.005)

How Vision Is Impaired From Aging to Early and Intermediate Age-Related Macular Degeneration: Insights From ALSTAR2 Baseline.

Translational Vision Science & Technology 2022 Jul 8

Owsley C, Swain TA, McGwin G Jr, Clark ME, Kar D, Crosson JN, Curcio CA.

Purpose: We hypothesize the first visual dysfunction in transitioning to early and intermediate age-related macular degeneration (AMD) is delayed rod-mediated dark adaptation (RMDA), owing to impaired photoreceptor sustenance from the circulation. This analysis from the Alabama Study on Early Age-related Macular Degeneration 2 provides insight on our framework's validity, comparing RMDA and other visual tests among older normal, early, and intermediate AMD eyes.

Methods: AMD disease severity was determined via fundus photos using the Age-Related Eye Disease Study nine-step system. Visual functions evaluated were RMDA 5°, acuity, contrast sensitivity (photopic, mesopic), and light sensitivity for a macular grid (scotopic, mesopic, photopic). Presence versus absence of subretinal drusenoid deposits (SDD) was identified through multimodal imaging.

Results: One eye from each of 481 persons (mean age, 72 years) was evaluated. All visual functions were significantly worse with increasing AMD disease severity. Using z-scores to standardize visual function measures across groups, the greatest difference in probability density functions between older normal and intermediate AMD was for RMDA. Early and intermediate AMD eyes with SDD present had longer rod intercept times than eyes with SDD absent. SDD absent eyes also exhibited delayed RMDA and wide probability density functions relative to normal eyes.

Conclusions: Among the visual functions evaluated, RMDA best discriminates among normal, early AMD, and intermediate AMD eyes. The Alabama Study on Early Age-related Macular Degeneration 2 will evaluate whether AMD's natural history confirms our hypothesis at the 3-year follow-up.

Translational Relevance: Results support a sequence of visual function impairments in aging and AMD, suggesting RMDA as a promising outcome for evaluating interventions in early disease.

DOI: [10.1167/tvst.11.7.17](https://doi.org/10.1167/tvst.11.7.17)