REVIEW ARTICLE

The influence of type-2 diabetes on cataract and their shared genetic basis through relevant genome-wide association studies

Janaki Sneha[1], Saravanan Yogaprabhu[1], Ranjit Mohan Anjana[1,2], Viswanathan Mohan[2] and Venkatesan Radha[1,*]

[1]Madras Diabetes Research Foundation, ICMR Centre for Advanced Research on Diabetes, University of Madras, Chennai 603 103, India
[2]Dr Mohan's Diabetes Specialities Centre, WHO Collaborating Centre for Non-Communicable Diseases Prevention and Control and IDF Centre of Excellence in Diabetes Care, Chennai 600 086, India

Cataract in type-2 diabetes (T2D) patients is a secondary complication and one of the leading causes of vision loss next to diabetic retinopathy. Various factors such as age, gender, diabetes duration, HbA1c, BMI and genetics contribute towards cataractogenesis. The genetic predisposition of patients with T2D to develop cataract remains unanswered. It is important to examine the underlying genetic etiology of cataract in T2D through large-scale genetic studies. Since there have been only a handful of genome-wide association studies (GWAS) on T2D-influenced cataract, multiple studies from various ethnicities are warranted to substantiate if T2D truly influences the development of cataract. This study provides an overview of possible mechanisms and factors that trigger the development of cataract in T2D patients, relevant GWAS and the role of genes associated with T2D-associated cataract.

Keywords: Aldose reductase, diabetic cataract, genome-wide association studies, polygenic risk score, sorbitol dehydrogenase.

TYPE-2 diabetes (T2D) is a polygenic disease increasing at an alarming rate worldwide. The primary risk factors for diabetes are age, ethnicity, lifestyle (physical inactivity and unhealthy diet) and genetics[1]. Previously, multiple genes have been reported to increase the susceptibility to diabetes[2]. Hyperglycaemia is a consequence of impaired insulin production and secretion by pancreatic β-cells progressing to insulin resistance in patients with T2D[3]. According to the International Diabetes Federation (IDF), there are about 590 million people with T2D, with more than 73 million patients in India and by 2045, it is projected to increase by 783 million worldwide[4]. Blindness due to diabetes is the most common cause of vision loss in developing and developed countries. Retinopathy, glaucoma and cataract can induce blindness in patients with diabetes[5].

Cataract is a progressive disease commonly occurring in the elderly population, causing opacification of crystalline lens and thereby leading to visual impairment, imposing a huge burden on the healthcare systems[6]. Cataract affects approximately 94 million people around the world, according to a report by the World Health Organization. Cataract is also responsible for 66.2% of blindness in India[7].

There are three types of age-related cataract based on where and how they develop. Nuclear cataract involves the central region of the lens and is the most common type of cataract. Cortical cataracts are developed due to opacification of the lens in the outer layer[8]. Posterior cataracts develop at the posterior part of the lens and are the most common in diabetic patients[9]. Based on age, cataract is classified as congenital and age-related. Congenital cataract develops at an earlier stage of birth, whereas age-related cataract develops much later due to various reasons such as smoking, hypertension, prolonged use of steroids and prolonged diabetes[10].

Diabetic cataract is a polygenic disorder contributed due to a complex interplay of genetic and environmental factors[11]. Diabetic cataract is a secondary complication of T2D, leading to visual impairment[12]. It is important to note that T2D only increases the risk and is not solely responsible for the development of cataract[6]. The Blue Mountains Eye Study[13], Wisconsin Epidemiologic Study of Diabetic Retinopathy[14], and Beaver Dam Eye Study[15] are some notable epidemiological surveys that have examined the incidence of cataract in T2D patients[16].

Proposing a polygenic risk score (PRS) through genome-wide association studies (GWAS) would help in identifying individuals who are likely to develop cataract in the future. Though there have been multiple GWAS on T2D so far, only a handful have been conducted to explore the shared genetic basis of diabetes and cataract. In this study, we discuss various factors that trigger cataractogenesis in patients with T2D, the mechanism of cataract formation and relevant GWAS from the past.

Pathogenesis of type-2 diabetes-driven cataract

Lens, an avascular organ, receives nutrients and oxygen from the aqueous humour, vitreous humour and endothelial blood vessels from the iris[17]. In the human lens, glucose uptake is

*For correspondence. (e-mail: radharv@yahoo.co.in)

insulin-independent but strongly depends on the anaerobic metabolism of glucose through glycolysis and pentose–phosphate pathway. The pathogenesis of diabetic cataract primarily depends on hyperglycaemia-associated changes in lens metabolism leading to cataract formation[18,19].

Aldose reductase (AR) plays a key role, wherein glucose is reduced to sorbitol in a nicotinamide adenine dinucleotide hydrogen (NADH)-dependent reaction catalysed by AR[6]. Nicotinamide adenine dinucleotide (NAD)-dependent oxidation of sorbitol to fructose is catalysed by the enzyme sorbitol dehydrogenase (SD) (Figure 1). The rate of sorbitol accumulation is higher compared to the rate of fructose conversion. Osmotic changes caused by the prolonged accumulation of sorbitol and a decrease in intracellular NAD^+/NADH lead to lens fibre degeneration and, thereby, to cataract formation[20].

Hyperosmosis caused by sorbitol accumulation increases the infusion of fluid to countervail the osmotic gradient. The polyols accumulated by the fluid infusion lead to liquefaction and swelling of lens fibres, ultimately triggering opacification of the lens. Furthermore, sorbitol accumulation can induce stress on the endoplasmic reticulum (ER), the primary site of protein synthesis and trigger apoptosis of lens epithelial cells (LECs). ER stress can induce the generation of free radicals by increasing the oxidative stress and impair the antioxidant capacity due to increased free radical accumulation and build-up of reactive oxygen species (ROS). In addition, prolonged hyperglycaemia may induce the formation of advanced glycation end-products (AGE) in the non-enzymatic pathways[18,21].

Animal studies related to diabetic cataract formation

Kador *et al.*[22] studied the formation of cataract in diabetic rats. They found accelerated cataract formation in diabetic rats in the presence of sorbitol dehydrogenase inhibitors, suggesting the potential role of sorbitol dehydrogenase (SD). By inhibiting the AR enzyme, sorbitol accumulation in the lens can be inhibited, thereby reducing cataract formation and inhibiting polyol formation. This was reported in rodents by Kinoshita *et al.*[23], Kador[24] and Lee *et al.*[25] developed a homozygous AR transgene with SD-deficient mice. Diabetes was induced in these mice using streptozotocin. Lenticular sorbitol levels were high, and there was increased cataract formation. Kikuchi *et al.*[26] studied the effect of T2D-associated cataract in spontaneously diabetic Torrii fatty rats. They observed higher levels of glucose, sorbitol and fructose in lens tissues compared to the control Sprague–Dawley rats. In 2023, Ranaei Pimardan *et al.*[27] described the role of immune cells in the transformation and death of LECs in diabetic cataract formation. They suggested that diabetes promotes epithelial–mesenchymal transformation in the LECs, leading to immune cell trafficking. Immune cell trafficking occurs through two routes. The first route is through the ciliary body. The macrophages get firmly attached to the ciliary body and transmigrate to the lens capsule through the epithelial bilayer, where they get firmly attached. The second route is where macrophages migrate through the vitreous body to reach the posterior part of the lens. The immune cell migration and invasion of the lens capsule are the underlying causes of diabetic cataract. AGE can occur in lens fibres and epithelial cells, thereby modifying the β- and γ-crystallins in the lens; this was recorded in diabetic mice by Nakayama *et al.*[28], whereas Franke *et al.*[29] suggested AGE inhibitors were ineffective in preventing cataractogenesis in diabetic mice. Though there have been multiple studies on animal models and human subjects, the role of non-enzymatic glycation and glycoxidation of AGE in the pathogenesis of cataract remains debatable.

Figure 1. Glucose conversion into fructose through oxidation and reduction.

Factors influencing cataractogenesis in patients with type-2 diabetes

The prevalence of senile or age-related cataract is 2–5 times higher in those with diabetes compared to those without it[6]. Figure 2 shows various factors contributing to T2D-associated driven cataract reported from various studies.

Srinivasan *et al.*[30] conducted a four-year follow-up study on a South Indian population to examine the incidence and progression of cataract in T2D patients. This study suggested that diabetes could have a greater influence on the development of posterior sub-capsular cataract compared to ageing. Kaliyaperumal *et al.*[31] reported the influence of serum magnesium as a pathogenic factor of diabetic cataract. Olafsdottir *et al.*[32] worked on the prevalence of cataract in T2D patients among the Swedish population. They found that age and diabetes duration were significant determinants of cataract in T2D patients. Also, there was a higher incidence of cataract among women with T2D.

In 2010, Raman *et al.*[33] reported the prevalence of cataract among T2D patients. In this study, there were 614 T2D subjects with cataract and 669 with only T2D; they were

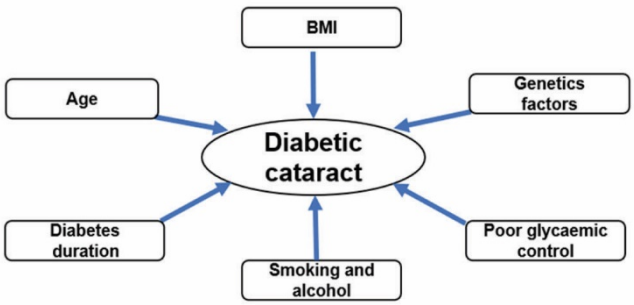

Figure 2. Various factors influencing diabetic cataract.

Table 1. Genes implicated in the pathogenesis of diabetic cataract

Susceptible loci	Authors	Population
Reported putative causality of *MIR4453HG* and *KCNK17* genes	Zhang *et al.*[44]	East Asian
Reported the association of rs2283290 in the *CACNAIC*	Chang *et al.*[6]	Scottish diabetic cohort
Reported variants from *PPARD*, *CCDC102A*, *GBA3*, *NEDD9*, *GABRR1/2*, *RPS6KA2*, *tcag7.1163*, *TAC1*, *GALNTL1* and *KIAA1671*	Lin *et al.*[12]	Han-Chinese
rs11129182–RARB, rs17047573–*TAFA1*, *rs17047586–TAFA1*, *rs11129182*, located on chromosome 3p14.2	Lin *et al.*[45]	Han-Chinese

recruited from rural areas of Kanchipuram and Thiruvallur, Tamil Nadu, India, as a part of the SN-DREAMS project. The researchers found that nearly 65.7% of T2D patients had cataract, and a high prevalence of cataract (64.5%) was found in patients with a longer duration of diabetes (>10 years). The other covariates contributing were age, diabetic duration, glycosylated haemoglobin, macroalbuminuria, poor glycaemic control and high triglycerides[34].

Drinkwater *et al.*[35] performed a systematic review to characterize the risk factors for T2D-associated cataract. This review compared all the epidemiological studies carried out in relation to diabetic cataract. A complete assessment of risk factors from randomized control trials and observational studies was done. From their analysis, age and glycaemic control (FBS and HbA1c) were found to be the risk factors for cataract in T2D patients. A positive association with BMI, smoking and gender was observed in T2D-associated cataract[36]. Three observational studies reported the association of diabetes duration with T2D-associated cataract[30,36,37]. Overall age, diabetes duration, poor glycaemic control, smoking and BMI play a pivotal role in influencing cataract in T2D patients. The influence of genetic factors in T2D patients with cataract is discussed below.

The advent of genome-wide association studies

Most of the previous studies carried out on diabetic cataract have primarily focused on the epidemiology, biochemistry and animal models, thus creating a huge lacuna on the shared genetic basis of T2D and cataract. Exploring their genetics will unravel the genetic determinants that predispose T2D patients to develop cataract. Identifying the genetic contributors to diabetic cataract can aid the generation of therapeutic and supplementary treatments. Since cataracts are treated only by surgery, a preventive intervention regimen would ease the disease burden[6,38].

GWAS is a powerful tool for studying genome-wide genetic variants in a population to understand the genotype–phenotype correlation[39]. It has the potential to identify the combined effect of common variants in a common disease and also identify rare variants[40]. Prediction of future risk for developing the disease is done by PRS[41].

PRS is a single-value estimate of the risk of developing a particular disease or a trait. An individual's genetic liability for developing a particular disease phenotype is estimated by the summation of their genotyped variants and weighted effect size[42]. Only the variants that have reached the GWAS threshold *P*-value ($P < 5 \times 10^{-8}$) are selected for PRS calculation[43].

Genome-wide association studies on diabetic cataract

There has been a plethora of GWAS identifying numerous risk variants associated with T2D. However, in the case of diabetic cataract, there have been only a handful of GWAS-identifying variants that increase the risk of developing cataracts in T2D patients. Numerous researchers have worked on GWAS of T2D and cataract separately, but they do not explain the influence of T2D on the development of cataract. In this study, we have combined all the GWAS carried out so far on diabetic cataracts and discussed the various genes increasing the risk for diabetic cataract (Table 1).

Zhang *et al.*[44] examined the shared genetics between T2D and cataract using GWAS summary statistics data from an East Asian population (BioBank Japan project) with T2D (cases = 36,614, control = 155,150) and cataract (cases = 24,622 and control = 187,331). The statistical data on average age, blood glucose and diabetes duration among the cases and controls were not included in this paper[44], and the entire analysis was performed only using the GWAS summary statistics data. Zhang *et al.*[44] found a strong correlation between T2D and cataract ($r_g = 0.58$; *P*-value = 5.60×10^{-6}). There was a putative causal effect of T2D on cataract, and two novel genes, *MIR4453HG* ($\beta_{SMR} = -0.34$, *P*-value = 6.41×10^{-8}) and *KCNK17* ($\beta_{SMR} = -0.07$, *P*-value = 2.49×10^{-10}) were reported using summary based Mendelian randomization analysis.

Chang *et al.*[6] performed a case-control GWAS from a Scottish diabetic cohort (GoDARTS dataset). Overall, 2878 controls (T2D) and 2341 cases (T2D patients with cataract) were analysed. Covariates such as age, HbA1c, HDL and baseline blood calcium were found to be statistically significant between the case-control groups. The average age was 67.92 ± 9.89 years in cases and 65.97 ± 10.38 years in controls. The study identified rs2283290 in the *CACNA1C* gene with a GWAS *P*-value of 8.81×10^{-8}, OR = 0.7 (95% CI for 'A' allele) and found to be not in linkage disequilibrium with the nearby single nucleotide polymorphisms (SNPs) ($R^2 > 0.8$). Since the *CACNA1C* gene encodes the alpha-1 subunit of CaV1.2 (voltage-dependent

Table 2. Role of identified genes in diabetic cataract through GWAS

Gene	Role
MIR4453HG	A long non-coding RNA gene.
CACNAIC	Encodes the alpha-1 subunit of voltage-dependent L-type calcium channel.
CCDC102A	Coiled-coil protein containing domain; predicted to be part of the myosin complex.
GBA3	Encoded protein is a cytosolic enzyme that hydrolyses glycosides.
NEDD9	Docking protein, tyrosine kinase-based signal transduction in cell adhesion.
GABRR1/2	An inhibitory neurotransmitter of ligand-gated chloride channel; belongs the family of rho subunits.
RPS6KA2	Member of ribosomal S6 kinase family of serine/threonine kinases. Major role in controlling cell growth and differentiation.
tcag7.1163	A heat-shock protein (HSP). Crystallins are main lens components. Some crystallins are HSPs and contain heat-shock element motif (HSE motif); post-translational modification in crystallins can reduce their solubility.
TAC1	Belongs to the tachykinin peptide hormone family, a neurotransmitter interacting with nerve receptors and smooth muscle; functions as a vasodilator and secretagogue.
GALNTL1	Belongs to the *N*-acetylgalactosaminyltransferase (GalNAc-T) family of enzymes; initiates O-linked glycosylation in the Golgi apparatus. Proven to inhibit BMP and TGF-β signalling.
KIAA1671	Associated with breast cancer and closely related to cell proliferation.
TAFA1	A member of CC-chemokine family; protein contains conserved cysteine residues at fixed positions, expressed at specific regions in brain; could act as a chemokine or neurokine in the regulation of immune and nervous cells.

L-type calcium channel), the difference in blood calcium between the case and control group suggests the potential role of calcium in cataractogenesis.

Lin *et al.*[12] reported more than ten variants associated with diabetic cataract from GWAS conducted in a Han-Chinese population in Taiwan. In this study, a total of 758 individuals with T2D were selected (only T2D = 659 and T2D with cataract = 109). The average age of T2D patients with cataract was 68.6 ± 8.7 years, whereas T2D patients without cataract had an average age of 57.9 ± 9.9 years. Also, patients with T2D and cataract had an average of 15.1 ± 8.9 years of diabetic duration. T2D patients without cataract had a diabetes duration of 9.0 ± 6.8 years. Through GWAS analysis, nearly 15 SNPs were found to be putatively associated with diabetic cataract and were nearby the genes *PPARD*, *CCDC102A*, *GBA3*, *NEDD9*, *GABRR1/2*, *RPS6KA2*, *tcag7.1163*, *TAC1*, *GALNTL1* and *KIAA1671*. All the genes reported had reached GWAS *P*-value of $<5 \times 10^{-8}$. In chromosomes 4p15.31 and 7q21.3, high linkage disequilibrium was observed. It is important to note that the sample size of this study was smaller, and hence, the variants association can be substantiated only with a larger sample size.

Other genetic studies on diabetic cataract

In a previous GWAS by Lin *et al.*[45] on a Taiwanese population, three SNPs near the locus of chromosome 3p14.1–3p14.2 were reported in diabetic cataract patients (rs11129182–*RARB*, *P*-value = 3.52×10^{-7} and OR = 3.03; rs17047573–*TAFAI*, *P*-value = 8.35×10^{-8} and OR = 7.47 and rs17047586–*TAFAI*, *P*-value = 7.65×10^{-8}, OR = 7.51).

Lee *et al.*[46] reported the association of AR gene in cataract development in patients with T2D among the Chinese population. A total of 567 Chinese patients with T2D were evaluated, of which 147 T2D patients had cataract. T2D patients with cataract had a higher age, age at diagnosis of T2D and diabetic duration compared to T2D patients without cataract. This is the only genetic study to have reported that age is an independent risk factor for diabetic cataract. A total of 14 microsatellite alleles were studied. The allele Z and its subtypes (Z, Zplus Z, and non-Z) were found to be over-presented in patients with cataract.

In 1995, Lee *et al.*[47] developed AR and SD transgenic mice to demonstrate that polyols accumulation from hexose reduction by AR leads to the formation of diabetic cataract *in vivo*. Diabetic transgenic mice overexpressing AR in their LEC were found to develop cataract. Further increased formation of cataract was observed in transgenic mice with succinate dehydrogenase-deficiency, where sorbitol accumulation accelerated cataract formation.

Genes identified in diabetic cataract

Type 2 diabetes, a complex disease have been extensively studied by multiple GWAS. On the other hand, GWAS of cataract have been limited. In 2021, Choquet *et al.*[48] performed GWAS meta-analysis in cataract cases and controls with a sample size of 585,243, collected from UKB, GERA and 23andMe research cohort. They reported 54 genome-wide significant loci and gender-stratified associations of *CASP7* and *GSTM2* in females with cataract. This study did not include patients with diabetes[48]. From the reported 54 variants, three genes, namely *CDKN2C*, *CDKN2B–DMRTA1* and *SLC24A3* were previously reported to be associated with T2D[49–51]. Variants from *KLHL42* (ref. 52), *PPARGD* (ref. 53), *KCNJ11* (refs 54, 55) and *KCNK17* (ref. 56) have been reported to be associated with T2D. Interestingly, *CACNA1D*, a member of the calcium L-type channel, was reported to be associated with T2D. *CACNA1C* also belongs to the same sub-family of calcium L-type channels[57]. Table 2 shows the list of genes and their functions reported in association with diabetic cataract. The genes *MIR4453HG*, *BRD3*, *CCDC102A*, *GBA3*, *NEDD9*, *GABRR1/2*, *RPS6KA2*, *tcag.1163*, *TAC1*, *GALNTL1*, *KIAA1671* and *TAFA1* have not been reported earlier in association with

T2D and cataract. A candidate gene study is warranted to confirm the role of these genes and their association with diabetic cataract.

Does diabetes truly influence cataract?

GWAS have been instrumental in understanding the genetic architecture of T2D and cataract. Multiple *in vivo* and *in vitro* studies have confirmed the process of diabetic cataract, but the lacuna lies in unravelling their shared genetic basis. From the above-discussed genetic studies, it is evident that there is a shared genetic basis for cataract and diabetes. The question is, to what extent does diabetes influence cataract?

It is important to note that age-adjusted genetic studies for T2D-associated cataract have not been carried out earlier. Whether age is the confounding factor for T2D-associated cataract, or is the influence of genetics and hyperglycaemia triggered by T2D the major cause of cataract in T2D patients, needs to be addressed. Since most studies focus on the older population, it is important to examine the patients with young-onset T2D and carry out a follow-up study on the effect of prolonged hyperglycaemia. Also, adjustment for diabetic duration plays a pivotal role. In most of the studies, T2D patients with cataract have been shown to have a longer diabetic duration, whereas patients with only T2D have comparatively lesser diabetic duration. To understand the true effect of diabetes duration and the influence of genetic variants, an uniform diabetic duration must be chosen for T2D patients with and without cataract. Above all, conducting a case–control analysis between T2D cataracts and normal glucose-tolerant cataracts will help us further confirm the influence of genetic factors exclusive for diabetic cataracts.

The road ahead for diabetic cataract – need of the hour

The growing importance of diabetic cataract demands extensive GWAS to unravel the shared genetic basis and determine the variants that increase the risk of developing cataract in T2D patients. Ethnicity could be an influencing factor since the variants identified in the Han-Chinese population had no effect on the Scottish diabetic cohort or on the East Asian population. We need large-scale and multi-ethnic GWAS to explore the genetic correlation and answer whether T2D truly influences the pathogenesis of cataract.

Conclusion

In conclusion, with the help of large-scale GWAS and replication studies, we can substantiate the shared genetic basis of T2D and cataract. Also, studying the ethnicity-specific variants associated with T2D-associated cataract will provide greater insight regarding the risk of developing diabetic cataract and thereby help in estimating a PRS specific for each population. For the variants identified so far in relation to diabetic cataract, it is important to functionally characterize them for a molecular-level understanding. By doing so, we can consider the molecular checkouts to determine whether the progression of cataract can be prevented in patients with T2D. This would aid in the prevention of cataract and precision medicine.

Conflict of interest: The authors declare that there is no conflict of interest.

1. Pradeepa, R. and Mohan, V., Epidemiology of type 2 diabetes in India. *Indian J. Ophthalmol*., 2021, **69**(11), 2932–2938.
2. Radha, V. and Mohan, V., Genetic predisposition to type 2 diabetes among Asian Indians. *Indian J. Med. Res*., 2007, **125**(3), 259–274.
3. Sanghera, D. K. and Blackett, P. R., Type 2 diabetes genetics: beyond GWAS. *J. Diabetes Metab*., 2012, **3**(198), 6948.
4. Magliano, D. J. and Boyko, E. J., IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th edn. International Diabetes Federation, Brussels, Belgium, 2021.
5. Radha, V., Rema, M. and Mohan, V., Genes and diabetic retinopathy. *Indian J. Ophthalmol*., 2002, **50**(1), 5–11.
6. Chang, C. *et al.*, A genome-wide association study provides new evidence that *CACNA1C* gene is associated with diabetic cataract. *Invest. Ophthalmol. Vis. Sci*., 2016, **57**(4), 2246–2250; doi:10.1167/iovs.16-19332. Erratum. *Invest. Ophthalmol. Vis. Sci*., 2017, **58**(5), 2637.
7. National Blindness and Visual Impairment Survey India 2015–2019: A Summary Report, Dr Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi, 2020.
8. Chylack Jr, L. T. *et al.*, The lens opacities classification system III. The longitudinal study of cataract study group. *Arch. Ophthalmol*., 1993, **111**(6), 831–836.
9. Bixler, J. E., Cataracts and their treatment in people with diabetes. In *Prevention and Management of Diabetes-Related Eye Disease*, American Diabetes Association, Arlington, VA, USA, 2019.
10. James, E. R., The etiology of steroid cataract. *J. Ocul. Pharmacol. Ther*., 2007, **23**(5), 403–420.
11. Reed, J., Bain, S. and Kanamarlapudi, V., A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. *Diabetes Metab. Syndr. Obes*., 2021, **14**, 3567–3602.
12. Lin, H. J. *et al.*, Novel susceptibility genes associated with diabetic cataract in a Taiwanese population. *Ophthal. Genet*., 2013, **34**(1–2), 35–42.
13. Rowe, N. G., Mitchell, P. G., Cumming, R. G. and Wans, J. J., Diabetes, fasting blood glucose and age- related cataract: the Blue Mountains Eye Study. *Ophthalmic Epidemiol*., 2000, **7**(2), 103–114.
14. Klein, B. E., Klein, R. and Moss, S. E., Incidence of cataract surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Am. J. Ophthalmol*., 1995, **119**(3), 295–300.
15. Klein, B. E., Klein, R. and Lee, K. E., Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. *Am. J. Ophthalmol.*, 1998, **126**(6), 782–790.
16. Jeganathan, V. S., Wang, J. J. and Wong, T. Y., Ocular associations of diabetes other than diabetic retinopathy. *Diabetes Care*, 2008, **31**(9), 1905–1912.
17. Dahm, R., van Marle, J., Quinlan, R. A., Prescott, A. R. and Vrensen, G. F., Homeostasis in the vertebrate lens: mechanisms of solute exchange. *Philos. Trans. R. Soc. London, Ser. B*, 2011, **366**(1568), 1265–1277.
18. Obrosova, I. G., Chung, S. S. and Kador, P. F., Diabetic cataracts: mechanisms and management. *Diabetes Metab. Res. Rev*., 2010, **26**(3), 172–180.

19. Kador, P. F. and Kinoshita, J. H., Diabetic and galactosaemic cataracts. *Ciba Found Symp*., 1984, **106**, 110–131.
20. Pollreisz, A. and Schmidt-Erfurth, U., Diabetic cataract – pathogenesis, epidemiology and treatment. *J. Ophthalmol*., 2010, **2010**, 608751.
21. Kiziltoprak, H., Tekin, K., Inanc, M. and Goker, Y. S., Cataract in diabetes mellitus. *World J. Diabetes*, 2019, **10**(3), 140–153.
22. Kador, P. F. *et al.*, Effect of sorbitol dehydrogenase inhibition on sugar cataract formation in galactose-fed and diabetic rats. *Exp. Eye Res.*, 1998, **67**(2), 203–208.
23. Kinoshita, J. H., Kador, P. and Catiles, M., Aldose reductase in diabetic cataracts. *JAMA*, 1981, **246**(3), 257–261.
24. Kador, P. F., The role of aldose reductase in the development of diabetic complications. *Med. Res. Rev*., 1988, **8**(3), 325–352.
25. Lee, A. Y., Chung, S. K. and Chung, S. S., Demonstration that polyol accumulation is responsible for diabetic cataract by the use of transgenic mice expressing the aldose reductase gene in the lens. *Proc. Natl. Acad. Sci. USA*, 1995, **92**(7), 2780–2784.
26. Kikuchi, K. *et al.*, Diabetic cataract in spontaneously diabetic Torii fatty rats. *J. Diabetes Res.*, 2020, **2020**, 3058547.
27. Ranaei Pirmardan, E., Zhang, Y., Barakat, A., Naseri, M., Russmann, C. and Hafezi-Moghadam, A., Pre-hyperglycemia immune cell trafficking underlies subclinical diabetic cataractogenesis. *J. Biomed. Sci*., 2023, **30**(1), 6.
28. Nakayama, H., Mitsuhashi, T., Kuwajima, S., Aoki, S., Kuroda, Y., Itoh, T. and Nakagawa, S., Immunochemical detection of advanced glycation end-products in lens crystallins from streptozocin-induced diabetic rat. *Diabetes*, 1993, **42**(2), 345–350.
29. Franke, S., Dawczynski, J., Strobel, J., Niwa, T., Stahl, P. and Stein, G., Increased levels of advanced glycation end-products in human cataractous lenses. *J. Cataract Refract. Surg*., 2003, **29**(5), 998–1004.
30. Srinivasan, S., Raman, R., Swaminathan, G., Ganesan, S., Kulothungan, V. and Sharma, T., Incidence, progression, and risk factors for cataract in type 2 diabetes. *Invest. Ophthalmol. Vis. Sci*., 2017, **58**(13), 5921–5929.
31. Kaliaperumal, R., Venkatachalam, R., Nagarajan, P. and Sabapathy, S. K., Association of serum magnesium with oxidative stress in the pathogenesis of diabetic cataract. *Biol. Trace Elem. Res*., 2021, **199**(8), 2869–2873.
32. Olafsdottir, E., Andersson, D. K. and Stefánsson, E., The prevalence of cataract in a population with and without type 2 diabetes mellitus. *Acta Ophthalmol*., 2012, **90**(4), 334–340.
33. Raman, R., Pal, S. S., Adams, J. S., Rani, P. K., Vaitheeswaran, K. and Sharma, T., Prevalence and risk factors for cataract in diabetes: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study, report no. 17. *Invest. Ophthalmol. Vis. Sci*., 2010, **51**(12), 6253–6261.
34. Saumya Pal, S., Raman, R., Ganesan, S., Sahu, C. and Sharma, T., Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN–DREAMS III): study design and research methodology. *BMC Ophthalmol.*, 2011, **11**, 7.
35. Drinkwater, J. J., Davis, W. A. and Davis, T. M. E., A systematic review of risk factors for cataract in type 2 diabetes. *Diabetes Metab. Res. Rev*., 2019, **35**(1), e3073.
36. Becker, C., Schneider, C., Aballéa, S., Bailey, C., Bourne, R., Jick, S. and Meier, C., Cataract in patients with diabetes mellitus-incidence rates in the UK and risk factors. *Eye* (*London*), 2018, **32**(6), 1028–1035.
37. Janghorbani, M. and Amini, M., Cataract in type 2 diabetes mellitus in Isfahan, Iran: incidence and risk factors. *Ophthalmic Epidemiol.*, 2004, **11**(5), 347–358.
38. Kim, S. I. and Kim, S. J., Prevalence and risk factors for cataracts in persons with type 2 diabetes mellitus. *Korean J. Ophthalmol*., 2006, **20**(4), 201–204.
39. Wang, Y. *et al.*, Additive effect of aldose reductase Z-4 microsatellite polymorphism and glycaemic control on cataract development in type 2 diabetes. *J. Diabetes Complicat*., 2014, **28**(2), 147–151.
40. Cirulli, E. T. *et al.*, Genome-wide rare variant analysis for thousands of phenotypes in over 70,000 exomes from two cohorts. *Nat. Commun*., 2020, **11**(1), 542.
41. Hahn, S. J., Kim, S., Choi, Y. S., Lee, J. and Kang, J., Prediction of type 2 diabetes using genome-wide polygenic risk score and metabolic profiles: a machine learning analysis of population-based 10-year prospective cohort study. *EBioMedicine*, 2022, **86**, 104383.
42. Choi, S. W., Mak, T. S. and O'Reilly, P. F., Tutorial: a guide to performing polygenic risk score analyses. *Nat. Protoc*., 2020, **15**(9), 2759–2772.
43. Euesdenm, J., Lewism, C. M. and O'Reilly, P. F., PRSice: Polygenic Risk Score software. *Bioinformatics*, 2015, **31**(9), 1466–1468.
44. Zhang, H., Xiu, X., Xue, A., Yang, Y., Yang, Y. and Zhao, H., Mendelian randomization study reveals a population-specific putative causal effect of type 2 diabetes in risk of cataract. *Int. J. Epidemiol*., 2022, **50**(6), 2024–2037.
45. Lin, H. J. *et al.*, Single-nucleotide polymorphisms in chromosome 3p14.1–3p14.2 are associated with susceptibility of type 2 diabetes with cataract. *Mol. Vis*., 2010, **16**, 1206–1214.
46. Lee, S. C., Wang, Y., Ko, G. T., Ma, R. C., Critchley, J. A., Cockram, C. S. and Chan, J. C., Risk factors for cataract in Chinese patients with type 2 diabetes: evidence for the influence of the aldose reductase gene. *Clin. Genet*., 2001, **59**(5), 356–359.
47. Lee, A. Y., Chung, S. K. and Chung, S. S., Demonstration that polyol accumulation is responsible for diabetic cataract by the use of transgenic mice expressing the aldose reductase gene in the lens. *Proc. Natl. Acad. Sci. USA*, 1995, **92**(7), 2780–2784.
48. Choquet, H. *et al.*, A large multiethnic GWAS meta-analysis of cataract identifies new risk loci and sex-specific effects. *Nat. Commun*., 2021, **12**(1), 3595.
49. Kong, Y., Sharma, R. B., Ly, S., Stamateris, R. E., Jesdale, W. M. and Alonso, L. C., *CDKN2A/B* T2D genome-wide association study risk SNPs impact locus gene expression and proliferation in human islets. *Diabetes*, 2018, **67**(5), 872–884.
50. Pereira, M. J. *et al.*, CDKN2C expression in adipose tissue is reduced in type II diabetes and central obesity: impact on adipocyte differentiation and lipid storage? *Transl. Res*., 2022, **242**, 105–121.
51. Pipal, K. V., Mamtani, M., Patel, A. A., Jaiswal, S. G., Jaisinghani, M. T. and Kulkarni, H., Susceptibility loci for type 2 diabetes in the ethnically endogamous Indian Sindhi population: a pooled blood genome-wide association study. *Genes* (*Basel*), 2022, **13**(8), 1298.
52. Viñuela, A. *et al.*, Genetic variant effects on gene expression in human pancreatic islets and their implications for T2D. *Nat. Commun*., 2020, **11**(1), 4912.
53. Villegas, R. *et al.*, Peroxisome proliferator-activated receptor delta (PPARD) genetic variation and type 2 diabetes in middle-aged Chinese women. *Ann. Hum. Genet*., 2011, **75**(5), 621–629.
54. Phani, N. M. *et al.*, Population specific impact of genetic variants in *KCNJ11* gene to type 2 diabetes: a case-control and meta-analysis study. *PLoS ONE*, 2014, **9**(9), e107021.
55. Qiu, L., Na, R., Xu, R., Wang, S., Sheng, H., Wu, W. and Qu, Y., Quantitative assessment of the effect of *KCNJ11* gene polymorphism on the risk of type 2 diabetes. *PLoS ONE*, 2014, **9**(4), e93961.
56. Varshney, A. and Kirilusha, A. *et al.*, Genetic regulatory signatures underlying islet gene expression and type 2 diabetes. *Proc. Natl. Acad. Sci. USA*, 2017, **114**(9), 2301–2306; doi:10.1073/pnas.1621192114.
57. Reinbothe, T. M., Alkayyali, S., Ahlqvist, E., Tuomi, T., Isomaa, B., Lyssenko, V. and Renström, E., The human L-type calcium channel Cav1.3 regulates insulin release and polymorphisms in CACNA1D associate with type 2 diabetes. *Diabetologia*, 2013, **56**(2), 340–349.

Received 26 May 2023; revised accepted 3 January 2024

doi: 10.18520/cs/v126/i3/320-325