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Relationship of rs1800470 polymorphism of TGFB1 gene with diabetic retinopathy in type 2 diabetes

Hudz A.S. [1], **Sergiienko V.O.** [1], **Kudryl I.V.** [1], **Mogilevskyy S.Iu.** [2], **Gulida A.O.** [2], **Ziablitsev S.V.** [3]

[1] Danylo Halytsky Lviv National Medical University
Lviv (Ukraine)

[2] Shupyk National Healthcare University of Ukraine
Kyiv (Ukraine)

[3] Bohomolets National Medical University
Kyiv (Ukraine)

Purpose: *To investigate the relationship between rs1800470 polymorphism of TGFB1 gene and diabetic retinopathy (DR) in type 2 diabetes mellitus (T2DM).*
Material and Methods: *Totally, 102 type 2 diabetes (T2DM) patients with DR were examined and divided into groups based on the stage of DR: group 1 (non-proliferative DR (NPDR), 35 patients), group 2 (pre-proliferative DR (PPDR), 34 patients), and group 3 (proliferative DR (PDR), 33 patients). The control group was composed of 61 individuals. Patients underwent a routine eye examination. rs1800470 (T869C; L10P) genotypes were determined by real time polymerase chain reaction (PCR) using Gene Amp® 7500 PCR System (Applied Biosystems, Foster City, CA) and TaqMan Mutation Detection Assays (Life Technologies, Carlsbad, CA).*
Results: *The ancestral GG genotype tended to be less frequent, whereas the minor AA genotype (and, correspondingly, the minor A allele) tended to be more frequent in patients with DR compared with controls. The minor AA genotype and, consequently, the minor A allele were more frequent in patients with a more severe DR, but the difference was not significant ($p > 0.05$). We found an association of rs1800470 genotype with the phenotype of DR: BCVA was lower ($p = 0.016$) and CRT and CRV were larger ($p < 0.001$ for both comparisons) in carriers of the minor AA genotype of rs1800470 compared to carriers of the ancestral GG genotype. After stratification of patients by the stage of DR, the greatest distinction in parameters among carriers of different genotypes was seen in PDR: in carriers of the AA genotype, CRT and CRV were 2.5 times and 1.4 times, respectively, larger, than in carriers of the GG genotype ($p < 0.001$).*
Conclusion: *rs1800470 polymorphism of TGFB1 gene affected the course of DR, which was more pronounced in PDR.*

Keywords:
T2DM, diabetic retinopathy, rs1800470, TGFB1, central retinal thickness, central retinal volume, retina

Introduction

Diabetes mellitus (DM) is a heterogenous, complex metabolic disorder characterized by elevated levels of blood glucose. It is one of the five non-communicable diseases that cause most deaths worldwide, and the prevalence increases rapidly [1].

According to the International Federation of Diabetes, in 2021, approximately 537 million people had DM (of whom only 20% had compensated DM), and this number was projected to reach 643 million by 2030, and 783 million by 2045 [2].

Hyperglycemia can lead to glucose toxicity and can cause serious diabetes-associated complications like diabetic retinopathy (DR), neuropathy, nephropathy, cardiovascular diseases, dementia, psoriasis, non-alcoholic steatohepatitis, methabolic syndrome, cancer, etc. These complications are generally progressive, often become irreversible and place a huge burden on public health and economy in general [3].

Transforming growth factor β (TGF-β) ligands and their mediators have been shown to be important mediators of ocular physiology, including angiogenesis and neurogenesis [4]. In DM, TGF-β induction is mediated by the hexosamine pathway and inflammatory response [5]. In DR, mild local inflammation induces neuronal and Müller cell apoptosis, endothelial proliferation, cellular matrix remodeling, and fibrosis through the involvement of TGF-β family signaling pathways [6]. Because blood TGF-β levels were significantly higher in patients with non-proliferative diabetic retinopathy (NPDR) compared to healthy controls, TGF-β may serve as a disease marker of biochemical alterations seen in NPDR [7]. In the aqueous humor, TGF-β levels increased in advanced NPDR/proliferative diabetic retinopathy (PDR) by a factor of 5.5 compared to the control group [8].

It has been demonstrated that polymorphisms in the gene that encodes TGF-β1 (TGFB1) are involved in a higher susceptibility to diabetic vascular damage due to the role the gene plays in tissue fibrosis [9]. In addition, TGFB1 polymorphisms are involved in complications and comorbidities (hypertension and obesity) in patients with type 2 diabetes mellitus (T2DM) [10]. Moreover, a study found an association between TGFB1 gene polymorphisms and PDR [11], which warrants further research [12].

The purpose of the study was to investigate the relationship between rs1800470 polymorphism of TGFB1 gene and DR in T2DM.

Material and Methods

The study was conducted at the Department of Ophthalmology, Danylo Halytsky Lviv National Medical University. The procedures followed were in accordance with the ethical standards stated in the Declaration of Helsinki of 1964 with its further amendments, European Convention on Human Rights and Biomedicine, and Ministry of Health Order No. 690, dated 23 September, 2009. The study was approved by the Ethics Committee of the Danylo Halytsky Lviv National Medical University (meeting minutes No. 12 of November 20, 2023).

This was a prospective, cohort, case-control study. Informed consent was obtained from all patients.

Totally, 102 individuals (33 (32.4%) men and 69 (67.6%) women) with T2DM and DR (mean age, 65.9 ± 0.84 years) were involved in the study. DR was classified into NPDR, preproliferative diabetic retinopathy (PPDR) and PDR as per recommendations by Kohner and Porta. Patients were divided into three groups based on the stage of DR: group 1 (35 patients with NPDR), group 2 (34 patients with PPDR), and group 3 (33 patients with PDR). The control group comprised 61 non-diabetic patients who had surgery for senile cataract.

Eye examination included visual acuity assessment, Goldmann tonometry, slit-lamp biomicroscopy (Haag-Streit BQ 900, Haag-Streit International, Koeniz, Switzerland), gonioscopy, ophthalmoscopy with contact and non-contact lenses (Volk Optical, USA), and optical coherence tomography (OCT; Optovue RTVue, USA). Best-corrected visual acuity (BCVA), intraocular pressure (IOP, mmHg), central retinal thickness (CRT, μm) and central retinal volume (CRV, mm3) were determined.

Fasting plasma glucose and glycated hemoglobin (HbA1c) levels were assessed to detect abnormal carbohydrate metabolism.

TGFB1 rs1800470 (T869C; L10P) genotypes were determined by real-time polymerase chain reaction (PCR) using Gene Amp® 7500 PCR System (Applied Biosystems, Foster City, CA). Genomic DNA was extracted from venous blood samples using PureLink Genomic DNA Kit for Purification of Genomic DNA (Invitrogen, Carlsbad, CA). Mutation detection was performed using TaqMan Mutation Detection Assays (Life Technologies, Carlsbad, CA). Genetic studies were conducted at the Research Institute of Experimental and Clinical Medicine, Bogomolets National Medical University (director, Cand Sc (Med) Iu.G. Klys).

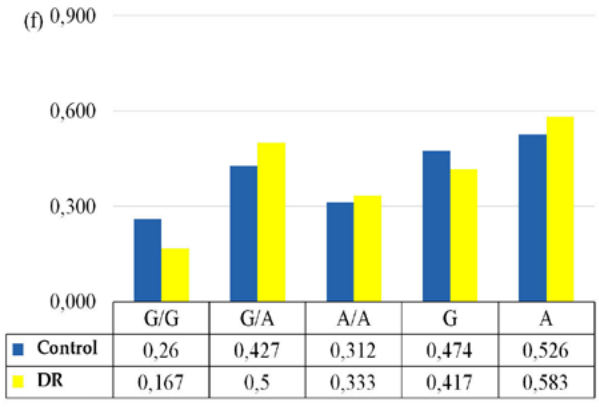
The genotype distribution among patients included in the current study was compared to the results of 1000 Genomes Project Phase 3 [13].

Statistical analyses were performed using MedStat and MedCalc v.15.1 (MedCalc Software bvba). Data are presented as mean value ± standard deviation (SD) If normally distributed and as median and interquartile range (25th and 75th percentiles) if non-normally distributed. Comparisons between groups were made with ANOVA with Scheffe's post-hoc test or Kruskal-Wallis test with Dunn's post-hoc test, as appropriate. In the course of genetic data analysis, we analyzed the general table for cases and genotype and allele frequencies. Thereafter, we analyzed the frequency differences indicating the effects of genotypes and alleles on the development of the disease. A chi-square test with Bonferroni correction was used to determine the significance of differences between groups. Odds ratio (OR) and 95% confidence interval (CI) values were considered for statistically significant difference related to the association with DR.

Results

The genotype distribution among patients included in the current study was similar to that reported for 1000 Genomes Project Phase 3 ($\chi^2 = 4.40$; $p = 0.111$). The project determined genotype frequencies of TGFB1 rs1800470 in 503 individuals of the European population, and found the frequencies of the ancestral GG genotype, heterozygous GA genotype, and minor homozygous AA genotype to be of 0.159, 0.445 and 0.396, respectively, versus 0.213, 0.465 and 0.323, respectively, in our studies.

The Hardy-Weinberg equilibrium was met for rs1800470 in cases ($p > 0.05$). The ancestral GG genotype tended to be less frequent, whereas the minor AA genotype tended to be more frequent in patients with DR compared with controls (Fig. 1). Correspondingly, the minor A allele



	G/G	G/A	A/A	G	A
Control	0,26	0,427	0,312	0,474	0,526
DR	0,167	0,5	0,333	0,417	0,583

Fig. 1. Distribution of genotypes and alleles of rs1800470 in groups of patients. P-values for differences in genotype and allele frequencies by chi square were 0.262 and 0.296, respectively. The abscess displays frequencies (f) and the ordinate displays genotypes and alleles.

was more frequent in patients with DR compared with controls.

Given the absence of significant difference in the distribution of genotypes and alleles, it could be hypothesized that rs1800470 polymorphism was not associated with the development of DR. Because of the tendency towards an increased frequency of the minor A allele in patients with DR, they were stratified by the stage of DR (Table 1).

The minor AA genotype and, consequently, the minor A allele were more frequent in patients with a more severe DR, but the difference was not significant ($p > 0.05$).

The difference in phenotype distribution between controls and patients with DR was assessed based on the rs1800470 genotype they carried.

There was no significant difference in any examined parameter for the control group (Table 2).

There was, however, a significant difference in BCVA, CRT and CRV (but not in other parameters) for patients with DR (Table 3).

BCVA was 1.8 times lower ($p = 0.016$), whereas CRT and CRV were 1.2-1.6 times higher ($p < 0.001$ for both comparisons) in carriers of the minor AA genotype of rs1800470 compared to carriers of the ancestral GG genotype. Of note, carriers of the minor genotype had worse visual function parameter (BCVA) and anatomical parameters (larger CRT and CRV) than carriers of the ancestral GG genotype, although the distributions by age, diabetes duration, and level of glycemia were comparable. Obviously, with other conditions being equal, the presence of rs1800470 polymorphism worsened the status of the eye and DR severity in T2DM.

The differences became more pronounced after stratification of patients by the stage of DR (Table 4). The examined parameters worsened with an increase in the severity of DR, but within any study group, visual acuity was worse and CRT and CRV were larger in carriers of the minor AA genotype than in carriers of any other genotype ($p < 0.05$).

Table 1. Distribution of genotypes and alleles of rs1800470 polymorphism of *TGFB1* gene in groups of patients

Genotype	Groups of patients, n (f)			
	Control group	Group 1 (NPDR)	Group 2 (PPDR)	Group 3 PDR
GG	25 (0.260)	6 (0.171)	6 (0.176)	5 (0.147)
GA	41 (0.427)	17 (0.486)	17 (0.500)	17 (0.500)
AA	30 (0.313)	12 (0.343)	11 (0.324)	12 (0.353)
p	0.823			
G	91 (0.474)	29 (0.414)	29 (0.426)	27 (0.397)
A	101 (0.526)	41 (0.586)	39 (0.574)	41 (0.603)
p	0.651			

Note: n, number of patient; *f*, frequency; P-values for differences in genotype and allele frequencies by chi-square test with Bonferroni correction; NPDR, non-proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy

Table 2. Impact of genotypes of rs1800470 polymorphism of *TGFB1* gene on the examined parameters in the control group

Parameter	G/G (n=25)	G/A (n=41)	A/A (n=30)	p
Age, years	70.76±9.73	69.68±10.72	68.87±11.82	0.812
Blood glucose, nmol/l	4.79±0.65	4.93±0.83	4.94±0.61	0.697
HbA1c, %	4.77±0.25	5.38±0.53	5.53±0.87	0.265
BCVA, units	1 (0.9–1)	1 (0.975–1)	1 (1–1)	0.621
IOP, mm Hg	16 (13.750–18)	14 (12–16.250)	15 (13–17)	0.127
CRT, μm	237 (225–247)	238 (226–245)	231 (210–245)	0.295
CRV, mm^3	5.4 (5.2–6.025)	5.7 (5.2–6.025)	5.3 (5.1–5.8)	0.147

Notes: Analysis of variance (ANOVA) was used for comparison of normally distributed variables, and the Kruskal-Wallis test was used for comparison of not normally distributed variables. BCVA, best-corrected visual acuity; CRT, central retinal thickness; CRV, central retinal volume; HbA1c, glycated hemoglobin; IOP, intraocular pressure; p, P-value of statistical significance

Table 3. Impact of genotypes of rs1800470 polymorphism of *TGFB1* gene on the examined parameters in diabetic retinopathy

Parameters	Genotypes			p
	GG (n=17)	GA (n=51)	AA (n=34)	
Age, years	63 (56-71.250)	66 (62-72.750)	67.5 (62-74)	0.260
Diabetes duration, years	6 (2.750-17.5)	7 (3-13)	8 (5-11)	0.835
Blood glucose, nmol/l	7.5 (6.25-8.53)	8.3 (6.93-10.65)	7.55 (6.1-9.8)	0.119
HbA1c, %	7.6 (7.04-8.16)	7.7 (7.1-8.9)	7.75 (6.8-8.8)	0.862
BCVA, units	0.9 (0.525-1)[3]	0.7 (0.4-0.9)	0.5 (0.150-0.8)[1]	0.016
IOP, mm Hg	16 (14.75-20)	15 (14-18)	16 (15-19)	0.437
CRT, μm	219 (199-263)[3]	258 (225-284.5)	360.5 (250-426)[1]	<0.001
CRV, mm^3	6.75 (5.4-6.95)[3]	6.78 (5.8-7.478)	7.885 (6.7-9.2)[1]	<0.001

Notes: Similar to Table 2.

Table 4. Impact of genotypes of rs1800470 polymorphism of *TGFB1* gene on the examined parameters in groups of patients

Parameter	Genotype			p
	GG	GA	AA	
Group 1 (NPDR)				
BCVA, units	1 (1–1)[2]	0.9 (0.8–0.9)[1]	0.9 (0.6–1)	0.014
CRT, μm	198 (195–211)[3]	222 (216–228)[3]	249 (242–25)[1,2]	<0.001
CRV, mm^3	5.3 (5.1–5.7)[3]	5.4 (5.2–5.95)[3]	6.4 (6.15–6.81)[1,2]	<0.001
Group 2 (PPDR)				
BCVA, units	0.8±0.14	0.59±0.3	0.48±0.32	0.106
CRT, μm	265 (263–265)[3]	275 (266.25–290.5)[3]	370 (350.2–455.2)[2,1]	<0.001
CRV, mm^3	6.915 (6.8–7.01)[3]	7.2 (6.76–7.595)	7.97 (7.2–8.96)[1]	0.019
Group 3 (PDR)				
BCVA, units	0.42±0.33	0.46±0.31[3]	0.12±0.09[1,2]	0.002
CRT, μm	211.4±36.95[3]	289.24±77.78[3]	521.36±205.78[1,2]	<0.001
CRV, mm^3	6.81 (5.79–7.073)[3]	7.25 (6.77–7.943)[3]	9.87 (8.27–13.35)[1,2]	<0.001

Note: Analysis of variance (ANOVA) with Scheffe's post-hoc test was used for comparison of normally distributed variables, and the Kruskal-Wallis test with Dunn's post-hoc test was used for comparison of not normally distributed variables. BCVA, best-corrected visual acuity; CRT, central retinal thickness; CRV, central retinal volume; HbA1c, glycated hemoglobin; IOP, intraocular pressure; NPDR, non-proliferative diabetic retinopathy; p, P-value of statistical significance of difference between groups; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; [1], significant difference from group 1, $p < 0.05$; [2], significant difference from group 2, $p < 0.05$; [3], significant difference from group 3, $p < 0.05$

The greatest distinction was seen in PDR (Table 4): in carriers of the AA genotype, CRT and CRV were 2.5 times and 1.4 times, respectively, larger, than in carriers of the GG genotype ($p < 0.001$). Carriers of the heterozygous genotype GA occupied the intermediate position between those of the AA genotype and those of the GG genotype with regard to any parameter examined.

Discussion

This study allowed substantiating the role of rs1800470 polymorphism of TGFB1 gene in the development and progression of DR. We found that the polymorphism tended to more frequent with an increasing disease severity, but this tendency was not statistically significant, possibly due to a rather small study sample. This finding is, however, in agreement with those from studies on patients with T2DM and DR of other populations [14].

In a study involving 992 diabetic patients of the southern Brazilian population, the homozygous ancestral genotype of rs1800470 was observed in 25.4% of the controls and 1.0% of the cases ($P = 0.015$), which was

confirmed in the recessive model (OR= 0.589; 95% CI 0.405 - 0.857; P= 0.006) [14].

In a study on 235 Caucasian subjects (73 patients with T2DM with PDR versus 172 patients with T2DM without PDR), TGF-β1 +869T/C (rs1800470) polymorphism was found more frequently in patients with DR (OR, 2.89; 95% CI, 1.6–5.1) [15]. In addition, TGF-β1 +915G/C (rs1800471) had a greater association with PDR (OR, 19.73; 95% CI, 2.6–146.8).

The TGFB1 gene has been regarded as an important mechanism in angiogenesis, endothelial cell proliferation, adhesion, and the deposition of extracellular matrix [12]. It is believed that the TGF-b1 gene may be involved in the development of DR through disrupting angiogenesis and blood retina barrier breakdown. However, studies investigating the relationship between 2509C/T and +869T/C(L10P) polymorphisms and DR yielded contradictory and inconclusive outcomes. A meta-analysis found that for +869T/C(L10P; rs1800470) polymorphism, significant association was observed in an allele model (L versus P: OR = 1.34, 95%CI = 1.03–1.73) and the recessive model (LL versus LP+PP: OR = 1.70, 95%CI = 1.13–2.56) [12].

Although in the current study the association with DR was not statistically significant, there was a clear association with the phenotype: carriers of the AA genotype of rs1800470 had a statistically significantly worse BCVA and thicker retinal thickness. This confirmed the role of this polymorphism in the progression of vascular abnormalities (retinal edema, cell proliferation and the deposition of extracellular matrix).

It is noteworthy that there was no difference between carriers of various rs1800470 genotypes with regard to other examined parameters (age, diabetes duration, levels of glucose and HbA1c, and IOP). In a case-control study on T2DM patients of Chinese population [16], multivariate logistic regression analysis [hypertension, gender, age, duration of diabetes, hemoglobin (HbA1c), usage of angiotensin-converting enzyme (inhibitor), and cholesterol level] showed that TGF-beta genotype (P = 0.03) is an independent predictor for type 2 diabetic nephropathy. Among patients with diabetic nephropathy, those with rs1800470 polymorphism also had worse renal function and increased risk for macroalbuminuria, which confirmed the universal role of this polymorphism in the development of diabetic microangiopathy. A study by Buraczynska et al [17] included 503 patients with T2DM of Polish population and aimed to investigate the role of molecular variants of the TGF-β1 and the TSC-22 genes in diabetic nephropathy and DR in T2DM. The authors concluded that their data suggested the association of T869C (rs1800470) polymorphism with an increased risk of nephropathy and retinopathy in T2DM.

A study by Mihoubi et al [18] explored an association of the 869C>T (rs1800470) polymorphism of TGFB1 gene with type 1 DR in Algerian population. No significant difference was found for allelic and genotypic frequencies of the 869C>T (rs1800470) (all P > 0.05) or associations between genotypes and clinical characteristics or risk factors for DR. These findings warrant further research in larger samples of patients with ophthalmologically verified DR in various populations (including the Ukrainian population).

Conclusion

We found rs1800470 polymorphism of TGFB1 gene to be not associated with DR (p > 0.5) in the examined sample of patients with T2DM. BCVA was lower (p = 0.016) and CRT and CRV were larger (p < 0.001 for both comparisons) in carriers of the minor AA genotype of rs1800470 compared to carriers of the ancestral GG genotype. After stratification of patients by the stage of DR, the greatest distinction in parameters among carriers of different genotypes was seen in PDR: in carriers of the AA genotype, CRT and CRV were 2.5 times and 1.4 times, respectively, larger, than in carriers of the GG genotype (p < 0.001).

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Corresponding author: *Hudz AS – anhudz@gmail.com*

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Data Availability Statement: *All the data obtained or analyzed during this study are reported in the article.*

Abbreviations: *BCVA, best-corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; CRV, central retinal volume; DM, diabetes mellitus; DR, diabetic retinopathy; HbA1c, glycated hemoglobin; IOP, intraocular pressure; IQR, interquartile range; NPDR, non-proliferative diabetic retinopathy; OCT, optical coherence tomography; OR, odds ratio; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SD, standard deviation; TGF-β, transforming growth factor β; TGFB1, the gene encoding TGF-β1*