Gene 965 (2025) 149665

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Association between the rs2279238 and rs12221497 of the *LXRA* gene variants and diabetic retinopathy in the Slovenian cohort

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ARTICLE INFO

Edited by: Matija Rijavec

Keywords:
Diabetic retinopathy
T2DM
LXRA
Variant
Rs2279238
Rs12221497

ABSTRACT

Aim: To investigate whether the rs2279238 and rs12221497 variants in the liver X receptor alpha (*LXRA*) gene are associated with diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM). Considering the involvement of LXRA in lipid metabolism and inflammatory pathways, we hypothesized that these genetic variants might participate in the pathogenesis of DR.
Methods: 1554 unrelated Caucasians who had type 2 diabetes mellitus (T2DM) for more than 10 years were included. Patients were divided into two groups: the cases (with DR, 577 subjects) and the control group (without DR, 977 subjects). Genetic analysis was performed using the KASPar assay.
Results: We found a significant association between the rs2279238 variant and DR. The participants with the TT or TC genotype were more likely to have DR in comparison with the CC genotype according to the dominant model of inheritance (95 % OR: 1.35 (1.05–1.74), p = 0.028). We did not find an association between the rs12221497 variant and DR.
Conclusions: The rs2279238 variant in the *LXRA* gene is significantly associated with diabetic retinopathy (DR) in Caucasians with T2DM. Individuals carrying the TT or TC genotype have a higher risk of developing DR compared to those with the CC genotype. However, no association was found between the rs12221497 variant and DR.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disease. According to the International Diabetes Federation in 2021, there are currently 537 million people with diabetes between the ages of 20 and 79, with a predicted increase to 785 million in 2045. In addition to the systemic effects, T2DM has numerous effects on the occurrence of various eye diseases such as glaucoma, diabetic retinopathy, cataract, etc.(Mansuri, Bhole and Parmar, 2023)(*IDF Diabetes Atlas*, no date). Diabetic retinopathy (DR) is a microvascular complication of diabetes. Clinically, there are two main forms of DR: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is DR that is usually asymptomatic but may progress to PDR. PDR is characterized by the growth of new fragile blood vessels in the retina

Abbreviations: **T2DM**, Type 2 Diabetes Mellitus; **LXRA**, Liver X receptor alpha; **DR**, Diabetic retinopathy; **NPDR**, non-proliferative diabetic retinopathy; **PDR**, proliferative diabetic retinopathy; **AGEs**, advanced glycation products; **LDL**, Low-density lipoprotein; **BRB**, blood-retinal barrier; **RPE cells**, retinal pigment epithelial cells; **ABCA1**, ATP Binding Cassette Subfamily A Member 1 gene; **ABCG1**, ATP Binding Cassette Subfamily G Member 1 gene; **NR1**, subfamily of the nuclear receptor superfamily; **NR1H3**, Nuclear Receptor Subfamily 1 Group H Member 3; **RXR**, retinoid X receptor; **NF-κB**, Nuclear Factor Kappa B; **SIRT1**, Sirtuin 1; **SNP**, Single nucleotide polymorphism; **HDL**, High-density lipoprotein; **HbA1c**, Hemoglobin A1 c; **TC**, Total cholesterol; **BMI**, Body mass index; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **AH**, arterial hypertension; **CAD**, Coronary artery disease; **HMGCR**, 3-Hydroxy-3-Methylglutaryl-CoA Reductase; **PCSK9**, Proprotein Convertase Subtilisin/Kexin Type 9; **NHANES**, National Health and Nutrition Examination Survey.

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https://doi.org/10.1016/j.gene.2025.149665
Received 31 May 2025; Received in revised form 5 July 2025; Accepted 10 July 2025
Available online 19 July 2025

that rupture and cause bleeding into the vitreous, leading to retinal scarring that can cause serious complications and result in vision loss (Sivaprasad and Pearce, 2018)(Perais et al., 2023). Approximately 75 % of people who have diabetes for at least 15 years develop DR. Loss of pericytes, endothelial cell failure, disruption of the blood-retinal barrier, non-perfusion of capillaries, microaneurysms, haemorrhages and neovascularization are the hallmarks of DR (Fan et al., 2020)(Lechner, O'Leary and Stitt, 2017). There are several pathophysiological pathways responsible for the development of diabetic retinopathy, of which glycation is the best known. In the elderly and diabetics, advanced glycation products (AGEs) are formed that activate receptors on cells and cause oxidative stress, damage to cells and vascular endothelium, inflammation and cell signalling dysfunction. AGEs alter circulating and extravasated proteins, such as LDL, and enhance their pathogenicity, particularly in the retina (Jenkins et al., 2015)(Gardiner, Anderson and Stitt, 2003). There is also growing evidence of a link between hyperlipidaemia and the consequences of DR, such as diabetic macular edema and hard exudates. The leakage of lipids from poorly functioning retinal capillaries is thought to cause hard exudates (Bryl et al., 2022).

In diabetic individuals, the disruption of the inner blood-retinal barrier (BRB) facilitates the infiltration of lipoproteins into the retinal tissue, leading to elevated cholesterol levels that exert cytotoxic effects on surrounding cells. The outer BRB, composed of retinal pigment epithelial (RPE) cells, transports cholesterol, which originates from either local biosynthesis or the choroidal circulation. After uptake, RPE cells export cholesterol back into the choroidal circulation or into the neural retina via ABCA1 and ABCG1 transporters. Both RPE cells and neural retina metabolize cholesterol into oxysterols using cytochrome P450, which activate liver X receptors (LXR) (Zheng et al., 2012; Busik, 2021; Mast et al., 2011).

Liver X Receptor-Alpha (*LXRA*)- also known as Nuclear Receptor Subfamily 1 Group H Member 3 – NR1H3, Gene ID: 10062, OMIM: 602423, HGCN: 7966 gene is a protein-coding gene located on the forward strand of chromosome 11 (NR1H3 Gene - GeneCards | NR1H3 Protein | NR1H3 Antibody (no date). The protein encoded by this gene belongs to the NR1 subfamily, whose members are important regulators of macrophage function and control transcriptional programs involved in lipid homeostasis and inflammation. Increased expression of this receptor has been observed in various organs (such as the liver, kidney, intestine, retina and RPE cells). This receptor forms a heterodimer with the retinoid X receptor (RXR) and regulates the expression of target genes containing retinoid response elements (NR1H3 Gene – GeneCards | NR1H3 Protein | NR1H3 Antibody, no date) (Xie et al., 2022).

LXR activation stimulates reverse cholesterol transport and reduces inflammation mediated by NF-κB. In diabetes, damage to the SIRT1-LXR axis decreases oxysterol production and hampers cholesterol elimination, leading to inadequate vascular repair and retinal damage. LXRA activation restores reverse cholesterol transport, reduces inflammation, and prevents the formation of acellular capillaries. Additionally, LXRA regulates lipid metabolism and participates in the insulin signalling pathway, influencing glucose metabolism. The role of the *LXRA* gene in the homeostasis of LDL in the retina is very important, and disturbances in the said axis could lead to disturbances in lipid metabolism and deterioration of the condition of the retina in diabetics (Bryl et al., 2022). Hyperlipidaemia therapy has shown significant effects in type 2 diabetics in slowing down the progression of DR or improving the current condition. Gordon et al. proved that therapy with statins and fenofibrates has a positive effect on DR. Pravastatin therapy reduced the number of hard exudates and improved the condition of microaneurysms (Gordon et al., 1991). Sen et al. found a significant slowing of the progression of DR in diabetics with hypercholesterolemia who used simvastatin (Sen et al., 2002). Similar results were obtained in a study on Taiwanese patients who used statin therapy. The authors found that statin therapy is associated with a reduced risk of DR and the need for treatment of sight-threatening DR in patients with type 2 diabetes and dyslipidaemia (Kang et al., 2019). In our other studies, we found an association of the *LXRA* gene variants rs12221497 and rs2279238 with stroke and coronary artery disease (Yang et al., 2015; FUKAE et al., 2011).

Data about the importance of *LXRA* gene variants regarding its role in DR development are lacking. We did not find any report of a genome-wide association study of *LXRA* in diabetes or its complications. Moreover, common genetic variation in *LXRA* (rs2279238 and rs12221497) was reported in a case-control association study in subjects with T2DM, and no association was reported (Dahlman et al., 2009). So far, a common genetic variation in *LXRA* has not been reported in subjects of any microvascular complications of diabetes.

The aim of our study was to investigate the association between the rs2279238 and rs12221497 variants of the *LXRA* gene and DR in patients with type 2 diabetes.

2. Materials and methods

2.1. Subjects

In the present case-control study, 1554 unrelated Caucasians with T2DM for more than 10 years were included. Participants were collected from the University Medical Center Ljubljana Diabetic Outpatient Clinic and Eye Clinic from January 2010 to January 2024. We classified them as having T2DM according to the 2003 American Diabetes Association criteria for the diagnosis and classification of T2DM (DM et al., 1993). Dilated fundus examination was performed by a senior ophthalmologist (M.G.P.), who used a slit lamp biomicroscope with non-contact lens. For this purpose, the pupils were dilated with 2.5 % tropicamide and phenylephrine. A 50-degree angle fundus camera (Topcon-TRC 40-IX, Tokyo, Japan) was used to electronically document the obtained results. Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity scale was taken into consideration when staging DR (Turner et al., 1998). According to the DR severity scale, subjects were categorized as having no retinopathy, NPDR (microaneurysms, retinal haemorrhages, soft and hard exudates) or PDR (new vessel formation and/or fibrous proliferation with or without vitreous haemorrhage). Patients were divided into two groups: cases with DR (577) and the control subjects – subjects with T2DM without DR (977). To avoid confounding effects, subjects with other eye diseases and subjects with overt nephropathy were excluded from the study.

2.2. Ethical statement

The research received approval from the National Medical Ethics Committee of Slovenia (number 118/12/2011) and was designed according to the principles outlined in the Declaration of Helsinki. All participants signed an informed consent.

2.3. Biochemical analyses

We measured fasting glucose, lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride) using standard colorimetric assays with standard analyzer (Ektachem 250 Analyser, Eastman Kodak Company, Rochester, MN, USA). LDL cholesterol levels were calculated using the Friedewald formula. Hyperlipidemia was defined as total cholesterol levels above 5 mmol/L, TG levels above 2 mmol/L, or the use of lipid-lowering medications. To assess glycosylated hemoglobin (HbA1c), we employed high-performance liquid chromatography, using the average of three measurements for analysis.

2.4. Genotyping

After the DNA isolation (Qiagen isolation kit), the rs2279238 and rs12221497 variants of the *LXRA* gene were genotyped by KBioscience Ltd. (LGC, Teddington, UK) using their own competitive allele-specific fluorescence-based PCR (KASPar) assay. Additional information is

available at http://www.kbioscience.co.uk/.

2.5. Statistical analysis

Numerical data (normal distribution) were reported as means ± standard deviation, while those without normal distribution were expressed as median and interquartile range. The normality of continuous variables was evaluated using the Kolmogorov–Smirnov test.

Discrete variables were compared using the Pearson χ^2 test. Moreover, Pearson χ^2 test was also used to assess genotype distribution (Hardy–Weinberg equilibrium). Multiple logistic regression was performed for variables showing significant deviations in univariate analysis (a p-value of less than 0.05 was used as a measure of a statistical significance).

Dataset was uploaded to Zenodo Data repository (DOI 10.5281/zenodo.15553682).

3. Results

The characteristics (clinical, laboratory) of cases (DR) and the control group (without DR) are demonstrated in Supplemental Table S1.

The genotype and allele frequencies of the rs2279238 and rs12221497 variants of the *LXRA* gene are shown in Table 1. Cases (with DR) and controls (without DR), were in Hardy-Weinberg equilibrium regarding genotype distribution (for the rs2279238: p = 0.16; p = 0.26 and for the rs12221497: p = 0.31; p = 0.0881, Pearson χ2 test; respectively). In the case group TT genotype of the *LXRA* rs2279238 was more frequent (p = 0.0255) than in the control group. However, the T allele was significantly more frequent in the control group (p = 0.0389) (Table 1). Genotype distribution and allele frequency of the rs12221497 *LXRA* gene variant was not statistically significantly different compared to the control group (Table 1).

We used logistic regression analysis to assess whether the rs2279238 and rs12221497 variants were independently associated with BMI, waist circumference, fasting glucose, T2DM duration and CAD. The results for the rs2279238 variant in the *LXRA* gene under the dominant genetic model indicate a statistically significant association (p = 0.028) (Table 2). To control for multiple testing, we applied a Bonferroni correction based on the number of SNPs tested (n = 2). However, the results for the rs12221497 variant in the *LXRA* gene in the dominant and recessive genetic models do not indicate a statistically significant association with DR (p = 0.22 and p = 0.40) (Table 2).

The statistical strength of the study was 0.80.

4. Discussion

In our study we reported an association of *LXRA* gene variants rs2279238 and rs12221497 with DR in Caucasians with T2DM. We found that there is an increased risk in carriers of the rs2279238 variant for DR in dominant genetic model (1.35 (1.05–1.74): p = 0.0141) compared to T2DM patients with no DR. Furthermore, we did not find a significant association of the rs12221497 *LXRA* gene variant with the onset and the development of DR in either the dominant or the recessive genetic model (p = 0.22; p = 0.40) in our cohort.

Unfortunately, we did not find other studies that investigated the association between the rs2279238 and rs12221497 variants of the *LXRA* gene and the occurrence of DR. However, many studies point to the important role of the *LXRA* gene in various mechanisms in the onset and development of DR. Zhang et al. emphasize the central role of the *LXRA* gene in the control of reverse cholesterol transport, inflammation and glucose metabolism, indirectly acting on downstream genes of the ABC transporter family (ABCA, ABCG1, ABCG5 and ABCG8) (Zhang et al., 2021). The authors hypothesize that disruption of *LXRA* gene expression may lead to DR. Furthermore, the authors emphasize the significantly higher localization of ABCA1 and ABCG1 on both sides of the epithelial cells (up to two times higher) in the retina compared to the liver and the important role of LXRA in their modulation. Hammer et al. also emphasize the important role of the LXRA gene in DR. Activation of the LXR signalling pathway shows a significant protective effect in diabetic retinopathy, as it directly activates the reverse cholesterol transport (RCT) via ABCA1 and ABCG1, which prevents pathological thickening of blood vessels in the retina. In pathological conditions, disturbances of the LXRA-ABCA1 axis lead to a disturbance of the cholesterol balance. The authors also point out that increased LXR activity shows a protective effect in mouse models with type 1 diabetes, while LXRα−/− and LXRα/β−/− mice developed retinal damage, including acellular capillaries, even without diabetes. LXR activation reduces inflammation, inhibits LPS-induced cytokines and increases RCT gene expression. In the retina, LXR signalling can restore capillary epithelial cell function, which supports vascular repair (Hammer et al., 2017).

Busik J. emphasized the important role of lipids and lipoproteins in plasma that could influence the development of DR, especially hard exudates, in addition to the usual risk factors such as hyperglycaemia and hypertension (Busik, 2021). The author stated that clinical studies show an association between high LDL cholesterol levels and an increased risk of developing retinopathy and vision loss. They also state that the retina maintains cholesterol balance through tightly controlled pathways of cholesterol uptake and excretion, with LXRA playing an important role by activating reverse cholesterol transport genes and reducing inflammatory responses. In diabetes, the reduction in LXRA activity due to the dysfunction of enzymes such as SIRT1 leads to reduced removal of cholesterol, which impedes vascular repair and causes macrophage activation, contributing to the spread of pathology in the retina. Activation of LXRA can restore reverse cholesterol transport, reduce inflammation and prevent the formation of acellular capillaries caused by diabetes, thereby improving the condition of the retina

Table 1
Genotype and allele frequencies of the rs2279238 and rs12221497.

LXRA rs2279238	Case (N = 577)	Control (N = 977)	*pvalue*
TT	11 (1.9 %)	15 (1.5 %)	***0.0255***
TC	110 (19.1 %)	244 (25.0 %)	
CC	456 (79.0 %)	718 (73.5 %)	
T (%) (MAF)	132 (11.4 %)	274 (14.0 %)	***0.0389***
C (%)	1022 (88.6 %)	1680 (86.0 %)	
HWE (p-value)	0.16	0.26	
LXRA rs12221497			
AA	14 (2.4 %)	31 (3.2 %)	*0.41*
AG	132 (22.9 %)	244 (25.0 %)	
GG	431 (74.7 %)	702 (71.9 %)	
A (%)(MAF)	160 (13.9 %)	306 (15.7 %)	*0.18*
G (%)	994 (86.1 %)	1648 (84.3 %)	
HWE (p-value)	0.31	0.0881	

Abbreviations: HWE—Hardy–Weinberg equilibrium; MAF—minor allele frequency.

Table 2
Logistic regression analysis of the association between rs2279238 and rs12221497 and DR respectively in Slovenian subjects with T2DM.

LXRA rs2279238	Cases/Controls	OR (95 % CI)	*p- value*
Dominant			
[TT + TC] vs.CC	121/456 vs. 259/718	1.35 (1.05–1.74)	***0.028***
Recessive			
TT vs.[TC + CC]	11/566 vs. 15/962	0.76 (0.33–1.83)	*0.58*
LXRA rs12221497			
Dominant			
[AA + AG] vs.GG	146/431 vs. 275/702	1.18 (0.91–1.53)	0.22
Recessive			
AA vs.[AG + GG]	14/563 vs. 31/946	1.34 (0.67–2.84)	0.40

Adjusted for: BMI, waist circumference, fasting glucose, T2DM duration, CAD.

and reducing the risk of further vascular damage. She concludes that disruption of cholesterol homeostasis may lead to increased cholesterol levels in the retina, which contributes to the development of DR (Busik, 2021). If we analyze the above studies, we find that the *LXRA* gene plays an important role in DR. However, in pathological conditions, inhibition of LXRA or certain variants can significantly impair its function, causing opposite effects compared to those mentioned above.

The importance of lipid metabolism in the development of DR was also reported in several other recent studies (Zou et al., 2025; Oh et al., 2025; Zhang, Chen and Wan, 2024; Zhang et al., 2025; Zong et al., 2025). Deranged lipid metabolism can alter the expression of various proteins in the retina as well as induce epigenetic modifications (Zou et al., 2025; Oh et al., 2025; Zong et al., 2025). A recently published Mendelian randomization study has also suggested an association between lipid-lowering drugs and the development of DR (Zhang, Chen and Wan, 2024). The authors reported an association between genetically proxied HMGCR expression and a reduced risk of diabetic retinopathy as well as an association between an increased genetically proxied PCSK9 expression and a decreased risk of diabetic retinopathy (Zhang, Chen and Wan, 2024). Recently published data from the 2005–2018 National Health and Nutrition Examination Survey (NHANES), demonstrated non-high-density lipoprotein cholesterol to be significantly linked to DR risk in diabetic patients. In clinical settings, 4935 participants (US adults with diabetes) were analysed, and 1193 had DR (Zhang et al., 2025).

Our study also had few limitations, first, the sample was homogeneous, consisting only of Caucasian subjects. The study on the *LXRA* genes association with DR focused on just two variants. Additionally, both patient groups had been on medication for an extended period, which could influence the results. We also did not measure LXRA levels in plasma, so we could not evaluate whether the studied variants influenced the plasma levels.

5. Conclusion

Our cross-sectional case-control study found an association between the rs2279238 *LXRA* gene variant and DR in a Slovenian cohort with type 2 diabetes. To validate the role of the rs2279238 variant in the onset and progression of DR, further studies involving large sample sizes on other populations are required. Future research should expand the sample size and investigate the functional impact of *LXRA* variants (rs2279238 and rs12221497) on lipid metabolism and inflammation in DR. Additionally, longitudinal studies, gene-environment interactions, and personalized medicine approaches are needed to better understand the role of LXRA in DR progression and to identify potential therapeutic targets.

CRediT authorship contribution statement

Emin Grbić: Writing – review & editing, Writing – original draft, Investigation. **Jernej Letonja:** Writing – original draft, Visualization, Supervision, Investigation, Formal analysis. **Mojca Globočnik Petrovič:** Writing – review & editing, Supervision, Conceptualization. **Izabella Karska-Basta:** Writing – review & editing, Visualization, Investigation. **Ines Cilenšek:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Danijel Petrovič:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Funding

This study was supported by a grant from the Slovenian research and Innovation agency (ARIS), grant number: P3-0326.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2025.149665.

Data availability

Data will be made available on request.

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