HGG Advances

ARTICLE

Genome-wide association study reveals genetic mechanisms underlie eye disorders and comorbidities

Chia-Ni Hsiung,[1,2] Wen-Cheng Chou,[3] Chih-Hsiung Hsu,[4,5] and Linyi Chen[1,6,7,*]

Summary

Eye diseases, including cataracts, glaucoma, diabetes retinopathy, and age-related macular degeneration, are major global health challenges and leading causes of blindness. This study leveraged genome-wide association studies (GWASs) involving over 100,000 individuals, integrating data from the Taiwan Biobank and National Health Insurance Research Database, to identify genetic loci associated with disease onset. Our findings suggest that these conditions are influenced by multifactorial etiologies, as pleiotropic loci including rs10811660, rs4710941, rs2283228, and rs7646518 were identified, linking ocular diseases to metabolic conditions. Notably, a strong genetic correlation was observed between cataract and depression. Mendelian randomization analysis further demonstrated a causal effect of depression on cataract risk, implicating shared biological pathways, particularly oxytocin signaling, in disease pathophysiology. This finding revealed a functional genetic variant near the *OXTR* gene, highlighting its potential as a causal candidate for genetic diagnosis in precision health. By bridging the gap between genetic discovery and clinical application, this research offers critical insights into shared genetic mechanisms across diverse health domains, paving the way for innovative diagnostic and therapeutic strategies.

Introduction

Eye diseases represent a rising global public health concern, with hundreds of millions of people are affected worldwide, which significantly impact the quality of life of these patients. Cataracts, the leading cause of blindness globally, result from clouding of the crystalline lens and predominantly affect the elderly.[1,2] Glaucoma, characterized by optic nerve damage often associated with elevated intraocular pressure, poses a progressive threat to vision if left untreated.[3] Retinal diseases encompass a spectrum of disorders affecting the retina, the eye's light-sensitive tissue, while age-related macular degeneration (AMD) specifically targets the macula, leading to central vision loss.[4] Retinal detachment, on the other hand, is a medical emergency requiring immediate intervention to preserve vision.[5] While many of these conditions are preventable or treatable through timely diagnosis and intervention, they collectively impose a significant burden on healthcare systems.[3–5] Additional factors such as aging, ultraviolet light exposure, and lifestyles are known major contributors to ocular diseases.[1] Nonetheless, accumulating evidence highlights the critical role of genetic predisposition in their onset and progression.[6–8] Genetic research thus serves to unravel the multifactorial and complex hereditary nature of these diseases, providing an indispensable foundation for understanding their etiology and informing personalized approaches to prevention and treatment.

Advances in genome-wide association studies (GWASs) and related genomic methodologies have revolutionized our understanding of the genetic underpinnings of ocular diseases.[9–12] Numerous genetic variants have been implicated in their development.[10,13] For example, in multi-ancestry, variants in the *MYOC* gene have been associated with primary open-angle glaucoma,[14] while variations in the *CFH* gene are strongly associated with AMD,[15] a leading cause of vision loss in older adults. Such findings underscore the power of genetic studies in elucidating the biological pathways underlying ocular diseases, offering critical insights into potential therapeutic targets.[10,16] Beyond disease-specific variants, GWASs have uncovered pleiotropic genetic factors—variants that influence multiple ocular diseases simultaneously, as demonstrated in large-scale cross-trait analyses.[12,17] These studies reported shared genetic susceptibility between diabetic retinopathy (DR), AMD, and glaucoma, implicating their frequent coexistence in clinical settings. These shared genetic risks highlight the interconnected biological pathways that underpin diverse ocular diseases and reinforce the need for comprehensive genomic investigations to identify mechanisms of overlap.

Despite the strides made in genetic research, significant knowledge gaps remain concerning the shared and distinct genetic architectures driving ocular disease progression. To address these challenges, we conducted a large-scale GWAS in a Taiwanese population. To fulfill the two-sample requirement of Mendelian randomization

[1]Program in Precision Medicine, National Tsing Hua University, Hsinchu, Taiwan; [2]Institute of Statistical Science, Academia Sinica, Taipei, Taiwan; [3]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan; [4]School of Public Health, National Defense Medical Center, Taipei, Taiwan; [5]Health Service and Readiness Section, Armed Forces Taoyuan General Hospital, Taoyuan, Taiwan; [6]Department of Medical Science and Institute of Molecular Medicine, National Tsing Hua University, Hsinchu, Taiwan
[7]Lead contact
*Correspondence: lchen@life.nthu.edu.tw
https://doi.org/10.1016/j.xhgg.2025.100520.
© 2025 The Authors. Published by Elsevier Inc. on behalf of American Society of Human Genetics.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

(MR). Overlapping individuals between the exposure and outcome datasets were excluded to focus specifically on cataracts, glaucoma, DR, and AMD. Our aim was to identify disease-specific and pleiotropic genetic variants in an East Asian population, distinguish specific loci from known susceptibility loci, and deepen our understanding of the biological pathways involved. We further explored genetic correlations between these eye diseases and relevant systemic conditions (metabolic and psychiatric disorders), and performed MR to evaluate potential causal relationships—particularly the unexpected link observed between depression and cataract risk. By integrating these approaches, we sought to expand the catalog of eye disease-associated loci and to elucidate how genetic factors contribute to both ocular disease and its comorbidities.

Methods

Study population

This study recruited 174,144 Taiwan Biobank (TWB) volunteers aged 20–70 years residing in Taiwan between January 2012 and December 2021. Biological specimens, personal, and clinical information were analyzed as delinked data. All subjects provided written informed consent. The study was approved by the Research Ethics Committee of National Tsing Hua University (no. 10705HM024) and the Institutional Review Board of the Tri-Services General Hospital (no. B202205057). All methods were conducted in accordance with the Declaration of Helsinki and relevant regulations. Individuals with missing data were excluded from the analysis. For GWAS analyses, we defined case and control groups based on ICD-9-CM and ICD-10-CM codes recorded in the National Health Insurance Research Database linked to TWB participants. Each GWAS compared a distinct set of individuals diagnosed with a specific eye disease to a common control group, consisting of participants without any of the four target eye diseases. Individuals with multiple eye disease diagnoses were excluded from case analyses to avoid group overlap.

Phenotype definition and covariates

This study focused on four major ophthalmic conditions: cataracts, glaucoma, DR, and AMD. To comprehensively define these diseases, both International Classification of Diseases 9-CM (ICD9-CM) and ICD10-CM coding systems were utilized, ensuring accurate case identification across different coding practices. Cataracts were defined by the codes ICD9-CM: 36610, 36630 and ICD10-CM: H259, H2620, encompassing senile (age-related), traumatic, and congenital cataracts. Although our dataset, which included diagnoses classified under ICD-9-CM code 366.30 ("Unspecified complicated cataract"), denotes lens opacities secondary to intraocular diseases, congenital and traumatic cataracts are classified separately; therefore, their contribution to this code is expected to be small.[18] DR was identified using ICD9-CM: 36201 and ICD10-CM: E11311, E11319, E11321, E11329, E11331, E11339, E11341, and E11349, reflecting its strong association. Macular degeneration was defined as ICD9-CM: 36250 and ICD10-CM: H3530, referring to unspecified macular degeneration. Glaucoma was identified using ICD9-CM: 3659, 36042 and ICD10-CM: H409, H44511, H44512, H44513, and H44519, covering various forms such as unspecified glaucoma, covering primary open-angle glaucoma (unspecified), glaucoma secondary to other ocular disorders, and absolute glaucoma. We acknowledge that our broad glaucoma definition includes multiple subtypes (with distinct etiologies); due to sample size constraints, we analyzed them as a group but noted this as a limitation. We identified depression patients based on ICD9: 296.2, 296, ICD10: F32.0−F32.9, F33.0−F33.9, ICD9-CM: 300.4, 311, and ICD10-CM: F34.1. Bipolar disorder was based on ICD9: 296.0-296.8, ICD10: F31. The control participants were defined as individuals without any of the four eye diseases (cataracts, glaucoma, AMD, DR).

Covariates included in the analysis were matched with age, sex, body mass index, and the first 10 principal components to account for population stratification, minimizing potential confounding and ensuring robust statistical analysis.

Genotyping and quality control

Genotyping was conducted using the TWBv1.0 and TWBv2.0 genotyping arrays, encompassing approximately 900,000 SNPs.[19] We performed quality control (QC) with PLINK v.2.0[20] and R v.4.0.3. For sample-level QC, we excluded samples with a call rate <95% and extreme heterozygosity (± 3 standard deviations from the mean). We identified and eliminated duplicates and greater than second-degree relatives (identity-by-descent >0.185), and performed principal-component analysis to detect and exclude population outliers.[21] We performed SNP-level QC and excluded SNPs with a call rate <95%, minor allele frequency (MAF) < 1%, or Hardy-Weinberg equilibrium $p < 1 \times 10^{-6}$. The remaining SNPs were plotted to visualize the association using R v.4.0.3. After QC, 87,532 participants and a high-quality set of genotyped SNPs remained for analysis.

GWAS and genetic correlation analysis

GWAS was conducted using PLINK v.2.0,[20] and additive genetic model was assumed for the outcome. Odds ratios (ORs) for individual SNPs associated with respective eye diseases were calculated using logistic regression with adjustment for the aforementioned covariates. Statistical significance was primary defined according to the conventional genome-wide significance threshold ($p < 5 \times 10^{-8}$). While, suggestive significance with $p < 1 \times 10^{-5}$ was considered as the observed and expected p values (quantile-quantile plot) deviated from the null distribution for SNPs with less stringent p values. Statistical power of the association was determined using the Genetic Association Study Power Calculator.[22]

Genetic correlation between eye diseases and related phenotypes were performed using GWAS summary statistics in employment of linkage disequilibrium (LD) score regression.[23] Summary statistics for the eye disease GWAS were correlated with GWAS summary data for three major metabolic disorders—type 2 diabetes, hyperlipidemia (hypercholesterolemia), and hypertension—and for two psychiatric disorders (major depressive disorder and bipolar disorder) were also from this study. For each pair of traits, LDSC computes a genetic correlation r_g and a p value. We applied false discovery rate (FDR) correction for the multiple correlation tests performed (20 tests for 5 traits by 4 eye diseases) and resulting in adjusted p values. An FDR-adjusted $p < 0.05$ was considered significant evidence of genetic correlation.

Imputation

Genotype imputation was performed using the combined reference panel consisted of East Asian population data from the 1000 Genomes Project phase 3 ($n = 504$) and Taiwan Biobank WGS data ($n = 1,451$).[24] Post-imputation QC excluded variants with imputation quality score (r^2) < 0.3 or MAF < 0.5%.

Pathway analysis and SNP prioritization

Pathway analysis was conducted using Ingenuity Pathway Analysis (IPA) (RRID: SCR_008653) to investigate potential biological pathways. To prioritize functional variant, we extracted SNPs from the 3p25.3 locus in LD with rs1465386 ($r^2 > 0.2$). Epigenetic regulation surrounding these SNPs was visualized by integrating DNase I hypersensitive site signals and H3K4me1 and H3K4me3 histone modification marks from ocular-related tissues available through the ENCODE project.[25] These included embryonic retina (combined signals from eight individual samples), conjunctival fibroblasts (HConF), retinoblastoma cells (WERI-Rb-1), iris pigment epithelium cells (HIPEpiC), and retinal pigment epithelium cells (HRPEpiC). The epigenetic signals were displayed as tracks on the UCSC Genome Browser for comprehensive visualization. Identification of transcription factors potentially binding to rs1465386 and rs237899 was performed using TRAP with approximately 100 bp sequences surrounding each SNP. Motifs with high binding affinity were further analyzed for site specificity using the find individual motif occurrences (FIMO) tool, with transcription factor binding motifs retrieved from JASPAR 2024. Functional interactions of RNA expression between OXTR and EPAS1, stratified by rs237899 genotypes, were assessed using transcripts per million-normalized RNA sequence data obtained from the Genotype-Tissue Expression (GTEx) project (Analysis v.10). Individual genotype information was accessed separately via dbGaP (Database of Genotypes and Phenotypes) under accession no. phs000424.v9.p2.[26] Additionally, structural modeling was performed using the AlphaFold Server to evaluate potential DNA-protein interactions.[27] The model included a segment of double-stranded DNA (AGTGGAAGTTCATCTTAACXTGAACTTA AAGTTGAAGGAGCTT, where "X" represents the G or A allele of rs237899) and the DNA-binding domain heterodimer of EPAS1 (amino acids 9–192, NP_001421.2) and ARNT2 (amino acids 62–124, NP_055677.3).

MR

To investigate causality between depression and cataract (motivated by their genetic correlation), we performed two-sample bidirectional MR analyses. We treated depression as the exposure and cataract as the outcome in the primary analysis, then reversed the roles for a secondary analysis. To satisfy the two-sample MR design, we ensured that the GWAS summary statistics for exposure and outcome came from non-overlapping samples. In practice, this meant removing any overlapping individuals: since both GWASs were derived from the TWB, we excluded from the depression GWAS any subjects who were also cataract cases (and vice versa), thereby using strictly separate subsets for each trait's association data.

Instrumental variable selection: for each exposure trait, we selected independent SNPs associated with the exposure at $p < 1 \times 10^{-5}$ as candidate instruments. Specifically, for depression we used the results of a GWAS on depression status within our TWB dataset (identified via ICD codes as described above; roughly 5,000 depression cases in TWB) to obtain genetic instruments. We opted to use our own depression GWAS rather than an external dataset to avoid potential sample overlap with our cataract cases. For cataract (in the reverse MR), we similarly took SNPs with $p < 1 \times 10^{-5}$ from our cataract GWAS as instruments. We then pruned these sets of SNPs to ensure each instrument was independent.

We also removed any SNP that was known or suspected to have pleiotropic effects on confounding traits. Specifically, we filtered out SNPs that have genome-wide significant associations (per the GWAS catalog) with potential confounders such as age, sex, smoking behavior, alcohol drinking, or type 2 diabetes, as such pleiotropy could violate MR assumptions. This process yielded a final set of 10 independent SNPs as instruments for depression (when testing its effect on cataract). Combined all selected instruments showed strong association with the exposure (all F statistics >> 10, indicating robust instruments with minimal weak instrument bias). For thoroughness, we applied the MR-PRESSO method to detect and remove any outlier instruments with disproportionate influence on the MR estimate. None were significant outliers, so all candidate instrumental variables (IVs) were retained in the analysis.

MR analysis: we carried out the MR using the inverse-variance weighted (IVW) method as the primary estimator, which combines the SNP-specific ratio estimates (effect of SNP on outcome divided by effect on exposure) in a meta-analytic framework. We also explored other MR estimators for sensitivity: the weighted median method (which provides a consistent estimate even if up to 50% of the instruments are invalid), MR-Egger regression (which can detect and adjust for directional pleiotropy, albeit with less power), and MR-PRESSO global test (to identify overall horizontal pleiotropy). For each analysis, we report the causal effect estimate (β coefficient for the effect of the exposure on outcome, with 95% CI) and p value. Where applicable, we checked the MR-Egger intercept to test for directional pleiotropy (intercept not significantly different from 0 indicates no strong unbalanced pleiotropy). All MR analyses were conducted in R using the MendelinaRandomization[28] and MR-presso R package.[29]

Results

Baseline characteristics of the subjects

In our study, we utilized data from the Taiwan Biobank and the National Health Insurance Research Database. Patients were included if they had one hospitalization or two outpatient visits with the same diagnosis within a year. After genotyping QC samples, we used 87,532 participants in the Taiwan Biobank to our target samples. We identified 26,736 cataract cases, 3,758 cases of glaucoma, 2,773 cases of DR, 2,757 cases of AMD, and others of controls. Demographic characteristics of participants are summarized in Table 1. Among individuals with eye diseases, female participants comprised 54%–68% of the study population, while male participants accounted for 31%–45%. The mean age of cases ranged from 50 to 70 years, notably higher than that of controls, whose mean age ranged from 40 to 50 years.

GWAS results for eye diseases

In this study, we identified several significant genetic loci associated with our ocular diseases (Table S1). Manhattan

Table 1. Characteristics of eye disorder cohorts

Group	Control	Cataract	Glaucoma	DR	AMD
Sample, *n*	52,278	26,376	3,578	2,773	2,527
Age (years), *n* (%)					
20–30	2,483 (4.75)	5 (0.02)	59 (1.65)	6 (0.22)	9 (0.37)
30–40	14,256 (27.27)	232 (0.88)	428 (11.97)	133 (4.8)	149 (5.9)
40–50	14,089 (26.95)	1,451 (5.5)	666 (18.61)	343 (12.37)	376 (14.89)
50–60	13,629 (26.07)	9,087 (34.45)	1,139 (31.82)	975 (35.17)	876 (34.66)
60–70	7,821 (14.96)	15,601 (59.15)	1,286 (35.95)	1,318 (47.53)	1,116 (44.18)
Sex, *n* (%)					
Male	19,573 (37.44)	8,277 (31.38)	1,417 (39.6)	1,249 (45.04)	912 (36.1)
Female	32,705 (62.56)	18,099 (68.62)	2,161 (60.4)	1,524 (54.96)	1,615 (63.9)
BMI, *n* (%)					
<18	1,270 (2.43)	443 (1.68)	72 (2.01)	25 (0.9)	44 (1.76)
18–24	26,353 (50.41)	13,130 (49.78)	1,801 (50.34)	848 (30.58)	1,319 (52.21)
24–27	13,509 (25.84)	7,836 (29.71)	924 (25.82)	898 (32.38)	708 (28)
>27	11,146 (21.32)	4,964 (18.82)	781 (21.83)	1,002 (36.13)	456 (18.03)
Smoking, *n* (%)					
Never	37,708 (72.13)	20,444 (77.51)	2,686 (75.06)	1,853 (66.84)	1,880 (74.41)
Ever	14,570 (27.87)	5,932 (22.49)	892 (24.94)	920 (33.16)	646 (25.56)
Drinking, *n* (%)					
Never	47,570 (91)	24,218 (91.82)	3,272 (91.45)	2,429 (87.6)	2,308 (91.35)
Quit	1,332 (2.55)	860 (3.26)	104 (2.91)	168 (6.07)	77 (3.05)
Currently	3,376 (6.46)	1,298 (4.92)	202 (5.65)	176 (6.33)	142 (5.6)
Betel chewing, *n* (%)					
Never	49,293 (94.29)	25,026 (94.88)	3,400 (95.02)	2,469 (89.03)	2,377 (94.05)
Ever	2,885 (5.71)	1,350 (5.12)	178 (4.98)	304 (10.97)	150 (5.95)

DR, diabetic retinopathy; AMD, age-related macular degeneration; BMI, body mass index.

and quantile-quantile plots for these associations are shown in Figures 1 and S1, with genomic control λ near 1, respectively, providing critical insights into their genetic underpinnings. For DR, four loci reached genome-wide significance, including rs10811660 (OR = 0.796, $p = 1.32 \times 10^{-10}$), rs4710941 (OR = 1.23, $p = 3.78 \times 10^{-9}$), rs2283228 (OR = 0.81, $p = 4.09 \times 10^{-9}$), and rs7646518 (OR = 1.24, $p = 8.51 \times 10^{-9}$) (Figure 1A). These loci are located near genes such as *CDKN2B-AS1*, *CDKAL1*, *KCNQ1*, and *IGF2BP2*, which have been linked to type 2 diabetes or fasting glucose,[19,30,31] illustrating the shared genetic mechanisms between DR and diabetes. For AMD, we identified one genome-wide significant locus in 18q22.2, rs12956753 (OR = 1.71, $p = 3.76 \times 10^{-8}$), and another nearly significant locus in 15q14, rs138597498 (OR = 1.75, $p = 1.02 \times 10^{-7}$), located near the genes *DOK6* and *DPH6*, respectively (Figure 1B). DOK6 (Docking protein 6) is involved in neuronal development and cell signaling, while *DPH6*-encoded diphthine-ammonia ligase plays a role in diphthamide biosynthesis, a post-translational modification essential for protein function. These genes have also been associated with metabolic syndrome and myocardial infarction, highlighting possible pleiotropic effects across these conditions. Notably, these loci have not been reported in prior large-scale AMD GWASs, including the recent multi-ethnic meta-analysis and a Taiwan-specific analysis.[11,32] Aside from these loci, rs10490924,[32–34] a well-known AMD-associated SNP, was also detected showing a modest association (OR = 1.09, $p = 0.00014$). The findings on 18q22.2 and 15q14 may therefore represent population-specific or previously unreported risk loci. However, given their borderline significance, replication in larger AMD cohorts, particularly in East Asian populations, is warranted to validate these associations. For cataracts, lack of loci reached genome-wide significance. This result reflects the substantial phenotypic heterogeneity of cataracts, as our analysis included multiple subtypes without stratification, potentially

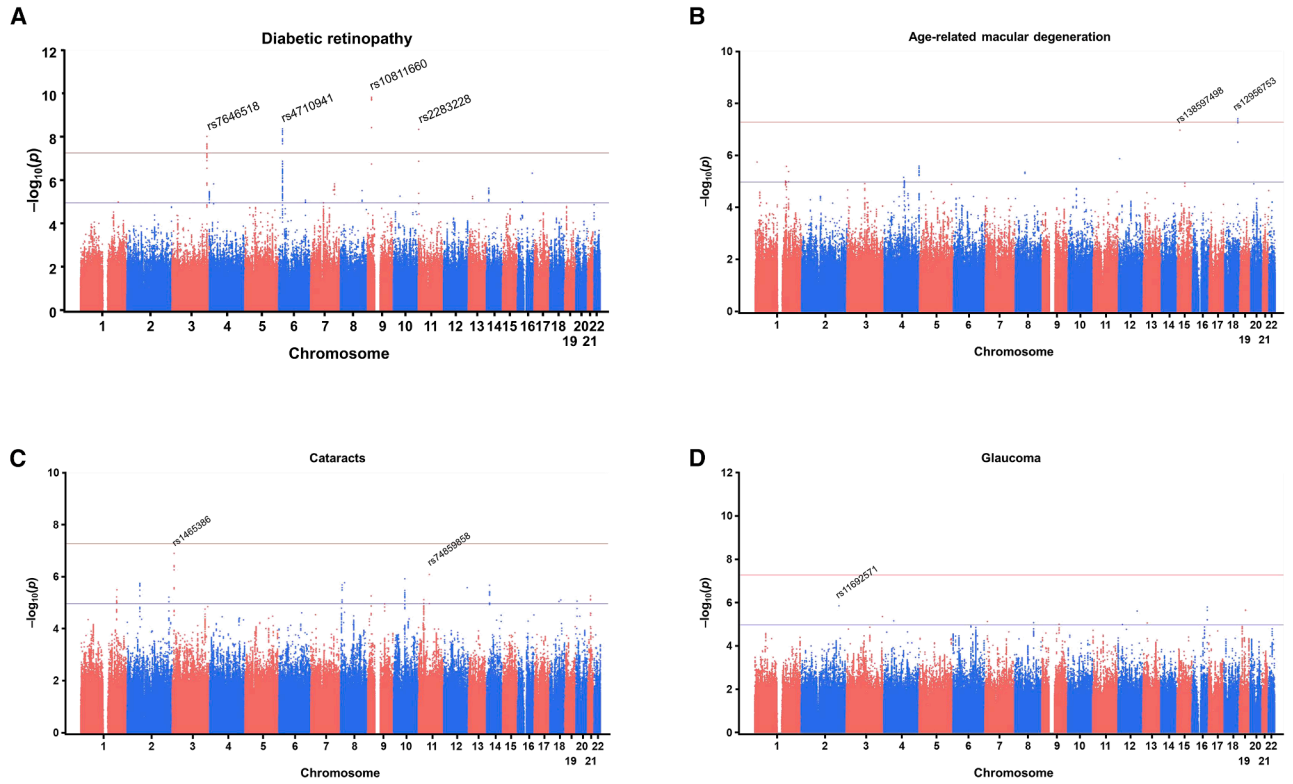


Figure 1. Genome-wide analysis of four major eye diseases

Manhattan plots illustrating the associations between SNPs and the risks of (A) diabetic retinopathy (DR), (B) age-related macular degeneration (AMD), (C) cataracts, and (D) glaucoma. SNPs are ranked by chromosomal position on the *x* axis, and their statistical significance is plotted on the *y* axis. The horizontal lines represent thresholds for suggestive significance ($p = 1 \times 10^{-5}$, lower) and genome-wide significance ($p = 5 \times 10^{-8}$, upper). The top SNPs in key loci are highlighted.

reducing statistical power. Nonetheless, several loci demonstrated suggestive associations ($p < 1 \times 10^{-5}$), as shown in Figure 1C. The most notable variant, rs1465386 (OR = 0.88, $p = 1.15 \times 10^{-7}$), is located near *OXTR* promoter in 3p25.3. Interestingly, rs1465386 exhibits moderate LD ($r^2 = 0.34$) with rs237899 in East Asian populations, a variant linked to depression and alcohol dependence. *OXTR* gene encodes the oxytocin receptor, which has been implicated in social cognition, anxiety, depression, and other psychological behaviors. Another notable variant, rs74859858 (OR = 0.78, $p = 7.57 \times 10^{-7}$), lies between *GLYATL1* and *GLYATL2* of 11q12.1, which are involved in glycine N-acyltransferase activity. Its role in ocular diseases remains unexplored, offering a promising avenue for future research. We also checked whether our top cataract loci overlapped genes known for congenital cataract or other eye development disorders. They do not appear to overlap with classic congenital cataract genes (e.g., crystallins or connexins), suggesting that our hits might be specific to age-related or adult cataract processes. We did observe that some known cataract susceptibility loci from a large multiethnic study[9] were also detected in our cohort (rs12777332 in *CASP7* had OR = 1.04, $p = 0.00032$). For glaucoma, while not genome-wide significant, the strongest association was for rs11692571 (OR = 1.18, $p = 1.35 \times 10^{-6}$), located in the *C2CD6* gene of 2q33.1 (Figure 1D). These findings highlight the value of studying Asian populations, as this locus was not flagged in primarily European-ancestry studies This gene plays a role in calcium-dependent signaling pathways, which are critical for optic nerve function and intraocular pressure regulation, both key factors in glaucoma pathophysiology. Collectively, these findings highlight the diverse genetic architectures underlying these ocular diseases. We have also included an overview of how our findings overlapped with previously reported loci for these diseases in Table S2. While some loci are unique to specific conditions, others suggest potential shared genetic pathways, particularly with metabolic and psychological traits.

Shared genetic architectures reveal an association between depression and cataract risk

Given that several loci identified in our GWAS for ocular diseases have also been linked to metabolic and psychological disorders, we investigated the potential of shared genetic architecture between ocular diseases and three major metabolic disorders (type 2 diabetes, hyperlipidemia, and hypertension), as well as two psychiatric disorders (depression and bipolar disorder). As shown in Table 2, a known genetic correlation was observed between type 2 diabetes and DR (r = 0.73, adjusted

Table 2. Genetic correlation r_g (adjusted p value) between eye disease and metabolic and psychiatric traits

	DR	AMD	Cataract	Glaucoma
Type 2 diabetes	0.73 (0.000172)	0.23 (0.02)	0.35 (0.06)	0.14 (0.0003)
Hyperlipidemia	0.23 (0.004)	0.02 (0.5)	0.41 (0.04)	−0.04 (0.2)
Hypertension	0.17 (0.000158)	0.13 (0.079)	0.10 (0.07)	0.12 (0.085)
Depression	0.17 (0.04)	0.187 (0.79)	0.46 (0.04)	0.154 (0.53)
Bipolar disorder	0.17 (0.02)	0.11 (0.24)	0.16 (0.03)	0.142 (0.27)

DR, diabetic retinopathy; AMD, age-related macular degeneration.

$p = 0.000172$), consistent with previous findings.[35] Type 2 diabetes also showed statistically significant although weaker genetic correlations with AMD (r = 0.23, adjusted $p = 0.02$) and glaucoma (r = 0.14, adjusted $p = 0.0003$). In contrast, hyperlipidemia exhibited a high and significant genetic correlation with cataracts, in line with prior studies evaluating the causal relationship of hyperlipidemia and type 2 diabetes.[36,37] Furthermore, cataracts demonstrated a positive genetic correlation with depression (r = 0.4685, adjusted $p = 0.04$), suggesting that individuals with a genetic predisposition to cataracts may also carry genetic markers associated with depression. This finding underscores the complexity of the genetic architecture underlying ocular diseases and highlights a potential link between ocular and psychiatric conditions. The observed genetic correlations, particularly between cataracts and depression, point to shared biological pathways that warrant further investigation to elucidate the underlying mechanisms connecting these traits.

The influence of depression on cataract risk

To further clarify the relationship and potential causal link between cataracts and depression, we conducted a bidirectional MR analysis. SNPs from GWAS summary statistics of depression that met a suggestive significance threshold ($p < 1 \times 10^{-5}$) were selected as IVs (Figure S2). After clumping to ensure independence, 10 SNPs were retained as IVs (Table 3; Figure 2A), and various MR models were applied to evaluate causal relationships. Using the IVW method, we identified a causal effect of depression on cataract risk, with an estimated β = 0.206 (95% CI, 0.152–0.26; $p < 1 \times 10^{-4}$) (Table 4). This finding was consistent across other MR methods, including the weighted median and MR-Egger, further suggesting that a genetic predisposition to depression may contribute to an increased risk of cataracts (Figure 2B). For thoroughness, we performed the reverse MR analysis, treating cataract as the exposure and depression as the outcome. We selected the top cataract-associated SNPs (from our GWAS, $p < 1 \times 10^{-5}$, clumped) as instruments (yielding 16 independent variants for cataract, listed in Table S3, primarily suggestive hits given no genome-wide hits), The reverse IVW analysis found no evidence of a causal effect of cataract genetic liability on depression (IVW β = 0.024; 95% CI, −0.099–0.147; $p = 0.70$) (Table S3; Figure 3A), indicating no significant causal effect of cataracts on depression (Table S4; Figure 3B). These findings reinforce the hypothesis of a shared biological pathway between depression and cataracts, while supporting the notion that depression may causally influence cataract development, rather than the reverse.

Table 3. Instrumental variables for depression on cataract

	Depression		Cataract	
SNP	β	SE	β	SE
rs710214	0.087864	0.018238	0.016714	0.013
rs4926844	−0.07063	0.015765	0.01424	0.011
rs17100422	0.085829	0.018834	0.017299	0.018
rs10863899	−0.07859	0.015746	0.014248	0.05
rs138952050	0.247251	0.054963	0.054489	0.04361
rs181905157	0.315446	0.065729	0.065833	0.0623
rs76318476	0.273624	0.058987	0.05804	0.04304
rs80237911	0.185965	0.040745	0.039044	0.027044
rs141290247	0.142645	0.030737	0.02898	0.01598
rs74002490	−0.10128	0.022899	0.020141	0.0307

SNP, single-nucleotide polymorphism; SE, standard error.

Mechanistic insight on the depression-cataract link

To investigate the causal relationship between depression and cataracts, pathway enrichment analysis using IPA was performed to identify potential molecular mechanisms. The analysis highlighted oxytocin-related signaling pathways as significantly associated with cataract risk (Figure S3A). Further examination of this pathway revealed key downstream components, such as CREB, which plays a role in synaptic plasticity and learning, and NF-κB, which regulates neuroinflammation and stress responses (Figure 4). Complementary expression quantitative trait locus analysis showed that the T allele of rs1465386, associated with a reduced risk of both cataracts and depression, is linked to higher OXTR expression (Figure S3B). This finding supports the pathway analysis, which indicates that OXTR expression influences social behavior (Figure 4). These mechanisms, essential for brain development, behavioral regulation, and inflammatory processes,

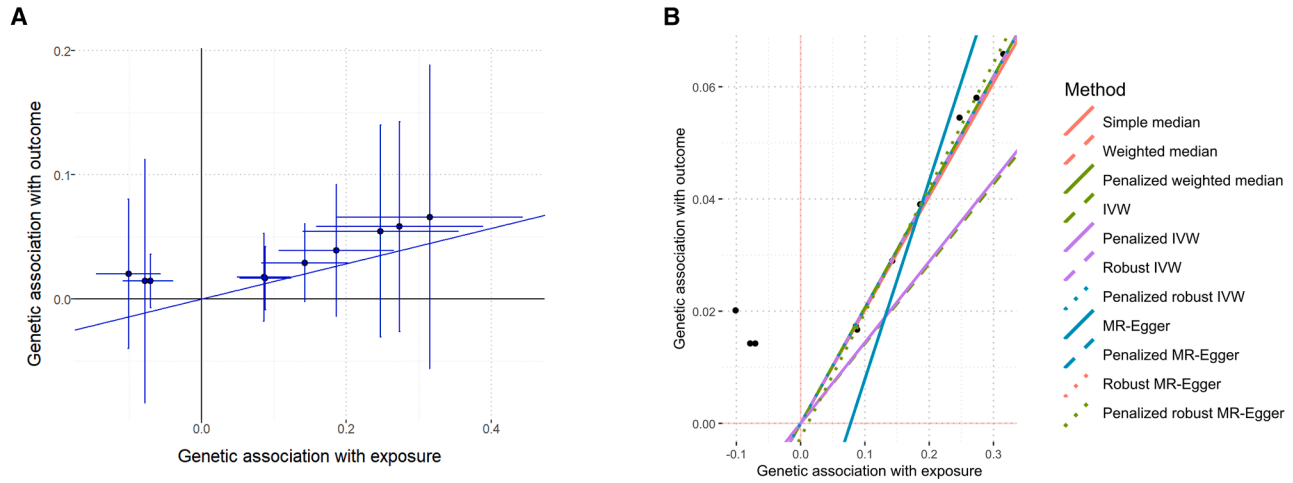


Figure 2. MR results and sensitivity analyses for the effect of depression on cataracts
(A) Scatterplot of MR-IVW results, where each data point represents the β value of an SNP associated with exposure (depression) and outcome (cataracts). The regression line indicates the overall causal estimate (details in Table 3).
(B) Sensitivity analyses using various MR methods, with regression results represented by solid or dashed lines, color coded for clarity. Comprehensive results and significance values are detailed in Table 4. IVW, inverse-variance weighted.

suggest that depression-related changes in neuroinflammation, stress response, and social behavior pathways may contribute to cataract formation, potentially through systemic effects or shared molecular mediators like inflammation and oxidative stress.

Exploring the genetic regulation of OXTR underlies the link between depression and cataract pathophysiology

To address the gap in understanding how genetic variants influence OXTR expression and corresponding signaling pathways in the context of depression and cataract risk, we conducted a functional genomic analysis of the 3p25.3 locus, focusing on 11 SNPs identified in GWASs with suggestive significance ($p < 1 \times 10^{-4}$) (Figure 5A). Among these, two SNPs—rs1465386, originally identified in GWAS, and rs237899, an imputed variant—emerged as candidate allele-specific expression sites based on the GTEx dataset analysis of heterozygous individuals (Figure 5B). rs1465386, located in the proximal upstream promoter region of *OXTR*, represents a G-to-T polymorphism, and *in silico* predictions suggested that the T allele may create a binding site for forkhead box transcription factors (Figure 5C), known regulators of ocular development and function. However, subsequent assays for DNA binding across multiple ocular-related forkhead factors revealed no significant allelic imbalance, suggesting that rs1465386 is unlikely to be a functional variant. Conversely, rs237899 (OR = 0.89, $p = 2.71 \times 10^{-6}$), located downstream of *OXTR*, demonstrated stronger evidence of functionality, with the G allele (major allele) predicted to harbor a binding element for hypoxia-inducible factor (HIF) (Figure 5D). Of the two major HIF isoforms, HIF1A mediates acute responses to hypoxia, while EPAS1 (HIF-2α) is associated with chronic hypoxia and long-term oxygen homeostasis. Structural modeling using AlphaFold predicted that the G allele binds to the EPAS1-ARNT2 heterodimer with higher affinity compared with the A allele (Figure 5E). Analysis of fibroblast tissues from the GTEx dataset revealed a reverse correlation between EPAS1 expression and OXTR levels in individuals with at least one rs237899-G allele, which harbors the HIF2 binding motif. Specifically, OXTR expression was downregulated in the presence of elevated EPAS1 expression in rs237899-GG/GA genotypes, while this correlation was absent in individuals with the rs237899-AA genotype, which lacks the HIF2 binding motif (Figure 5F). These

Table 4. Mendelian randomization analyses for depression on cataract

Method	Estimate (95% CI)	*p* value
Simple median	0.202 (0.054–0.351)	0.007
Weighted median	0.204 (0.061–0.348)	0.005
Penalized weighted median	0.206 (0.06–0.352)	0.006
IVW	0.142 (0.037–0.247)	0.008
Penalized IVW	0.144 (0.039–0.25)	0.007
Robust IVW	0.206 (0.152–0.26)	<0.0001
Penalized robust IVW	0.206 (0.152–0.26)	<0.0001
MR-Egger	0.353 (0.11–0.597)	0.004
(Intercept)	−0.027 (−0.056–0.001)	0.06
Penalized MR-Egger	0.353 (0.11–0.597)	0.004
(Intercept)	−0.027 (−0.056–0.001)	0.06
Robust MR-Egger	0.222 (0.12–0.325)	<0.0001
(Intercept)	−0.002 (−0.017–0.012)	0.743
Penalized robust MR-Egger	0.222 (0.12–0.325)	<0.0001
(Intercept)	−0.002 (−0.017–0.012)	0.743

IVW, inverse-variance weighted; MR, Mendelian randomization.

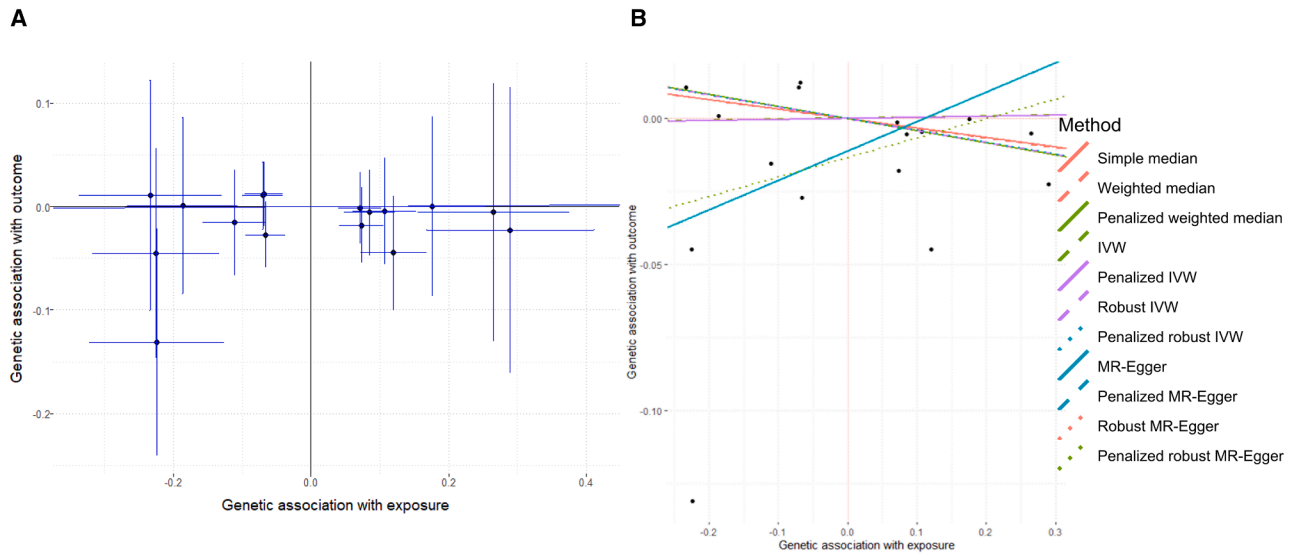


Figure 3. Reverse MR analysis assessing the causal effect of cataracts on depression

(A) Scatterplot illustrating the MR-IVW analysis, where each point represents the genetic association (β) of an instrumental SNP with cataracts (exposure) and depression (outcome). The fitted regression line represents the overall causal estimate derived from the IVW method (details in Table S3).

(B) Sensitivity analyses conducted using multiple MR methods. Each colored line denotes the regression slope corresponding to a specific MR approach, with regression results represented by solid or dashed lines, color coded for clarity. Full estimates and adjusted *p* values for all methods are reported in Table S4.

findings highlight rs237899 as a plausible causal variant regulating OXTR expression via hypoxia-related pathways. Given the established link between chronic hypoxia and depression episodes, our results suggest that HIF2-mediated regulation of OXTR is likely the underlying mechanism connecting depression with cataract pathophysiology, strengthening the biological plausibility of our MR findings and providing a potential target for therapeutic intervention in conditions involving depression and cataracts.

Discussion

This study provides a comprehensive exploration of the genetic underpinnings of cataracts, glaucoma, DR, and AMD through a large-scale GWAS. By identifying loci and elucidating shared genetic pathways, our findings offer critical insights into the complex interplay between ocular, metabolic, and psychiatric conditions, advancing both academic understanding and clinical applications.

A key finding of this study is the causal influence of depression on cataract risk, established through bidirectional MR. This analysis clarifies a long-standing observational assumption: improvements in depression symptoms following cataract surgery are solely due to restored vision and reduced social isolation.[38] By employing a bidirectional two-sample MR analysis with non-overlapping datasets,[39] we demonstrated that depression plays a direct role in cataractogenesis, potentially mediated through systemic inflammation, oxidative stress, or hormonal signaling pathways such as oxytocin. In this study, we prioritized internal data to ensure population homogeneity and independence between exposure and outcome samples. Acknowledging that this may reduce statistical power, and that future use of external East Asian datasets (when available and non-overlapping) could improve precision, this finding challenges prevailing clinical narratives and underscores the importance of integrating mental health considerations into cataract prevention and management strategies.

We also recognize an alternative or complementary explanation: certain antidepressant medications may themselves contribute to cataract risk. Selective serotonin reuptake inhibitors, a widely prescribed class of antidepressants, have been associated in observational studies with an increased risk of cataract or cataract surgery.[40,41] Possible biological mechanisms include effects on lens epithelial cell viability, increased oxidative stress, and dysregulation of glucose metabolism.

In this study, the available medical records did not allow precise classification of antidepressant exposure or dosage, as they generally lack information on patient adherence and actual intake. Consequently, our MR analysis is more likely to reflect the genetic contribution of depression itself, rather than medication-induced effects. Nonetheless, integrating genetic analyses with detailed treatment histories and adherence data in future research would be valuable for disentangling the potential contributions of antidepressant use from the direct biological impact of depression.

In this study, glaucoma case definition encompassed multiple subtypes (e.g., primary open-angle glaucoma,

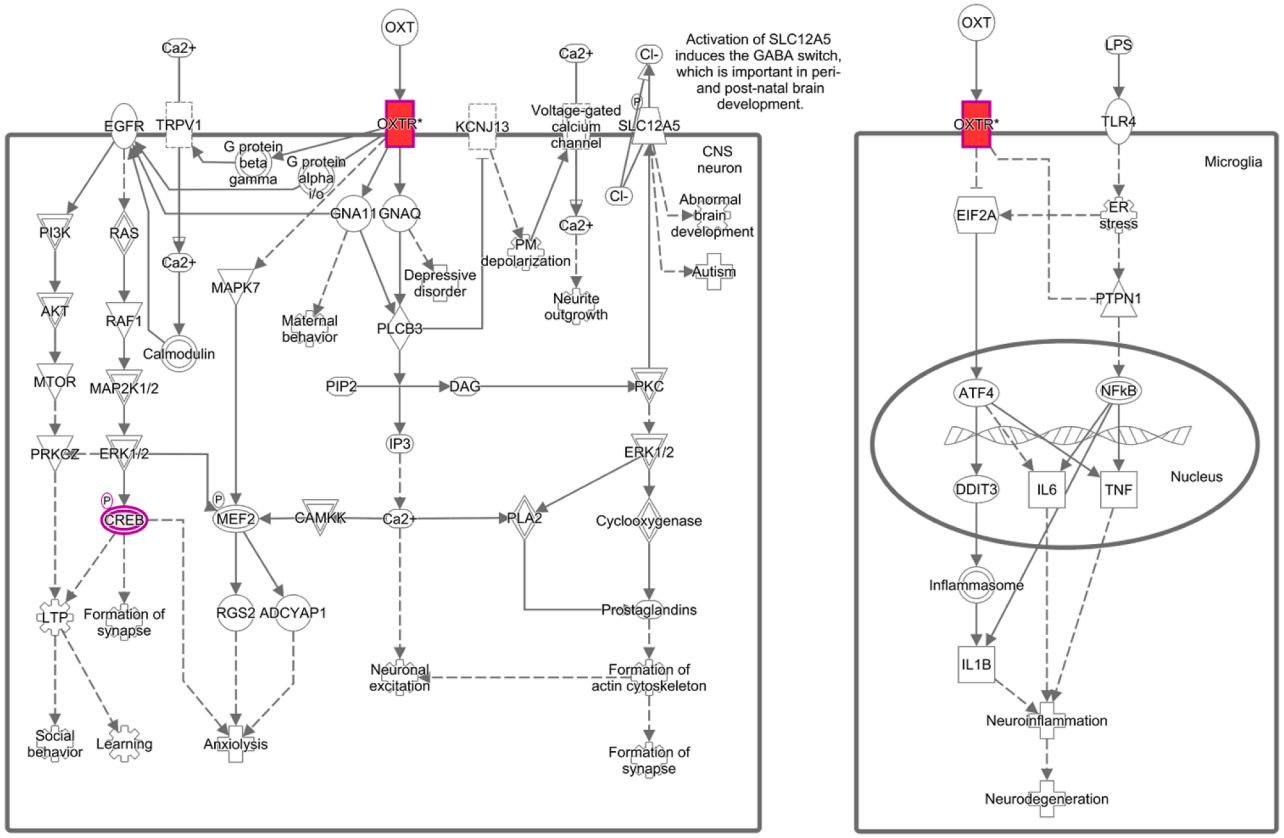


Figure 4. Identification of the oxytocin signaling pathway in cataract GWASs
Comprehensive visualization of molecular and signaling interactions mediated by oxytocin (OXT) and its receptor OXTR in neurons and microglia. Key pathways include calcium signaling, protein kinase pathways (e.g., PKC and ERK1/2), and transcription factors such as CREB, which regulate processes such as social behavior, synaptic formation, and learning.

angle-closure glaucoma, secondary glaucoma, and congenital glaucoma). This heterogeneity reflects the available case information in the Taiwan Biobank and may partly explain why no loci reached genome-wide significance. Given the total number of glaucoma cases in our dataset (~3,500), further subdivision into subtypes would have substantially reduced statistical power. To address this pitfall, one could perform subtype-specific GWAS and meta-analyses to increase power and better characterize the genetic architecture of each subtype.

The integration of oxytocin signaling into cataract pathophysiology represents another key innovation of this study. Variants in the *OXTR* gene, particularly rs237899, were shown to have functional relevance through HIF2-mediated regulation, linking chronic hypoxia to both mood disorders and ocular health. This hormonal signaling axis provides a plausible explanation for the genetic correlation between depression and cataracts, bridging neuroinflammation, behavioral regulation, and lens opacity development. Importantly, the oxytocin signaling pathway opens new avenues for exploring targeted therapies that address systemic influences on ocular health, an area that remains underexplored.

Another major contribution of this study lies in the identification of pleiotropic genetic loci, such as those near *CDKN2B-AS1*, *CDKAL1*, *KCNQ1*, and *IGF2BP2*, which connect DR to type 2 diabetes.[42,43] These findings support the hypothesis that hyperglycemia and dysregulated insulin signaling are major drivers of retinopathy, not only through vascular complications but also via genetic susceptibility. Similarly, the discovery of DOK6 and DPH6 variants in AMD suggests a convergence of metabolic and neuronal pathways in its pathogenesis.[44,45] These results align with prior research, including findings from the UK Biobank,[12] which highlight genetic overlaps between ophthalmic diseases and mood disorders.[46–48] The consistency across datasets strengthens the validity of the genetic correlation between cataracts and depression. Otherwise, weaker but positive correlations were noted between depression and DR, likely due to smaller sample sizes for these conditions in this study. This limitation suggests that future research with larger cohorts is necessary to fully elucidate the genetic architecture of these conditions.

While our study advances the understanding of genetic contributions to eye diseases, several limitations warrant discussion. The predominantly East Asian ancestry of our cohort may limit the generalizability of these findings, necessitating replication in more diverse populations. Although we did not have another population for

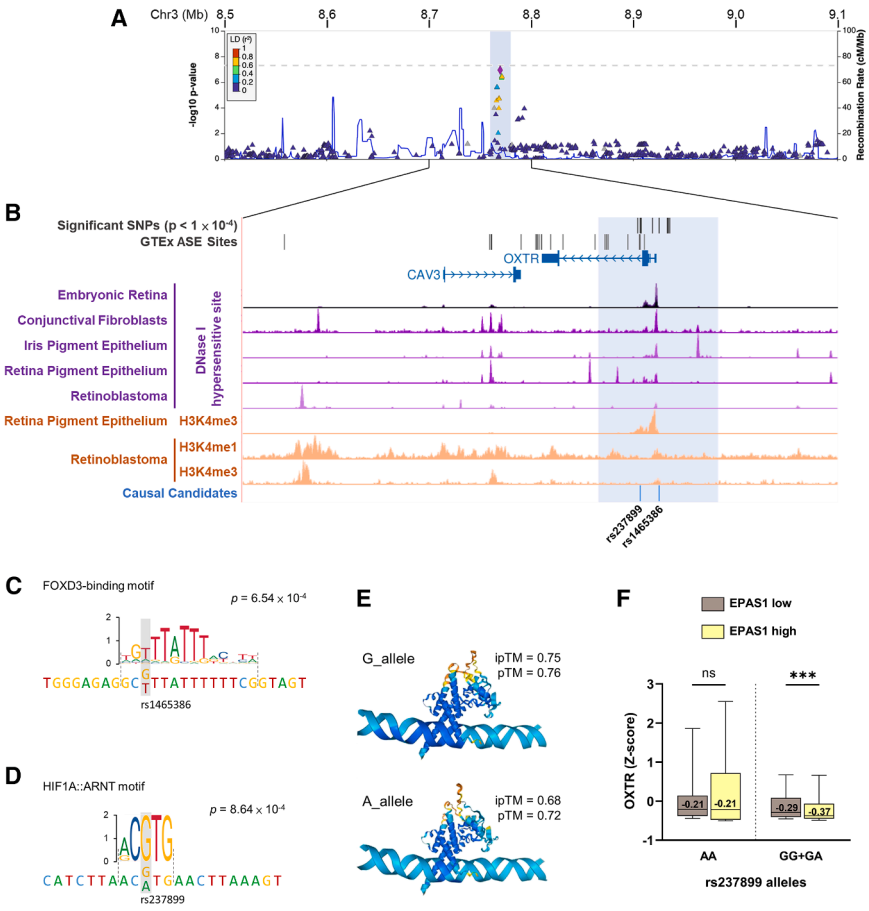


Figure 5. Functional assessment of rs237899 in regulating OXTR through the HIF2 pathway

(A) Regional association plot for cataracts, highlighting rs1465386 (purple diamond) as the top SNP, with other SNPs color coded based on LD (r^2) with rs1465386.

(B) Functional annotation of 11 candidate SNPs within the light blue region in ocular-related cell types. Features include GTEx allele-specific expression (ASE) sites, DNase I hypersensitive (DHS) regions, and histone modifications (H3K4me1, H3K4me3), visualized using the UCSC Genome Browser (hg38 assembly) with ENCODE data. Vertical lines at the bottom mark the chromosomal locations of potential functional variants.

(C) Predicted DNA-binding motif for forkhead box transcription factors (e.g., FOXD3, MA0041.3) surrounding the G and T alleles of rs1465386.

(D) Predicted DNA-binding motif for the HIF1A-ARNT complex (MA0259.2) surrounding the G and A alleles of rs237899, retrieved from JASPAR 2024 and analyzed with FIMO tool for *p* values.

(E) AlphaFold molecular modeling showing the DNA-binding domain heterodimer of the EPAS1-ARNT2 complex bound to DNA oligonucleotides with either the G allele (upper panel) or A allele (lower panel) of rs237899. Predicted template modeling (pTM) and interface predicted template modeling (ipTM) scores are provided.

(F) *Z* scores for OXTR expression stratified by rs237899 genotypes and EPAS1 expression, based on GTEx fibroblast data. Median values and 10th–90th percentile ranges are shown. Statistical differences between groups were assessed using Student's t test; ***$p < 0.001$.

validation, it is possible to apply the analysis using other population groups in Taiwan in the future. Furthermore, the functional validation of key loci, such as rs237899, remains incomplete, and experimental studies are needed to confirm their roles in OXTR regulation and downstream effects. Although our MR analysis provides robust causal evidence, residual confounding cannot be entirely ruled out, especially given the complexity of traits such as depression. Future research should focus on validating these findings across multi-ethnic cohorts and further exploring the shared molecular mechanisms connecting ocular and systemic diseases. Functional experiments investigating the interaction between oxytocin signaling, chronic hypoxia, and lens physiology will be crucial to translating these insights into clinical applications. Additionally, the integration of advanced multi-omics approaches, such as epigenomics and proteomics, could provide a more holistic view of the pathways underlying ocular diseases and their comorbidities.

Collectively, our study advances the understanding of the genetic basis of major eye diseases by identifying disease-specific and pleiotropic loci and elucidating potential biological pathways connecting ocular, metabolic, and psychiatric conditions. By bridging genetic discovery and clinical application, this research lays the foundation for precision medicine approaches that address the shared and unique mechanisms underlying ocular diseases and their comorbidities.

Data and code availability

The data utilized in this study are available under a restricted license and are not publicly accessible. However, individual-level data can be obtained directly from the Taiwan Biobank (contact: biobank@gate.sinica.edu.tw), subject to their data access policies. Data from the National Health Insurance Research Database, extensively used in epidemiological studies, are accessible to researchers in Taiwan strictly for academic purposes and require formal application and approval. Summary statistics from the GWAS conducted in this research have been has been uploaded to Figshare and is publicly available at https://doi.org/10.6084/m9.figshare.30121135.v2.

Acknowledgments

This work was supported by grants from the Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan (TYAFGH_B_113020 to C.-H.H.), Tri-Service General Hospital, Taipei, Taiwan (TSGH_E_113207 to C.-H.H.), and National Science and

Technology Council, Taiwan (NSTC 113-2320-B-007-006-MY3 to L.C.). We thank the Taiwan Biobank for providing the biological information and genotyping data for this research (TWBR11004-03 to L.C. and TWBR11201-04 to C.-H.H.) and express our deep gratitude to Dr. Chen-Yang Shen for his pioneering work in establishing Taiwan Biobank, which has significantly advanced biomedical research globally. We also thank the investigators of ENCODE and GTEx projects who have made their invaluable data available to the scientific community.

Author contributions

C.-N.H. and L.C. conceived and designed the study. C.-N.H. and W.-C.C. carried out the statistic and public database analyses with the help and inputs from C.-H.H. C.-H.H. applied for the individual data from Taiwan Biobank and the National Health Insurance Research Database. L.C. and C.-H.H. obtained funding. C.-N.H. and W.C.C. wrote the draft of the manuscript. L.C. revised the manuscript. All authors read and approved this manuscript.

Declaration of interests

The authors declare no competing interests.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.xhgg.2025.100520.

Web resources

TRAP, https://trap.molgen.mpg.de/cgi-bin/trap_form.cgi
FIMO, https://meme-suite.org/meme/tools/fimo
GTEx, https://www.gtexportal.org/home/
AlphaFold Server, https://alphafoldserver.com/

Received: March 27, 2025
Accepted: September 17, 2025

References

1. Cooke Bailey, J.N., Sobrin, L., Pericak-Vance, M.A., Haines, J. L., Hammond, C.J., and Wiggs, J.L. (2013). Advances in the genomics of common eye diseases. Hum. Mol. Genet. *22*, R59–R65. https://doi.org/10.1093/hmg/ddt396.
2. Pascolini, D., and Mariotti, S.P. (2012). Global estimates of visual impairment: 2010. Br. J. Ophthalmol. *96*, 614–618. https://doi.org/10.1136/bjophthalmol-2011-300539.
3. Weinreb, R.N., Leung, C.K.S., Crowston, J.G., Medeiros, F.A., Friedman, D.S., Wiggs, J.L., and Martin, K.R. (2016). Primary open-angle glaucoma. Nat. Rev. Dis. Primers *2*, 16067. https://doi.org/10.1038/nrdp.2016.67.
4. Mitchell, P., Liew, G., Gopinath, B., and Wong, T.Y. (2018). Age-related macular degeneration. Lancet *392*, 1147–1159. https://doi.org/10.1016/S0140-6736(18)31550-2.
5. Vujosevic, S., Aldington, S.J., Silva, P., Hernández, C., Scanlon, P., Peto, T., and Simó, R. (2020). Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol. *8*, 337–347. https://doi.org/10.1016/S2213-8587(19)30411-5.
6. Armento, A., Ueffing, M., and Clark, S.J. (2021). The complement system in age-related macular degeneration. Cell. Mol. Life Sci. *78*, 4487–4505. https://doi.org/10.1007/s00018-021-03796-9.
7. Wang, J., Yusufu, M., Khor, C.C., Aung, T., and Wang, N. (2019). The genetics of angle closure glaucoma. Exp. Eye Res. *189*, 107835. https://doi.org/10.1016/j.exer.2019.107835.
8. Johnston, T., Chandra, A., and Hewitt, A.W. (2016). Current Understanding of the Genetic Architecture of Rhegmatogenous Retinal Detachment. Ophthalmic Genet. *37*, 121–129. https://doi.org/10.3109/13816810.2015.1033557.
9. Choquet, H., Melles, R.B., Anand, D., Yin, J., Cuellar-Partida, G., Wang, W., 23andMe Research Team, Hoffmann, T.J., Nair, K.S., Hysi, P.G., et al. (2021). A large multiethnic GWAS meta-analysis of cataract identifies new risk loci and sex-specific effects. Nat. Commun. *12*, 3595. https://doi.org/10.1038/s41467-021-23873-8.
10. Diaz-Torres, S., Lee, S.S.Y., García-Marín, L.M., Campos, A.I., Lingham, G., Ong, J.S., Mackey, D.A., Burdon, K.P., Hunter, M., Dong, X., et al. (2024). Uncovering genetic loci and biological pathways associated with age-related cataracts through GWAS meta-analysis. Nat. Commun. *15*, 9116. https://doi.org/10.1038/s41467-024-53212-6.
11. Gorman, B.R., Voloudakis, G., Igo, R.P., Jr., Kinzy, T., Halladay, C.W., Bigdeli, T.B., Zeng, B., Venkatesh, S., Cooke Bailey, J.N., Crawford, D.C., et al. (2024). Genome-wide association analyses identify distinct genetic architectures for age-related macular degeneration across ancestries. Nat. Genet. *56*, 2659–2671. https://doi.org/10.1038/s41588-024-01764-0.
12. Xue, Z., Yuan, J., Chen, F., Yao, Y., Xing, S., Yu, X., Li, K., Wang, C., Bao, J., Qu, J., et al. (2022). Genome-wide association meta-analysis of 88,250 individuals highlights pleiotropic mechanisms of five ocular diseases in UK Biobank. EBioMedicine *82*, 104161. https://doi.org/10.1016/j.ebiom.2022.104161.
13. Le, N.Q., He, W., and MacGregor, S. (2024). Polygenic Risk Scores and Genetically Complex Eye Disease. Annu. Rev. Vis. Sci. *10*, 403–423. https://doi.org/10.1146/annurev-vision-102122-103958.
14. Kumar, A., Han, Y., and Oatts, J.T. (2024). Genetic changes and testing associated with childhood glaucoma: A systematic review. PLoS One *19*, e0298883. https://doi.org/10.1371/journal.pone.0298883.
15. Tzoumas, N., Hallam, D., Harris, C.L., Lako, M., Kavanagh, D., and Steel, D.H.W. (2021). Revisiting the role of factor H in age-related macular degeneration: Insights from complement-mediated renal disease and rare genetic variants. Surv. Ophthalmol. *66*, 378–401. https://doi.org/10.1016/j.survophthal.2020.10.008.
16. Ortin Vela, S., Beyeler, M.J., Trofimova, O., Iuliani, I., Vargas Quiros, J.D., de Vries, V.A., Meloni, I., Elwakil, A., Hoogewoud, F., Liefers, B., et al. (2024). Phenotypic and genetic characteristics of retinal vascular parameters and their association with diseases. Nat. Commun. *15*, 9593. https://doi.org/10.1038/s41467-024-52334-1.
17. Yao, X., Yang, H., Han, H., Kou, X., Jiang, Y., Luo, M., Zhou, Y., Wang, J., Fan, X., Wang, X., et al. (2023). Genome-wide analysis of genetic pleiotropy and causal genes across three age-related ocular disorders. Hum. Genet. *142*, 507–522. https://doi.org/10.1007/s00439-023-02542-4.
18. Shaw, E., and Patel, B.C. (2025). Complicated Cataract (StatPearls).

19. Lee, C.J., Chen, T.H., Lim, A.M.W., Chang, C.C., Sie, J.J., Chen, P.L., Chang, S.W., Wu, S.J., Hsu, C.L., Hsieh, A.R., et al. (2022). Phenome-wide analysis of Taiwan Biobank reveals novel glycemia-related loci and genetic risks for diabetes. Commun. Biol. *5*, 1175. https://doi.org/10.1038/s42003-022-04168-0.
20. Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S. M., and Lee, J.J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience *4*, 7. https://doi.org/10.1186/s13742-015-0047-8.
21. Marees, A.T., de Kluiver, H., Stringer, S., Vorspan, F., Curis, E., Marie-Claire, C., and Derks, E.M. (2018). A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. Int. J. Methods Psychiatr. Res. *27*, e1608. https://doi.org/10.1002/mpr.1608.
22. Johnson, J.L., and Abecasis, G.R. (2017). GAS Power Calculator: web-based power calculator for genetic association studies. Preprint at bioRxiv. https://doi.org/10.1101/164343.
23. Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.R., ReproGen Consortium, Psychiatric Genomics Consortium, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Duncan, L., et al. (2015). An atlas of genetic correlations across human diseases and traits. Nat. Genet. *47*, 1236–1241. https://doi.org/10.1038/ng.3406.
24. Wei, C.Y., Yang, J.H., Yeh, E.C., Tsai, M.F., Kao, H.J., Lo, C.Z., Chang, L.P., Lin, W.J., Hsieh, F.J., Belsare, S., et al. (2021). Genetic profiles of 103,106 individuals in the Taiwan Biobank provide insights into the health and history of Han Chinese. NPJ Genom. Med. *6*, 10. https://doi.org/10.1038/s41525-021-00178-9.
25. Luo, Y., Hitz, B.C., Gabdank, I., Hilton, J.A., Kagda, M.S., Lam, B., Myers, Z., Sud, P., Jou, J., Lin, K., et al. (2020). New developments on the Encyclopedia of DNA Elements (ENCODE) data portal. Nucleic Acids Res. *48*, D882–D889. https://doi.org/10.1093/nar/gkz1062.
26. GTEx Consortium (2020). The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science *369*, 1318–1330. https://doi.org/10.1126/science.aaz1776.
27. Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., Ronneberger, O., Willmore, L., Ballard, A.J., Bambrick, J., et al. (2024). Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature *630*, 493–500. https://doi.org/10.1038/s41586-024-07487-w.
28. Patel, A., Ye, T., Xue, H., Lin, Z., Xu, S., Woolf, B., Mason, A. M., and Burgess, S. (2023). MendelianRandomization v0.9.0: updates to an R package for performing Mendelian randomization analyses using summarized data. Wellcome Open Res. *8*, 449. https://doi.org/10.12688/wellcomeopenres.19995.1.
29. Verbanck, M., Chen, C.Y., Neale, B., and Do, R. (2018). Publisher Correction: Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat. Genet. *50*, 1196. https://doi.org/10.1038/s41588-018-0164-2.
30. Karjalainen, M.K., Karthikeyan, S., Oliver-Williams, C., Sliz, E., Allara, E., Fung, W.T., Surendran, P., Zhang, W., Jousilahti, P., Kristiansson, K., et al. (2024). Genome-wide characterization of circulating metabolic biomarkers. Nature *628*, 130–138. https://doi.org/10.1038/s41586-024-07148-y.
31. Walters, R.G., Millwood, I.Y., Lin, K., Schmidt Valle, D., McDonnell, P., Hacker, A., Avery, D., Edris, A., Fry, H., Cai, N., et al. (2023). Genotyping and population characteristics of the China Kadoorie Biobank. Cell Genom. *3*, 100361. https://doi.org/10.1016/j.xgen.2023.100361.
32. Huang, Y.C., Liao, W.L., Lin, H.J., Huang, Y.T., Chang, Y.W., Liu, T.Y., Chen, Y.C., Weng, A.L., and Tsai, F.J. (2024). Identification of Genetic Variants for Risk Prediction and Early Diagnosis of Age-Related Macular Degeneration in the Taiwanese Population. Int. J. Mol. Sci. *25*, 3230. https://doi.org/10.3390/ijms25063230.
33. Cipriani, V., Leung, H.T., Plagnol, V., Bunce, C., Khan, J.C., Shahid, H., Moore, A.T., Harding, S.P., Bishop, P.N., Hayward, C., et al. (2012). Genome-wide association study of age-related macular degeneration identifies associated variants in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21.3. Hum. Mol. Genet. *21*, 4138–4150. https://doi.org/10.1093/hmg/dds225.
34. Verma, A., Huffman, J.E., Rodriguez, A., Conery, M., Liu, M., Ho, Y.L., Kim, Y., Heise, D.A., Guare, L., Panickan, V.A., et al. (2024). Diversity and scale: Genetic architecture of 2068 traits in the VA Million Veteran Program. Science *385*, eadj1182. https://doi.org/10.1126/science.adj1182.
35. Li, L., Cheng, W.Y., Glicksberg, B.S., Gottesman, O., Tamler, R., Chen, R., Bottinger, E.P., and Dudley, J.T. (2015). Identification of type 2 diabetes subgroups through topological analysis of patient similarity. Sci. Transl. Med. *7*, 311ra174. https://doi.org/10.1126/scitranslmed.aaa9364.
36. Kafeel, S., Fawwad, A., Basit, A., and Nawab, S.N. (2022). Clinical Association of Biochemical Variations Among Multilocus Genotypes of Antioxidant Enzymes with Susceptibility of Cataract in Hyperglycemia. Appl. Biochem. Biotechnol. *194*, 3871–3889. https://doi.org/10.1007/s12010-022-03957-x.
37. Zhang, H., Xiu, X., Xue, A., Yang, Y., Yang, Y., and Zhao, H. (2022). Mendelian randomization study reveals a population-specific putative causal effect of type 2 diabetes in risk of cataract. Int. J. Epidemiol. *50*, 2024–2037. https://doi.org/10.1093/ije/dyab175.
38. Chen, P.W., Liu, P.P.S., Lin, S.M., Wang, J.H., Huang, H.K., and Loh, C.H. (2020). Cataract and the increased risk of depression in general population: a 16-year nationwide population-based longitudinal study. Sci. Rep. *10*, 13421. https://doi.org/10.1038/s41598-020-70285-7.
39. Hartwig, F.P., Davies, N.M., Hemani, G., and Davey Smith, G. (2016). Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. Int. J. Epidemiol. *45*, 1717–1726. https://doi.org/10.1093/ije/dyx028.
40. Etminan, M., Mikelberg, F.S., and Brophy, J.M. (2010). Selective serotonin reuptake inhibitors and the risk of cataracts: a nested case-control study. Ophthalmology *117*, 1251–1255. https://doi.org/10.1016/j.ophtha.2009.11.042.
41. Fu, Y., Dai, Q., Zhu, L., and Wu, S. (2018). Antidepressants use and risk of cataract development: a systematic review and meta-analysis. BMC Ophthalmol. *18*, 31. https://doi.org/10.1186/s12886-018-0699-0.
42. Cao, J., Yan, W., Ma, X., Huang, H., and Yan, H. (2021). Insulin-like Growth Factor 2 mRNA-Binding Protein 2-a Potential Link Between Type 2 Diabetes Mellitus and Cancer. J. Clin. Endocrinol. Metab. *106*, 2807–2818. https://doi.org/10.1210/clinem/dgab391.
43. Unoki, H., Takahashi, A., Kawaguchi, T., Hara, K., Horikoshi, M., Andersen, G., Ng, D.P.K., Holmkvist, J., Borch-Johnsen,

K., Jørgensen, T., et al. (2008). SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat. Genet. *40*, 1098–1102. https://doi.org/10.1038/ng.208.

44. Zhang, S., Jiang, W., Ma, R.C., and Yu, W. (2019). Region-based interaction detection in genome-wide case-control studies. BMC Med. Genomics *12*, 133. https://doi.org/10.1186/s12920-019-0583-7.
45. Park, S., Kim, S., Kim, B., Kim, D.S., Kim, J., Ahn, Y., Kim, H., Song, M., Shim, I., Jung, S.H., et al. (2024). Multivariate genomic analysis of 5 million people elucidates the genetic architecture of shared components of the metabolic syndrome. Nat. Genet. *56*, 2380–2391. https://doi.org/10.1038/s41588-024-01933-1.
46. Zhang, X., Liang, Y., Huang, Y., Liu, S., Li, Q., Wang, S., Wu, G., Du, Z., Wang, Y., Wang, J., et al. (2024). Evaluation of the Observational Associations and Shared Genetics Between Glaucoma With Depression and Anxiety. Investig. Ophthalmol. Vis. Sci. *65*, 12. https://doi.org/10.1167/iovs.65.3.12.
47. Chang, K.J., Wu, H.Y., Chiang, P.H., Hsu, Y.T., Weng, P.Y., Yu, T.H., Li, C.Y., Chen, Y.H., Dai, H.J., Tsai, H.Y., et al. (2025). Decoding and reconstructing disease relations between dry eye and depression: a multimodal investigation comprising meta-analysis, genetic pathways and Mendelian randomization. J. Adv. Res. *69*, 197–213. https://doi.org/10.1016/j.jare.2024.03.015.
48. Jiang, C., Melles, R.B., Sangani, P., Hoffmann, T.J., Hysi, P.G., Glymour, M.M., Jorgenson, E., Lachke, S.A., and Choquet, H. (2023). Association of Behavioral and Clinical Risk Factors With Cataract: A Two-Sample Mendelian Randomization Study. Investig. Ophthalmol. Vis. Sci. *64*, 19. https://doi.org/10.1167/iovs.64.10.19.