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The association between *ALR2* -106C > T gene polymorphisms and diabetic retinopathy susceptibility in diabetes mellitus patient: a systematic review and meta-analysis

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HIGHLIGHTS

Diabetic retinopathy is one of the most serious complications in diabetes mellitus.
Aldose reductase gene polymorphisms are associated with diabetic retinopathy.
Polyol pathway is linking with diabetic retinopathy.

ABSTRACT

Aldose reductase gene polymorphisms has been indicated to be associated with diabetic retinopathy (DR). The research data were from PubMed and EMBASE. We identified -106C > T single nucleotide polymorphism (SNP). Pool odds ratio (OR) with 95% CI were calculated. Nine studies were included. *ALR2* 106C > T gene polymorphisms was associated with the increased risk of DR in T1DM (C vs. T, OR = 2.07, p = 0.001; CC vs. CT + TT, OR = 2.56, p = 0.005). T allele and TT genotype were associated with decreased risk of DR in T1DM (OR = 0.48, p = 0.0001 and OR = 0.12, p = 0.0005). In conclusion, C allele and CC genotype may be a risk factor, while T allele and TT genotype may serve as protective factor for DR in T1DM patient.

Key words: *ALR2* gene, diabetic retinopathy, diabetes mellitus, gene polymorphism, polyol pathway

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INTRODUCTION

Diabetic retinopathy (DR) is a common chronic complication of diabetes mellitus and a leading cause of visual loss in diabetes mellitus patient [1]. Its prevalence is higher in type 1 diabetes mellitus than in type 2 diabetes mellitus (36.3% vs. 19.4%) [2]. DR is clinically divided into two stages: non-proliferative diabetic retinopathy (NPDR), which represents the early stage, and proliferative diabetic retinopathy (PDR), which represents late stage [1]. Early detection, tight glycemic control, and treat the comorbid may reduce the developing of diabetic retinopathy.

Chronic hyperglycemia plays an important role in the pathogenesis of retinal microvascular injury through multiple metabolic pathways, including polyol pathway, the production of advanced glycation end products (AGEs), protein kinase C (PKC) pathway, hexosamine pathway, inflammation, and the production of reactive oxygen species (ROS) [1, 3]. Polyol pathway is a major metabolic pathway linking hyperglycemia and chronic complication of DM, including DR. Its first enzyme, aldose reductase (AR), converts glucose into sorbitol with its co-factor nicotinamide adenine dinucleotide phosphate (NADPH). Sorbitol is impermeable to membrane cell. In chronic hyperglycemia, AR activity will increase. Therefore, there will be an increase of sorbitol influx in the cell, result in cell death [3, 4]. Recent studies also demonstrated that AR activity was increased in pericytes, retinal endothelial cells, ganglion cells, Müller cells, retinal pigment epithelial cells, and neurons. Besides cell death, several mechanisms have been proposed on how AR activity leads to diabetic retinopathy. AR might increase AGE formation because the increase activity of polyol pathway will increase fructose and its metabolites fructose-3-phosphate (F-3-P) and 3-deoxyglucosone (3DG) [5]. AR also might lead to oxidative stress due to fewer NADPH. NADPH is also the co-factor for glutathione reductase (GSH) to produce reduced glutathione from oxidized glutathione. Nevertheless, increase AR activity would lead to decrease of GSH, a major cellular antioxidant [5, 6].

AR activity is also influenced by AR (ALR2) gene (*ALR2*) polymorphisms. *ALR2* gene is located on chromosome 7q35 and its pseudogenes have been found on chromosomes 1q35-q42, 3p12, 7q31-q35, 9q22, 11p14-p15, and 13q14-q21 [7]. The gene consist of 10 exons. The basal promotor activity is located between position -192 and +31. In human retinal pigmen epithelial cells, *ALR2* can be stimulated by hyperglycemia through glucose response elements (GRE) in the promotor region [8, 9].

Recently, studies have found that *ALR2* -106C > T gene polymorphisms were associated with the risk of DR, but the results are inconclusive. Studies conducted by Deng et al. [10], Santos et al. [11], and Fan et al. [12] showed that *ALR2* -106C > T gene polymorphisms had no significant association with diabetic retinopathy. In contrast, studies by dos Santos et al. [13], Katakami et al. [14], Kaur et al. [15], and Wang et al. [16] showed that *ALR2* -106C > T gene polymorphisms had significant association with diabetic retinopathy. Therefore, we perform this meta-analysis to identify the association between *ALR2* 106C > T gene polymorphisms and the risk of DR in patient with DM.

MATERIALS AND METHODS

Literature searching

This systematic review and meta-analysis was carried out following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guideline [17]. Review authors (Indah Sagitaisna Putri and Bastomy Eka Rezkita) independently selected and assessed the literatures. Literature searching was performed in the following databases: PubMed and EMBASE. The search strategy uses a combination of several words: (diabetic retinopathy or DR or microvascular complication) AND (*ALR2* gene or aldose reductase gene or AKR1B1 or aldo-keto reductase family 1) AND (polymorphisms or single nucleotide polymorphisms or SNP). The language was restricted in English. No limitation of study's publication year. The searching process was done until September 2022. If more than one article was published using the same study data, only recent study was included. Reviews on longevity were also hand-searched to identify additional potentially relevant studies. Where necessary, authors were contacted directly for any additional data required.

Eligibility criteria

The eligibility criteria consisted of inclusion and exclusion criteria. Studies were included in the analysis if they met the following inclusion criteria: (i) case-control; (ii) cohort; (iii) cross-sectional studies; (iv) comparative study; (v) case group was a group of DM patient with DR; (vi) control group was a group of DM patient without DR and any eye vascular disease; (vii) the primary outcome was the association between the *ALR2* -106C > T gene polymorphism and the risk of diabetic retinopathy in diabetes mellitus patient; and (viii) sufficient data for calculation of OR 95% CI. The major reasons for exclusion were as follows: (i) the distribution genotypes in the control group were not in Hardy-Weinberg equilibrium (HWE); (ii) they lacked a control group; (iii) they had overlapping study populations; (iv) they had fewer than 100 cases; (v) the article was unavailable in English; or (vi) results were only described in conference abstracts.

Data extraction

Reviewing authors (Indah Sagitaisna Putri and Bastomy Eka Rezkita) independently extracted data on the study characteristics as follow: the name of first author, year of publication, country of origin, population ethnicity, type of diabe-

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tes, onset of diabetes, method of DR diagnosing, sample size of cases and controls, size of each allele, genotyping method, and HWE for control group. We resolved the disagreements by discussion. If the data were not available, we would contact the study's authors to request missing data.

Quality assessment

We assess the quality of included studies using The Newcastle-Ottawa Scale (NOS). This scale contains eight items under the three categories (selection, comparability, and outcome). We considered a study high quality if the study had a score > 6, studies with scores of 4–6 were deemed moderate quality, and studies with a score < 4 were deemed low quality.

Statistical analysis

The association between the *ALR2* -106C > T gene polymorphism and the risk of DR in DM patient was estimated by calculating the pooled ORs and 95% CIs. The significance of pooled ORs was determined by Z tests ($p < 0.05$ was considered statistically significant). A Q test was performed to evaluate whether heterogeneity existed. A random effects model was used to calculate OR 95% CI if heterogeneity existed ($p < 0.10$). In contrast, a fixed effect model was used to calculate OR 95%CI if no heterogeneity existed. Publication bias was assessed by Egger's test ($p < 0.05$ was considered statistically significant). Subgroup analyses was done based on continent (Asia), type of diabetes (T1DM and T2DM), duration of diabetes (< 10 years and ≥ 10 years), and severity of DR (NPDR and PDR). We used software Review Manager (Rev-Man) 5.4 to analyze the data.

Critical appraisal

A critical review was carried out using the *Oxford Center for Evidence-Based Medicine* which included *the validity*, *importance*, and *applicability* of the journals that had been selected.

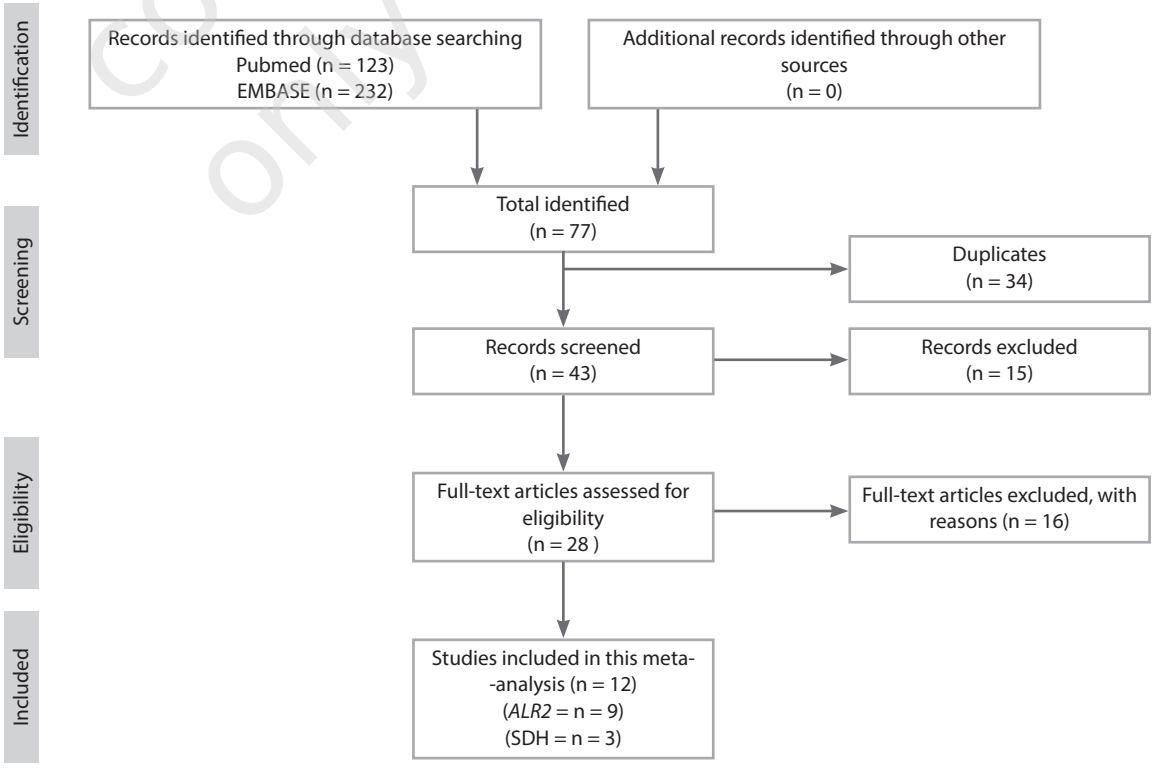
RESULTS

Characteristics of eligible studies

A total of 355 potentially relevant papers were identified based on the search strategy. Of these, 278 papers were excluded because of duplicates. After we do the screened records, 49 studies were excluded because of obvious irrelevance by reading their titles and abstracts. After the full texts were read, nine papers were excluded because they did not provide sufficient data for calculation of OR with 95% CI; three papers were excluded because they were family-based studies. In addition, seven reviews were excluded. A flow chart demonstrating the inclusion or exclusion of studies is displayed in figure 1.

FIGURE 1

PRISMA flow.



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Nine studies (4722 cases/5939 controls) were included in this study. Six studies from Asian ethnicity, 1 study from Caucasian ethnicity, 1 study from African ethnicity, and 1 study from mixed ethnicity. Table 1 describes the characteristics of the included studies. All of them met the quality assessment by NOS (tab. 2).

TABLE 1

Characteristic of studies included in this meta-analysis

Study	Year	Country	Ethnic	SNP	Sample Size (DR/NDR)	Type of Diabetes	Onset of DM in DR	Case							Control							Genotyping	HWE (p)
								CC	CT	TT	N	C	T	n	CC	CT	TT	N	C	T	n		
Demaine et al.	2000	UK	Caucasian	*ALR2* -106C > T	105/36	T1DM	24.2	49	53	3	105	151	59	210	9	22	5	36	40	32	72	PCR	0.154
Deng et al.	2014	China	Asian	*ALR2* -106C > T	128/139	T2DM	14.59	92	31	5	128	41	41	82	90	44	5	139	224	54	278	Mass Array	0.894
dos Santos et al.	2006	Brazil	African	*ALR2* -106C > T	100/55	T2DM	10.59	51	36	13	100	138	62	200	30	18	7	55	78	32	110	PCR	0.125
Katakami et al.	2010	Japan	Asian	*ALR2* -106C > T	1505/2902	T2DM	10.5	1086	381	38	1505	2553	457	3010	1416	596	80	2092	3428	756	4184	PCR	0.002
Li et al.	2019	China	Asian	*ALR2* -106C > T	1500/1500	T2DM	8.2	812	574	114	1500	2198	802	3000	963	466	71	1500	2392	608	3000	PCR	0.084
Rezaee et al.	2015	Iran	Asian	*ALR2* -106C > T	109/97	T2DM	N/A	58	39	12	109	155	63	218	37	47	13	97	121	73	194	PCR	0.094
Richeti et al.	2007	Brazil	Mixed	A *ALR2* -106C > T	29/33	T1DM	>10	15	13	1	29	43	15	58	10	18	5	33	38	28	66	PCR	0.75
Wihandani et al.	2018	Indonesia	Asian	*ALR2* -106C > T	35/35	T2DM	5.7	17	18	0	35	52	18	70	34	1	0	35	69	1	70	PCR	0.56
Yang et al.	2014	China	Asian	*ALR2* -106C > T	205/266	T2DM	13.44	145	54	6	205	344	66	410	167	91	8	266	425	107	532	PCR	0.931

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TABLE 2

Quality assessment of included studies using the Newcastle-Ottawa Scale.

Study	Year	Selection				Comparability	Exposure			Total
		Case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for all subjects	Non-response rate	
Demaine et al.	2000	*	-	-	*	**	*	*	*	7
Deng et al.	2014	*	-	-	*	**	*	*	*	7
dos Santos et al.	2006	*	-	-	*	*	*	*	*	6
Katakami et al.	2010	*	*	-	*	**	*	*	*	8
Li et al.	2019	*	*	-	*	*	*	*	*	8
Rezaee et al.	2015	*	*	-	*	*	*	*	*	7
Richeti et al.	2007	*	*	-	*	*	*	*	*	7
Wihandani et al.	2018	*	-	-	*	*	*	*	*	6
Yang et al.	2014	*	*	-	*	*	*	*	*	6

Validity, importance, applicability

Four studies were assessed using validity, importance, and applicability. Validity was assessed with inclusion and exclusion criteria. Importance was used to determine the effect and accuracy of the studies result. Applicability was purposed to determine whether the *ALR2* -106C > T gene polymorphism would be a risk factor of retinopathy DM in society.

Based on the inclusion and exclusion criteria, the validity of four studies were valid for critical study. Importance of the study had effect based on the odds ratio of *ALR2* -106C > T gene polymorphisms. From the assessment of applicability, all four studies capable to apply in society.

Quantitative data synthesis

Overall, the results showed no association between *ALR2* -106C > T gene polymorphisms and the risk of DR in DM patient in all genetic models. Significant heterogeneity was shown in some models.

Because of the significant heterogeneity found in the above comparisons, we performed a set of subgroup analysis based on the continent, type of diabetes, duration of diabetes, and severity of DR. In subgroup analysis according to the ethnicity, we only did for Asian ethnicity. It showed no association between *ALR2* -106C > T gene polymorphisms and the risk of DR. In subgroup analysis based on the type of DM, *ALR2* 106C > T gene polymorphisms was associated with the increased risk of DR in T1DM (C vs. T, OR 95% CI = 2.07 [1.32–3.24], p = 0.001; CC vs. CT + TT, OR 95% CI = 2.56 [1.33–4.94], p = 0.005). The forest plots were shown on figure 2 and figure 3. T allele and TT genotype were determined to be a protective factor for DR in T1DM (OR 95% CI = 0.48 [0.31–0.76], p = 0.0001 and OR 95% CI = 0.12 [0.04–0.39], p = 0.0005 respectively), with forest plots shown on figure 4 and figure 5. Nevertheless, there were no association between *ALR2* 106C > T gene polymorphisms and the risk of DR in T2DM patient in all genetic models.

FIGURE 2

Forest plot of association between *ALR2* -106C > T gene polymorphisms and risk of diabetic retinopathy in T1DM patient (C vs. T).

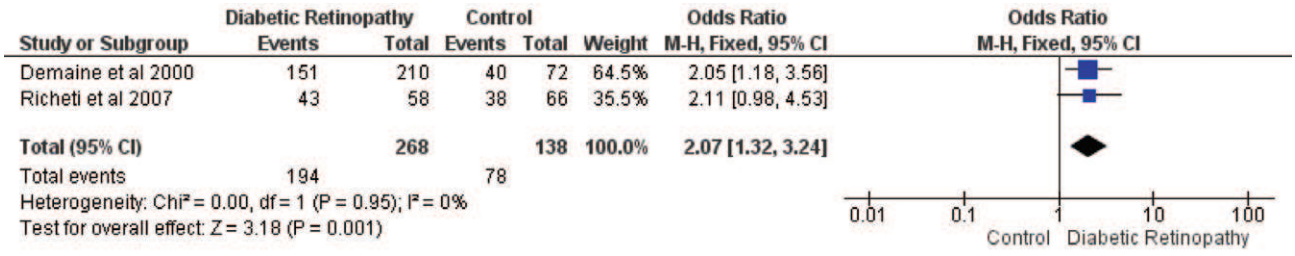

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FIGURE 3

Forest plot of association between ALR2 -106C > T gene polymorphisms and risk of diabetic retinopathy in T1DM patient (CC vs. CT + TT).

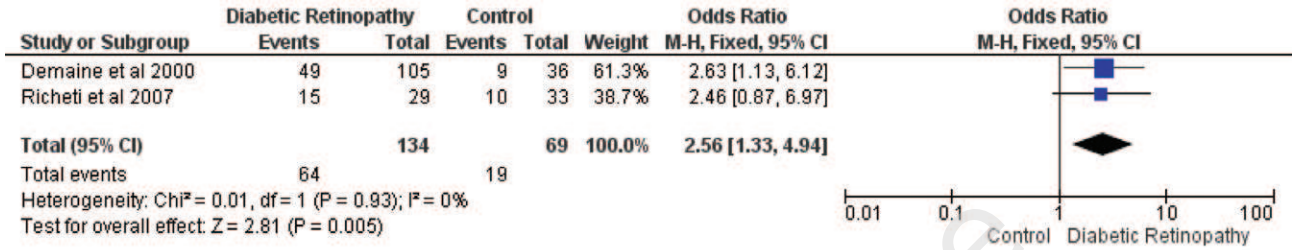


FIGURE 4

Forest plot of association between ALR2 -106C > T gene polymorphisms and risk of diabetic retinopathy in T1DM patient (T vs. C).

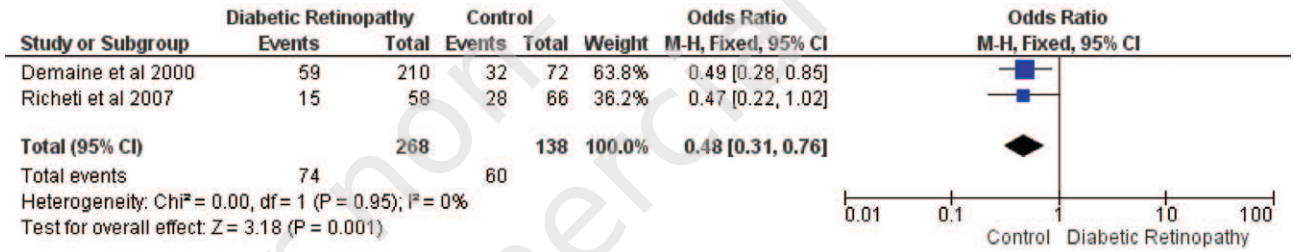
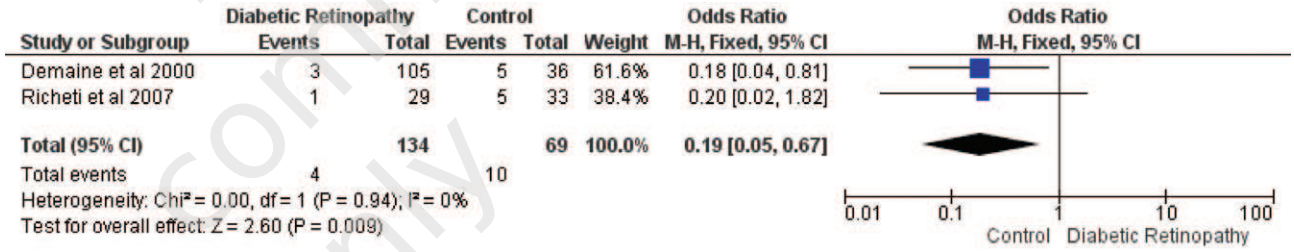


FIGURE 5

Forest plot of association between ALR2 -106C > T gene polymorphisms and risk of diabetic retinopathy in T1DM patient (TT vs. CC + CT).



In subgroup analysis based on the duration of DM, CC genotype was associated with the increase risk of DR in DM patient who had been diagnosed ≥ 10 years (OR 95% CI = 1.29 [1.13–1.46], p = 0.0001). In contrast, CT and TT genotype was associated with the decrease risk of DR in DM patient who had been diagnosed ≥ 10 years (CT vs. CC + TT, OR 95% CI = 0.82 [0.72–0.94], p = 0.003; TT vs. CC + CT, OR 95% = 0.67 [0.49–0.92], p = 0.01). No significant association between *ALR2* -106C > T gene polymorphisms and DR in subgroup revealed by the severity of DR. Significant heterogeneity was observed in most subgroups. Detailed is presented in table 3.

Furthermore, we evaluated the potential publication bias for all involved studies by using funnel plot. The symmetrically distributed shape of funnel plots indicates no potential publication bias in any genetic model of studied *ALR* -106C > T SNP (fig. 6).

DISCUSSION

The *ALR2* C to T polymorphism in the position of -106 occurs in the basal promoter region of nucleotide. In previous studies, its role in the pathogenesis of DR was inconclusive. So, we performed this meta-analysis. Our study consists of nine studies, including 4722 DR patients and 5939 DNR patients.

In the present study, substantial heterogeneity was detected all genetic models. To investigate the sources of heterogeneity, we performed several stratified analyses of ethnicity, types of DM, duration of DM, and severity of DR. However, we failed to identify the source of heterogeneity in the subgroup analysis, and heterogeneity remained in most subgroups of the studies.

In this study, among the allelic, dominant, recessive, homozygote, and heterozygote genetic models showed the lack of significant association between *ALR2* -106C > T

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TABLE 3

Summary of association between ALR2 -106C > T gene polymorphisms and diabetic retinopathy.

Allele & genotype	Categories		Number of Study	Model	OR	95% CI I^2	Heterogeneity		p
							p		
C vs. T	All		9	Random	0.96	0.67–1.37	92%	< 0.00001	0.81
	Continent	Asian	6	Random	0.77	0.50–1.19	94%	< 0.00001	0.24
	Type of diabetes	T1DM	2	Fixed	2.07	1.32–3.24	0%	0.95	0.001
		T2DM	7	Random	0.79	0.54–1.17	93%	< 0.00001	0.25
	Type of DR	PDR	2	Random	1.29	0.54–3.08	57%	0.13	0.56
		NPDR	2	Fixed	1.15	0.71–1.87	48%	0.16	0.56
	Duration of DM	< 10 years	2	Random	0.21	0.01–3.21	86%	0.007	0.26
		≥ 10 years	6	Random	1.06	0.67–1.69	88%	< 0.00001	0.81
T vs. C	All		9	Random	1.04	0.73–1.49	92%	< 0.00001	0.81
	Continent	Asian	6	Random	1.30	0.84–2.00	94%	< 0.00001	0.24
	Type of diabetes	T1DM	2	Fixed	0.48	0.31– 0.76	0%	0.95	0.001
		T2DM	7	Random	1.26	0.85–1.86	93%	< 0.00001	0.25
	Type of DR	PDR	2	Random	0.77	0.32–1.84	57%	0.13	0.56
		NPDR	2	Fixed	0.87	0.53–1.41	48%	0.16	0.56
	Duration of DM	< 10 years	2	Random	4.84	0.31–75.1	86%	0.007	0.26
		≥ 10 years	6	Random	0.94	0.59–1.50	88%	< 0.00001	0.81
CC vs. CT + TT	All		9	Random	1.19	0.82–1.72	88%	< 0.00001	0.36
	Continent	Asian	6	Random	1.05	0.68–1.62	92%	< 0.00001	0.81
	Type of diabetes	T1DM	2	Fixed	2.56	1.33–4.94	0%	0.93	0.005
		T2DM	7	Random	1.03	0.70–1.53	90%	< 0.00001	0.88
	Type of DR	PDR	2	Fixed	1.22	0.62–2.40	22%	0.26	0.56
		NPDR	2	Random	1.30	0.42–4.06	60%	0.11	0.65
	Duration of DM	< 10 years	2	Random	0.16	0.01–3.58	89%	0.003	0.25
		≥ 10 years	6	Fixed	1.29	1.13–1.46	20%	0.28	0.0001
CT vs. CC + TT	All		9	Random	0.90	0.66–1.22	82%	< 0.00001	0.49
	Continent	Asian	6	Random	0.93	0.64–1.35	88%	< 0.00001	0.69
	Type of diabetes	T1DM	2	Fixed	0.66	0.36–1.21	0%	0.95	0.18
		T2DM	7	Random	0.95	0.67–1.34	85%	< 0.00001	0.77
	Type of DR	PDR	2	Fixed	0.87	0.43–1.77	0%	0.93	0.70
		NPDR	2	Fixed	1.07	0.56–2.05	34%	0.22	0.83
	Duration of DM	< 10 years	2	Random	7.32	0.65–82.61	82%	0.02	0.11
		≥ 10 years	6	Fixed	0.82	0.72–0.94	0%	0.73	0.003
TT vs. CC + CT	All		9	Random	0.82	0.50–1.35	68%	0.002	0.43
	Continent	Asian	6	Random	1.00	0.59–1.68	72%	0.006	0.99
	Type of diabetes	T1DM	2	Fixed	0.12	0.04–0.39	0%	0.39	0.0005
		T2DM	7	Random	1.00	0.63–1.59	65%	0.01	0.99
	Type of DR	PDR	2	Fixed	0.89	0.33–2.39	38%	0.20	0.81
		NPDR	2	Fixed	0.68	0.25–1.87	0%	0.58	0.45
	Duration of DM	< 10 years	2	Fixed	n/a	n/a	n/a	n/a	n/a
		≥ 10 years	6	Fixed	0.67	0.49–0.92	15%	0.32	0.01

gene polymorphism and DR risk. In the severity of DR and Asia ethnicity, it also showed no association. This result is consistent with the findings of the previous meta-analysis [17, 18].

In type of DM, we found no association between the polymorphisms and the risk of DR in T2DM patient. It is contradictive to study by dos Santos et al. [13], Katakami et al. [14], Kaur et al. [15], and Li et al. [19], which was stated that *ALR2* -106C > T gene polymorphisms were associated with the risk of DR in T2DM patient. The discrepancy among different studies could be due to the different genetic background, sampling or experimental bias, or the presence of confounding factors. In contrast, there were association between the polymorphisms and the risk of DR in T1DM patient. C allelic and CC genotype were associated with the increase risk of DR in T1DM patient. Study by Yang et al. [20] showed that promoter region that contains C-106 alleles had significantly higher transcriptional activity than promoter regions con-

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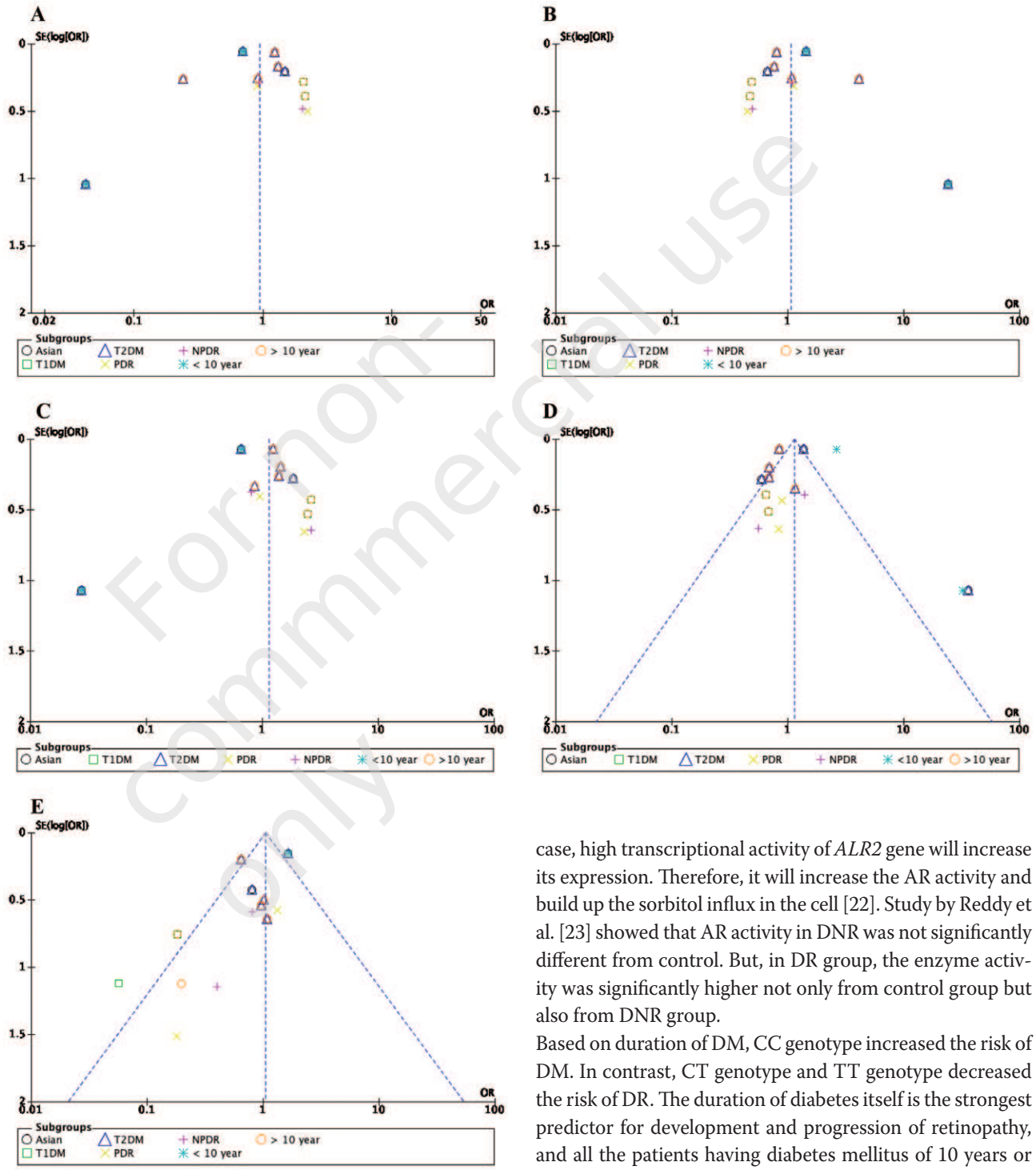
FIGURE 6

Funnel plot of association between ALR2 -106C > Y gene polymorphisms and diabetic retinopathy in diabetes mellitus patient. A. C vs. T. B. T vs. C. CC vs. CT + TT. D. CT vs. CC + TT. E. TT vs. CC + CT.



taining any other combination of alleles. In study by Stevens et al. [21] also showed that C-106 allele alone has been associated with enhanced transcriptional activity in cultured human retinal pigmented epithelial cells. High transcriptional activity of the gene will overexpress the gene. In this case, high transcriptional activity of *ALR2* gene will increase its expression. Therefore, it will increase the AR activity and build up the sorbitol influx in the cell [22]. Study by Reddy et al. [23] showed that AR activity in DNR was not significantly different from control. But, in DR group, the enzyme activity was significantly higher not only from control group but also from DNR group.

Based on duration of DM, CC genotype increased the risk of DM. In contrast, CT genotype and TT genotype decreased the risk of DR. The duration of diabetes itself is the strongest predictor for development and progression of retinopathy, and all the patients having diabetes mellitus of 10 years or longer duration should be screened for diabetic retinopathy [24, 25].

CONCLUSIONS

In conclusion, the result showed that C allele and CC genotype in *ALR2* -106C > T gene polymorphisms may be a risk

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factor for DR in T1DM patient, while T allele and TT genotype may serve as protective factor for DR in T1DM patient. CC genotype was associated with the increased risk of DR in DM patient who had been diagnosed ≥ 10 years. In contrast, CT and TT genotype was associated with the decreased risk of DR in DM patient who had been diagnosed ≥ 10 years. No association between the polymorphisms and the risk of DR in T2DM and the severity of DR. Because of relatively small sample size and high heterogeneity, the result should be interpreted with caution. Future studies with a larger sample of homogeneous patients and unbiased genotyping methods should be done.

Figures: from the author's own materials.

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