

FEATURED ARTICLE

Genetic treatment for autosomal dominant inherited retinal dystrophies: approaches, challenges and targeted genotypes.

British Journal of Ophthalmology. 2022 Aug 29

Daich Varela M, Georgiadis T, Michaelides M.

Inherited retinal diseases (IRDs) have been in the front line of gene therapy development for the last decade, providing a useful platform to test novel therapeutic approaches. More than 40 clinical trials have been completed or are ongoing, tackling autosomal recessive and X-linked conditions, mostly through adeno-associated viral vector delivery of a normal copy of the disease-causing gene. However, only recently has autosomal dominant (ad) disease been targeted, with the commencement of a trial for rhodopsin (RHO)-associated retinitis pigmentosa (RP), implementing antisense oligonucleotide (AON) therapy, with promising preliminary results (NCT04123626). Autosomal dominant RP represents 15%-25% of all RP, with RHO accounting for 20%-30% of these cases. Autosomal dominant macular and cone-rod dystrophies (MD/CORD) correspond to approximately 7.5% of all IRDs, and approximately 35% of all MD/CORD cases, with the main causative gene being BEST1. Autosomal dominant IRDs are not only less frequent than recessive, but also tend to be less severe and have later onset; for example, an individual with RHO-adRP would typically become severely visually impaired at an age 2-3 times older than in X-linked RPGR-RP. Gain-of-function and dominant negative aetiologies are frequently seen in the prevalent adRP genes RHO, RP1 and PRPF31 among others, which would not be effectively addressed by gene supplementation alone and need creative, novel approaches. Zinc fingers, RNA interference, AON, translational read-through therapy, and gene editing by clustered regularly interspaced short palindromic repeats/Cas are some of the strategies that are currently under investigation and will be discussed here.

DOI: [10.1136/bjo-2022-321903](https://doi.org/10.1136/bjo-2022-321903)

RISK OF DISEASE

Elevated Plasma Levels of C1qTNF1 Protein in Patients with Age-Related Macular Degeneration and Glucose Disturbances.

Journal of Clinical Medicine. 2022 Jul 28

Budnik A, Sabasińska-Grześ M, Michnowska-Kobylińska M, Lisowski Ł, Szpakowicz M, Łapińska M, Szpakowicz A, Kondraciuk M, Kamiński KA, Konopińska J.

In recent years, research has provided increasing evidence for the importance of inflammatory etiology in age-related macular degeneration (AMD) pathogenesis. This study assessed the profile of inflammatory cytokines in the serum of patients with AMD and coexisting glucose disturbances (GD). This prospective population-based cohort study addressed the determinants and occurrence of cardiovascular, neurological, ophthalmic, psychiatric, and endocrine diseases in residents of Białystok, Poland. To make the group homogenous in terms of inflammatory markers, we analyzed only subjects with glucose disturbances (GD: diabetes or prediabetes). Four hundred fifty-six patients aged 50-80 were included. In the group of patients without macular degenerative changes, those with GD accounted for 71.7%, while among those with AMD, GD accounted for 89.45%. Increased serum levels of proinflammatory cytokines were observed in both AMD and GD groups.

C1qTNF1 concentration was statistically significantly higher in the group of patients with AMD, with comparable levels of concentrations of other proinflammatory cytokines. C1qTNF1 may act as a key mediator in the integration of lipid metabolism and inflammatory responses in macrophages. Moreover, C1qTNF1 levels are increased after exposure to oxidized low-density lipoprotein (oxLDL), which plays a key role in atherosclerotic plaque formation and is also a major component of the drusen observed in AMD. C1qTNF1 may, therefore, prove to be a link between the accumulation of oxLDL and the induction of local inflammation in the development of AMD with concomitant GD.

DOI: [10.3390/jcm11154391](https://doi.org/10.3390/jcm11154391)

DRUG TREATMENT

Naïve subretinal haemorrhage due to neovascular age-related macular degeneration. pneumatic displacement, subretinal air, and tissue plasminogen activator: subretinal vs intravitreal aflibercept-the native study.

Eye (London). 2022 Aug 29

Iglicki M, Khoury M, Melamud JI, Donato L, Barak A, Quispe DJ, Zur D, Loewenstein A.

Objective: We aimed to compare visual and anatomical outcome in subretinal aflibercept vs. intravitreal aflibercept in the context of Pars Plana Vitrectomy (PPV), pneumatic displacement with subretinal air and subretinal tPA in patients with naïve submacular haemorrhage (SMH) secondary to neovascular age-related macular degeneration (nAMD).

Design: Retrospective interventional cohort study.

Participants: 80 patients treated with subretinal aflibercept vs. intravitreal aflibercept in the context of PPV, subretinal air and subretinal tPA in patients with SMH secondary to naïve nAMD.

Methods: Records were reviewed. Best corrected visual acuity (BCVA), central subfoveal thickness (CST), and intraocular pressure (IOP) were recorded at baseline and 24 months after treatment.

Main Outcome Measures: BCVA, CST, and number of anti VEGF treatment over follow-up period.

Results: The average duration from onset of symptoms to surgery was 1.26 days (range 0-3 days). Based on review of OCT images, SMH was subretinal in all 80 patients (100%), and sub-RPE in 29 patients (36.3%). Forty-one patients (51.25%) were treated with subretinal aflibercept ("subretinal group"), and 39 patients (48.75%) were treated with intravitreal aflibercept injections ("intravitreal group"). The groups were well balanced for age and gender $p = 0.6588$, and $p = 0.263$, respectively). Both groups showed statistically significant improvement in BCVA and CST (for all groups: $p < 0.001$). The mean number of anti VEGF given during follow-up period was statistically significantly lower in the "subretinal group" ($p < 0.0001$).

Conclusion: This study shows better management of the CNV, with a statistically significant lower need for anti-VEGF injections when treated with subretinal aflibercept compared to intravitreal application.

DOI: [10.1038/s41433-022-02222-z](https://doi.org/10.1038/s41433-022-02222-z)

Faricimab for Treatment-Resistant Diabetic Macular Edema.

Purpose: To assess the short-term outcomes in treatment-resistant diabetic macular edema (DME) patients changed from intravitreal aflibercept (IVA) to intravitreal faricimab (IVF).

Methods: A retrospective review was undertaken on DME subjects receiving IVA therapy at a single private practice. Patients were separated into study and control cohorts. Both study and control patients had received more than or equal to six IVA injections during the preceding 12 months, more than or equal to four IVA injections during the preceding 6 months, had a central macular thickness (CMT) on optical coherence tomography (OCT) of ≥ 300 μm , and had retinal fluid on OCT before cohort assignment. Study patients were switched to IVF and underwent three injections within 4 months, whereas control patients stayed on IVA during the same period and received three injections within 4 months.

Results: There were 51 patients analyzed. There were 37.5% (9/24) in the study group and 3.7% (1/27) in the control group who achieved a CMT of less than 300 μm without retinal fluid on OCT at the end of the 4-month study ($p=0.001$). There were 41.7% (10/24) in the study group and 11.1% (3/27) in the control group who had gained two or more lines of visual acuity at the end of the 4-month study ($p=0.01$).

Conclusion: For a significant minority, IVF can improve the short-term visual and anatomic outcomes in treatment-resistant DME patients formerly managed with IVA. Longer follow-up is needed to determine if such improvements can be preserved.

DOI: [10.2147/OPTH.S381503](https://doi.org/10.2147/OPTH.S381503)

Association between structural and functional treatment outcomes in neovascular age-related macular degeneration.

Acta Ophthalmologica. 2022 Aug 29.

Haji H, Gianniou C, Brynskov T, Sørensen TL, Olsen R, Krogh Nielsen M.

Purpose: The administration frequency of intravitreal anti-vascular endothelial growth factor (anti-VEGF) in neovascular age-related macular degeneration (AMD) have been widely discussed. The primary objective of the study was to explore the association between anatomical outcomes and changes in functional outcome.

Methods: This was a retrospective cohort study of patients with newly diagnosed neovascular AMD with a minimum of 12 months of follow-up. Only one eye per patient was included. Patients were treated according to the observe-and-plan or the pro-re-nata regimen. All patients were regularly examined from the time of diagnosis up to 24 months. The effect of intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelium detachment (PED) at any time point on visual acuity (VA) was tested, as well as the long-term effect and the risk of losing VA. Further, the variability of central retinal thickness (CRT) was calculated for each eyes' individual measures during the observation period, excluding the monthly loading phase. The prognostic effect of each factor on VA was estimated by regression analysis. The primary outcome measure was VA, which was correlated with the presence or absence of fluid, seen as IRF, SRF or PED.

Results: A total of 504 treatment naïve eyes from 504 patients was included. The presence of IRF was associated with lower VA at all visits ($p < 0.001$). However, the presence of SRF or PED was not significantly associated with worse VA at any time point during the observation period. Patients in the upper quartile of CRT variance had a greater loss in VA after 12 and 24 months ($p < 0.001$).

Conclusions: In this retrospective cohort study, the presence of intraretinal fluid was associated with poorer visual outcome in neovascular AMD patients treated with anti-VEGF, but the presence of subretinal fluid and PEDs was not. This suggests that IRF is worse than subretinal fluid and PEDs for AMD outcomes and therefore requires the most intensive treatment. Further, we found that patients with the highest CRT variability during the study period had poorer visual outcomes after 12 and 24 months, indicating that stringent control of retinal fluid volume fluctuations is important to prevent visual acuity decline over time.

DOI: [10.1111/aos.15233](https://doi.org/10.1111/aos.15233)

DIAGNOSIS AND IMAGING

Comparison of hyperreflective foci in macular edema secondary to multiple etiologies with spectral-domain optical coherence tomography: An observational study.

BMC Ophthalmology 2022 Aug 29

Zhu R, Xiao S, Zhang W, Li J, Yang M, Zhang Y, Gu X, Yang L.

Background: Hyperreflective foci (HRF) features in macular edema associated with different etiologies may indicate the disease pathogenesis and help to choose proper treatment. The goal of this study is to investigate the retinal microstructural features of macular edema (ME) secondary to multiple etiologies with spectral-domain optical coherence tomography (SD-OCT) and analyze the origin of HRF in ME.

Methods: This was a retrospective study. SD-OCT images were reviewed to investigate macular microstructural features such as the number and distribution of HRF and hard exudates and the internal reflectivity of the cysts. The differences in microstructural features between groups and the correlations between the number of HRF and other parameters were analyzed.

Results: A total of 101 eyes with ME from 86 diabetic (diabetic macular edema, DME) patients, 51 eyes from 51 patients with ME secondary to branch retinal vein occlusion (branch retinal vein occlusion-macular edema, BRVO-ME), 59 eyes from 58 central retinal vein occlusion (central retinal vein occlusion-macular edema, CRVO-ME) patients, and 26 eyes from 22 uveitis (uveitic macular edema, UME) patients were included in this study. The number of HRF, the frequency of hard exudates and the enhanced internal reflectivity of the cysts were significantly different among the groups. The number of HRF in the DME group was significantly higher than that in the other groups (all $P < 0.05$). The frequency of hard exudates and enhanced internal reflectivity of the cysts in the DME group were significantly higher than ME secondary to other etiologies (all $P < 0.001$). Within the DME group, the number of HRF in the patients with hard exudates was significantly higher than that in the patients without hard exudates ($P < 0.001$).

Conclusion: HRF detected with SD-OCT were more frequent in DME patients than in BRVO-ME, CRVO-ME, or UME patients. The occurrence of HRF was correlated with the frequency of hard exudates. HRF may result from the deposition of macromolecular exudates in the retina, which is speculated to be a precursor of hard exudates.

DOI: [10.1186/s12886-022-02575-9](https://doi.org/10.1186/s12886-022-02575-9)

GENETICS

Common and rare variants in patients with early onset drusen maculopathy.

Clinical Genetics. 2022 Aug 21

de Breuk A, Lechanteur YTE, Astuti G, Corominas Galbany J, Klaver CCW, Hoyng CB, den Hollander AI.

Early onset drusen maculopathy (EODM) can lead to advanced macular degeneration at a young age, affecting quality of life. However, the genetic causes of EODM are not well studied. We performed whole genome sequencing in 49 EODM patients. Common genetic variants were analysed by calculating genetic risk scores based on 52 age-related macular generation (AMD)-associated variants, and we analysed rare variants in candidate genes to identify potential deleterious variants that might contribute to EODM development. We demonstrate that the 52 AMD-associated variants contributed to EODM, especially variants located in the complement pathway. Furthermore, we identified 26 rare genetic variants predicted to be pathogenic based on in silico prediction tools or based on reported pathogenicity in literature. These variants are located predominantly in the complement and lipid metabolism pathways. Last, evaluation of 18 genes causing inherited retinal dystrophies that can mimic AMD characteristics, revealed 11 potential deleterious variants in eight EODM patients. However, phenotypic characteristics did not point towards a retinal dystrophy in these patients. In conclusion, this study reports new insights into rare variants that are potentially involved in EODM development, and which are relevant for future studies unravelling the aetiology of EODM.

DOI: [10.1111/cge.14212](https://doi.org/10.1111/cge.14212)

PATIENT EXPERIENCE

Associations with baseline visual acuity in 12,414 eyes starting treatment for neovascular AMD.

Eye (London). 2022 Aug 26

Relton SD, Chi GC, Lotery AJ, West RM; Real world AMD treatment outcomes EMR User Group, McKibbin M.

Aims: To determine baseline visual acuity before the start of treatment for neovascular age-related macular degeneration (AMD), compare median and visual acuity states between treatment sites and investigate the association of socio-demographic and clinical characteristics with baseline acuity.

Methods: Anonymised demographic and clinical data, collected as part of routine clinical care, were extracted from electronic medical records at treating National Health Service (NHS) Trusts. Analyses were restricted to eyes with baseline visual acuity recorded at treatment initiation. Associations with baseline acuity were investigated using multivariate linear regression.

Results: Analysis included 12,414 eyes of 9116 patients at 13 NHS Trusts. Median baseline acuity was LogMAR 0.46 (interquartile range = 0.26-0.80) and 34.5% of eyes had good acuity, defined as LogMAR \leq 0.3. Baseline acuity was positively associated with second-treated eye status, younger age, lower socio-economic deprivation, independent living, and female sex. There was little evidence of association between baseline acuity and distance to the nearest treatment centre, systemic or

ocular co-morbidity. Despite case-mix adjustments, there was evidence of significant variation of baseline visual acuity between sites.

Conclusions: Despite access to publicly funded treatment within the NHS, variation in visual acuity at the start of neovascular AMD treatment persists. Identifying the characteristics associated with poor baseline acuity, targeted health awareness campaigns, professional education, and pathway re-design may help to improve baseline acuity, the first eye gap, and visual acuity outcomes.

DOI: [10.1038/s41433-022-02208-x](https://doi.org/10.1038/s41433-022-02208-x)

PATHOPHYSIOLOGY

Integrating transcriptomics, metabolomics, and GWAS helps reveal molecular mechanisms for metabolite levels and disease risk.

American Journal of Human Genetics 2022 Aug 30

Yin X, Bose D, Kwon A, Hanks SC, Jackson AU, Stringham HM, Welch R, Oravilahti A, Fernandes Silva L; FinnGen, Locke AE, Fuchsberger C, Service SK, Erdos MR, Bonnycastle LL, Kuusisto J, Stitzel NO, Hall IM, Morrison J, Ripatti S, Palotie A, Freimer NB, Collins FS, Mohlke KL, Scott LJ, Fauman EB, Burant C, Boehnke M, Laakso M, Wen X.

Transcriptomics data have been integrated with genome-wide association studies (GWASs) to help understand disease/trait molecular mechanisms. The utility of metabolomics, integrated with transcriptomics and disease GWASs, to understand molecular mechanisms for metabolite levels or diseases has not been thoroughly evaluated. We performed probabilistic transcriptome-wide association and locus-level colocalization analyses to integrate transcriptomics results for 49 tissues in 706 individuals from the GTEx project, metabolomics results for 1,391 plasma metabolites in 6,136 Finnish men from the METSIM study, and GWAS results for 2,861 disease traits in 260,405 Finnish individuals from the FinnGen study. We found that genetic variants that regulate metabolite levels were more likely to influence gene expression and disease risk compared to the ones that do not. Integrating transcriptomics with metabolomics results prioritized 397 genes for 521 metabolites, including 496 previously identified gene-metabolite pairs with strong functional connections and suggested 33.3% of such gene-metabolite pairs shared the same causal variants with genetic associations of gene expression. Integrating transcriptomics and metabolomics individually with FinnGen GWAS results identified 1,597 genes for 790 disease traits. Integrating transcriptomics and metabolomics jointly with FinnGen GWAS results helped pinpoint metabolic pathways from genes to diseases. We identified putative causal effects of UGT1A1/UGT1A4 expression on gallbladder disorders through regulating plasma (E,E)-bilirubin levels, of SLC22A5 expression on nasal polyps and plasma carnitine levels through distinct pathways, and of LIPC expression on age-related macular degeneration through glycerophospholipid metabolic pathways. Our study highlights the power of integrating multiple sets of molecular traits and GWAS results to deepen understanding of disease pathophysiology.

DOI: [10.1016/j.ajhg.2022.08.007](https://doi.org/10.1016/j.ajhg.2022.08.007)