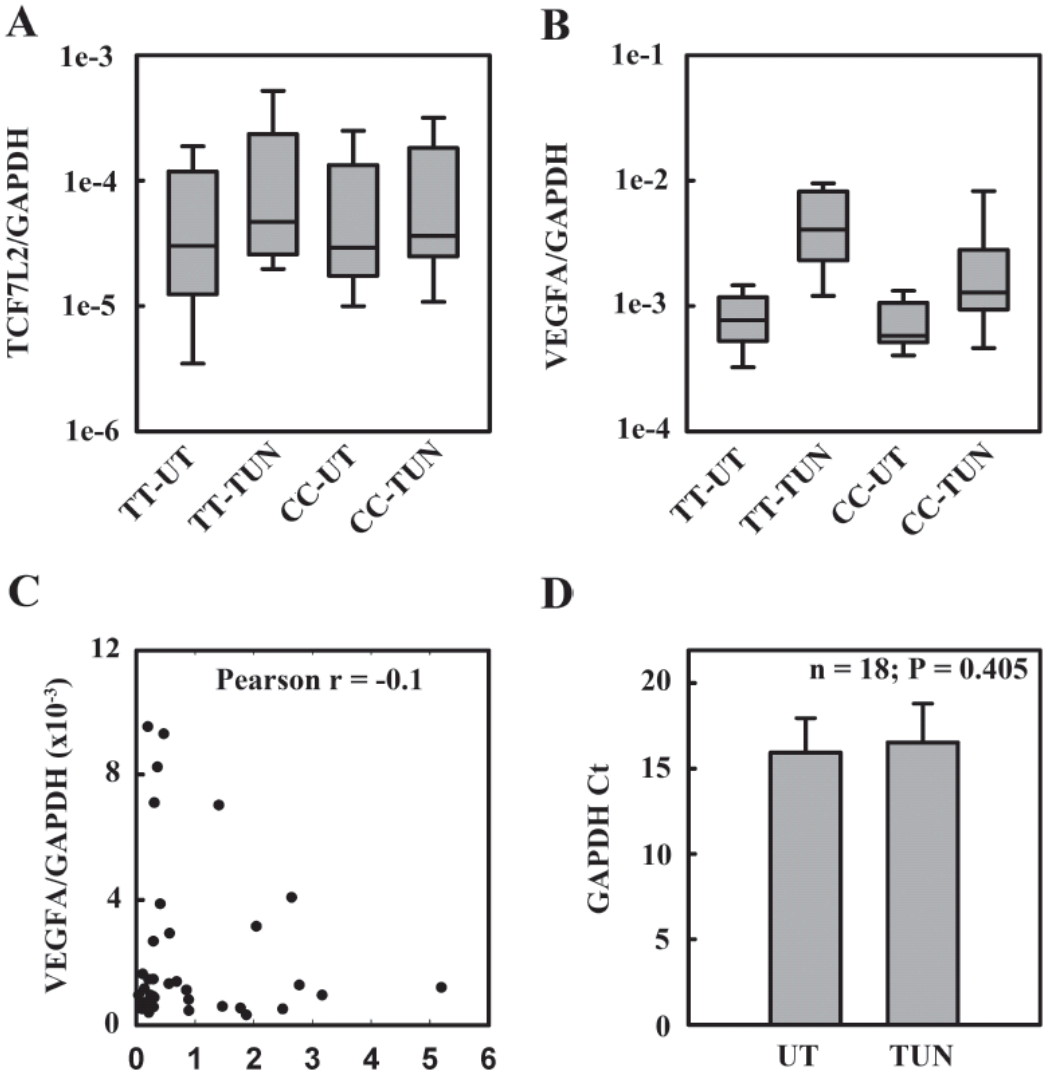
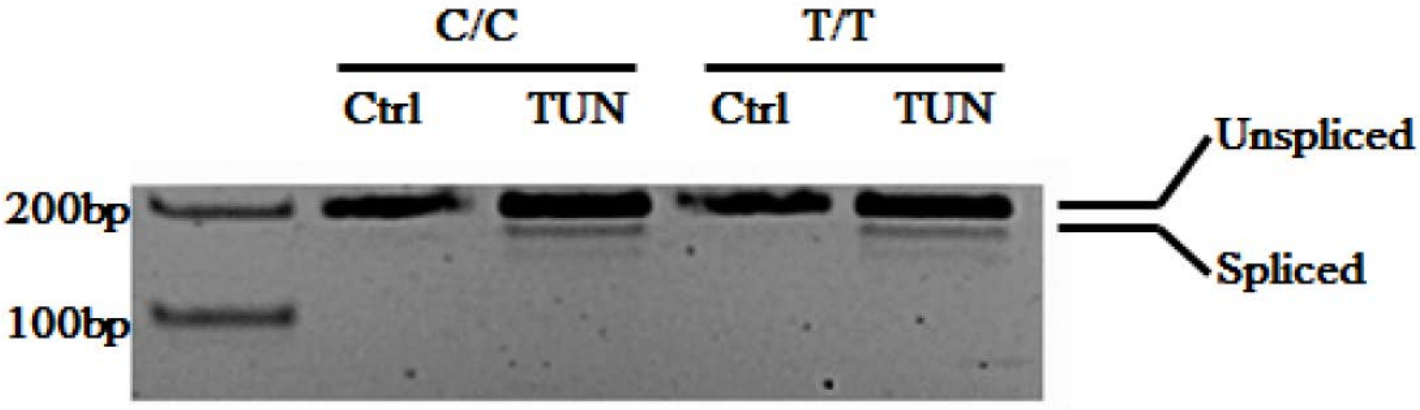
SUPPLEMENTARY DATA

Supplementary Figure 1. The expression of *VEGFA* and *TCF7L2* in tunicamycin-treated lymphoblastoid cells. A. There is no significant difference in total expression levels of *TCF7L2* in cell lines with a *TCF7L2* rs7903146-CC or rs7903146-TT genotype at the baseline or after tunicamycin-treatment (at the baseline, $P = 0.853$; after tunicamycin-treatment, $P = 0.390$). B. There is no significant difference between the expression of *VEGFA* in cell lines with a *TCF7L2* rs7903146-CC or rs7903146-TT genotype at the baseline ($P = 0.927$); However, there was a significant higher expression of *VEGFA* in the cell lines with a *TCF7L2* rs7903146-TT than in rs7903146-CC after tunicamycin-treatment ($P = 0.004$). C. Without calculation of fold change, there was no correlation of the expression of the total transcripts between *TCF7L2* and *VEGFA* at the baseline or after tunicamycin-treatment (pearson r = -0.1). D. Compared with the expression of *GAPDH* at the baseline, the expression of *GAPDH* is not significantly altered after tunicamycin treatment. ($P = 0.405$, n = 18).

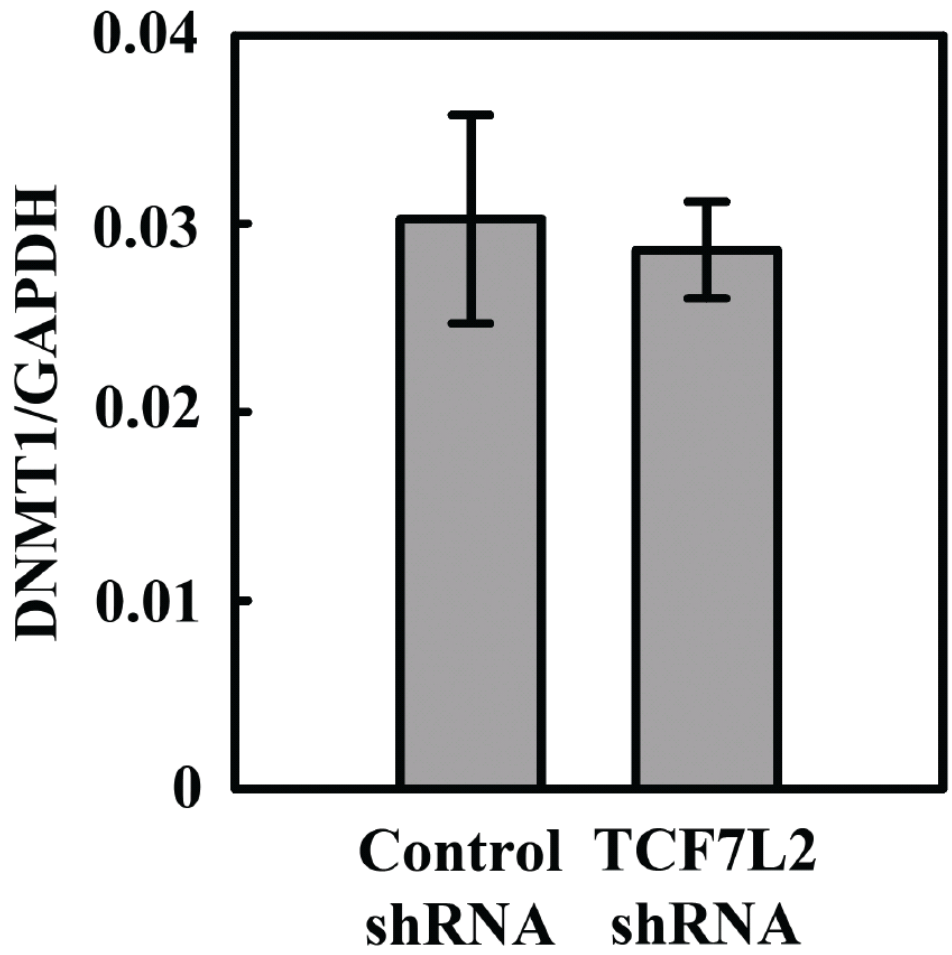


SUPPLEMENTARY DATA

Supplementary Figure 2. Activation of ER stress in the lymphoblastoid cells treated with tunicamycin. In the cells treated with tunicamycin, ER stress was induced as shown by alternative splicing of *XBP1*. Two bands (unspliced and spliced band) were detected for the tunicamycin-treated cells.

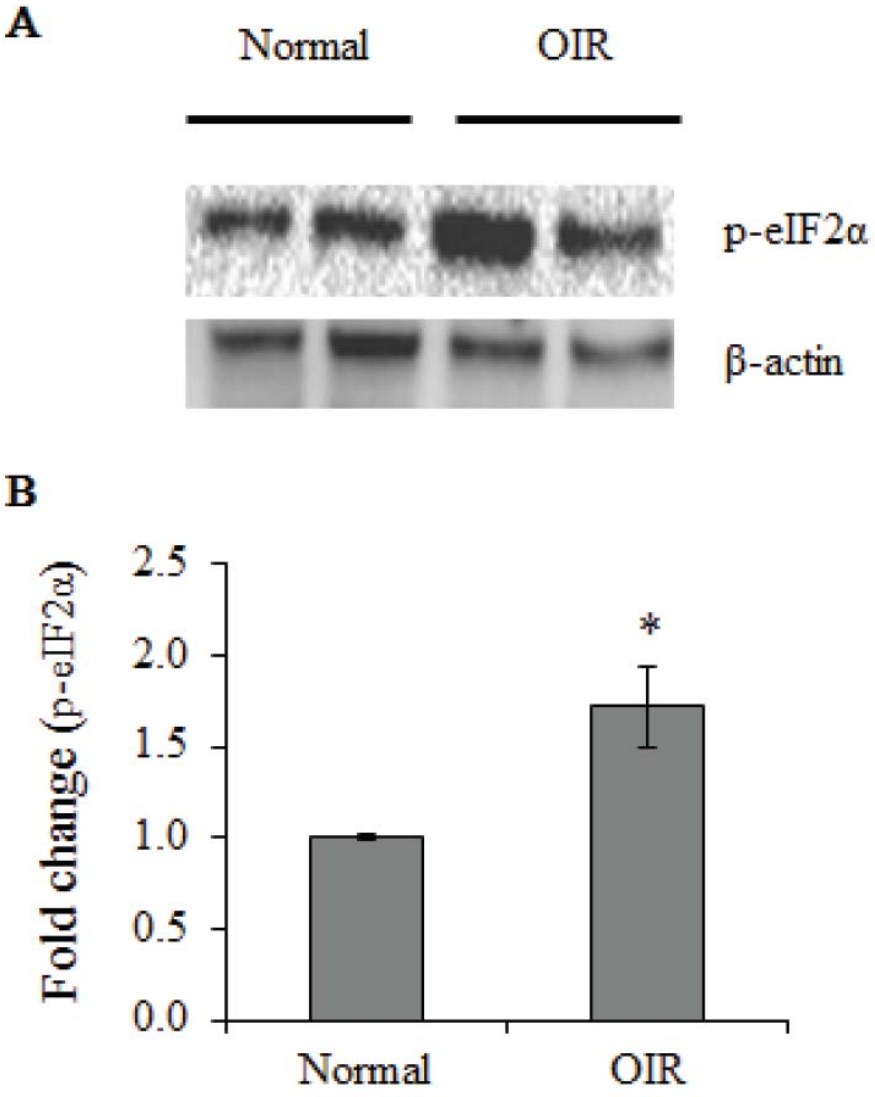


Supplementary Figure 3. The expression of *DNMT1* in the ARPE-19 cells before or after shRNA treatment **.***DNMT1* was used as an endogenous control to test the off-target effect of shRNA. The results showed that the expression of *DNMT1* gene remained the same before or after shRNA treatment.



SUPPLEMENTARY DATA

Supplementary Figure 4. Activation of ER stress in the retinas of OIR mice. A. Western blot analysis of p-eIF2a in the normal and OIR mice retinas. B. Compared with normal mice retinas, the protein level was significantly upregulated in OIR mice retinas by calculating the intensity ratio of p-eIF2a/β-actin (n = 3). *denotes $P < 0.05$.



SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of the studied populations.

Items	Caucasian (Discovery cohort)			Caucasian (Replication cohort)		
	T2DM-PDR (n=209)	T2DM-no DR (n =442)	*P*	T2DM-PDR (n =174)	T2DM-no DR (n =314)	*P*
Gender (m/f)	129/80	252/190	0.255	109/65	181/133	0.281
Age (year)	65.02 ± 0.72	69.79 ± 0.56	<0.05	66.32 ± 0.85	73.49 ± 0.62	<0.05
BMI (kg/m^2)	32.65 ± 0.51	31.57 ± 0.39	<0.05	31.27 ± 0.50	30.26 ± 0.37	<0.05

The data are presented as mean ± SEM (standard error of the mean); *P*-values are calculated from *t*-test or Chi-square test when comparing T2DM-PDR and T2DM-no DR within population; m/f, male/female; BMI, body mass index.

Supplementary Table 2. The primers used for genotyping and qRT-PCR.

Gene/SNP	Sequence (5'-3')
Genotyping	
rs7903146-Forward	GGCTTTCTCTGCCTCAAAACCT
rs7903146-Reverse	TCACTATGTATTGTTGCCAGTCAG
rs7903146-Extension	GCTGTTATTTACTGAACAATTAGAGAGCTAAGCACTTT TTAGATA
qPCR	
hGAPDH-Forward	GAGTCAACGGATTTGGTCGT
hGAPDH-Reverse	GACAAGCTTCCCGTTCTCAG
hTCF7L2-Forward	TCAAAACAGCTCCTCCGATTC
hTCF7L2-Reverse	CCCTTAAAGAGCCCTCCATC
hVEGFA-Forward	GGTCCCAGGCTGCACCCAT
hVEGFA-Reverse	GATGGCTTGAAGATGTACTCGAT
hXBP1-Forward	GCTGAAGAGGAGGCGGAAG
hXBP1-Reverse	GTCCAGAATGCCCAACAGG
hDNMT1-Forward	CCCAGGATTACAAGGAAAAGC
hDNMT1-Reverse	GGGTGTTGGTTCTTTGGTTTG
mGAPDH-Forward	GTCAAGGCCGAGAATGGGAA
mGAPDH-Reverse	TTGGCTCCACCCTTCAAGTG
mTCF7L2-Forward	GCCTCCGCACCCTCCAGATATCT
mTCF7L2-Reverse	GTGTGATGGGGAGGGACCATAT
mVEGFA-Forward	GGTGGACATCTTCCAGGAGT
mVEGFA-Reverse	TGATCTGCATGGTGATGTTG

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Supplementary Table 3. Genotype and association results of *TCF7L2*-rs7903146 in patients with T1DM-PDR and T1DM-no DR.

Group	T1DM-PDR	T1DM-no DR
Sample size, n	372	417
CC genotype, n	200	196
CT genotype, n	136	189
TT genotype, n	36	32
T allele frequency	0.280	0.303
HWE *p* value	0.075	0.140
Allelic *P* value, OR (95% CI)	0.300, 0.89 (0.71-1.11)	
Dominant *P* value, OR (95% CI)	0.058, 0.76 (0.57-1.02)	
Recessive *P* value, OR (95% CI)	0.317, 1.29 (0.76-2.18)	

HWE, Hardy-Weinberg equilibrium; OR (95% CI), odds ratio with 95% confidence interval; *P*, *P*-value calculated from $\chi 2$ test.

SUPPLEMENTARY DATA

Supplementary Table 4. Distribution of genotype of the *TCF7L2*- rs7903146 in Caucasian T2DM and Control populations.

Study (Ref. No.)	Year	Allelic *P* value	Genotype distribution											Frequency of the risk allele (T) (%)	
			Cases					Controls							
			N	TT	CT	CC	*p*HWE	N	TT	CT	CC	*p*HWE		Cases	Controls
Grant (1)	2006	1.64E-07	350	64	155	131	0.321	494	39	201	254	0.996		40.4	28.2
Cauchi (2)	2006	6.02E-35	2367	431	1149	787	0.949	2499	231	1060	1208	0.998		42.5	30.5
Groves (3)	2006	1.09E-11	2001	270	960	771	0.570	2476	217	1084	1175	0.334		37.5	30.7
Kimber (4)	2007	5.10E-14	3225	361	1459	1405	0.826	3291	248	1329	1714	0.909		33.8	27.7
Marzi (5)	2007	7.73E-05	651	73	296	282	0.939	1641	121	678	842	0.623		33.9	28.0
Van V-O (6)	2007	4.39E-05	496	72	221	203	0.645	907	83	365	459	0.699		36.8	29.3
Humphries (7)	2006	8.56E-14	1459	193	665	601	0.914	2493	197	1001	1295	0.983		36.0	28.0
Sladek (8)	2007	4.41E-20	694	149	348	197	0.980	654	65	254	335	0.266		46.5	29.4
Sladek (8)	2007	1.06E-34	2499	408	1215	876	0.652	2849	238	1194	1417	0.854		40.6	29.3
Cauchi (9)	2007	3.00E-07	486	78	208	200	0.163	1075	88	432	555	0.954		37.4	28.3
De Silva (10) **Our study**	2007 2012	2.45E-04 1.56E-13	487 1139	70 156	208 507	209 476	0.303 0.259	2099 3835	180 298	887 1544	1032 1993	0.862 0.965		35.7 36.0	29.7 27.9
Pooled		8.86E-160	15854	2325	7391	6138	0.193	24313	2005	10029	12279	0.499		**38.0**	**28.9**

HWE, Hardy-Weinberg equilibrium; *P*, *P*-value calculated from $\chi 2$ test.

SUPPLEMENTARY DATA

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