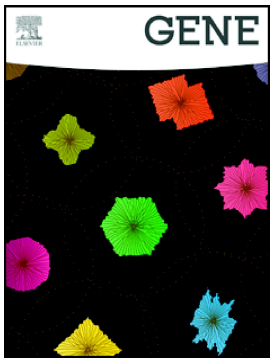

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Mingfeng Cao, Zhenhua Tian, Lin Zhang, Ruiting Liu, Qingbo Guan, Jinjiao Jiang

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Genetic association of *AKR1B1* gene polymorphism rs759853 with diabetic retinopathy risk: A meta-analysis

Mingfeng Cao, Zhenhua Tian, Lin Zhang, Ruiting Liu, Qingbo Guan, Jinjiao Jiang @

Department of Endocrinology, Shandong Provincial Hospital Affilated to Shandong University, Jinan 250100, Shandong, China.

@Corresponding author: Jinjiao Jiang, Department of Endocrinology, Shandong Provincial Hospital Affilated to Shandong University, Jinan 250100, Shandong, China. Email: uy76gh4@yeah.net

Declarations

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Abstract

Objective: The study aimed to ascertain the correlation between *AKR1B1* polymorphism rs759853 and the risk of diabetic retinopathy (DR) through a meta-analysis.

Methods: Crude odds ratios (ORs) and the corresponding 95% confidence interval (95% CIs) were calculated to assess the association of *AKR1B1* rs759853 polymorphism with DR risk. Stratification analyses were further conducted based on ethnicity, diabetes mellitus (DM) type, Hardy-Weinberg equilibrium (HWE) status, and genotyping method. Heterogeneity was detected by Q test. Sensitivity analysis was implemented to check the robustness of final results. Additionally, Begg's funnel plot and Egger's test were used to evaluate underlying publication bias.

Results: Our meta-analysis ultimately incorporated 21 eligible publications with 22 independent case-control studies. The overall results demonstrated that *AKR1B1* rs759853 polymorphism had no association with DR risk under all genetic models. However, after subgroup analysis by DM type, the rs759853 polymorphism was a protective factor against the DR onset in patients with type 1 DM (TT vs. CC: OR=0.33, 95% CI=0.17-0.67; TT + CT vs. CC: OR=0.49, 95% CI=0.36-0.68; TT vs. CC + CT: OR=0.48, 95% CI=0.28-0.83; allele T vs. allele C: OR=0.56, 95% CI=0.44-0.72; CT vs. CC: OR=0.52, 95% CI=0.37-0.74). Furthermore, subgroup analysis by genotyping method suggested that rs759853 genotyped using MassARRAY assay was significantly correlated with decreased risk of DR under dominate model (TT + CT vs. CC: OR=0.71, 95%CI=0.52-0.96).

Conclusion: *AKR1B1* polymorphism rs759853 may inhibit the occurrence of DR in patients with type 1 DM.

List of abbreviations

Crude odds ratios = ORs

diabetic retinopathy = DR

diabetes mellitus = DM

type 1 DM = T1DM

type 2 DM = T2DM

nitric oxide synthase = NOS

aldo-keto reductase family 1, member B1 = *AKR1B1*

vaseular endothelial growth factor = VEGF

angiotensin-converting enzyme = ACE

Methylenetetrahydrofolatereductase = MTHFR

aldose reductase = AR

Hardy-Weinberg equilibrium = HWE

Keywords: *AKR1B1*; Polymorphism; Diabetic retinopathy; DR; Meta-analysis

Introduction

With the rapid developments of society and economy, the prevalence of diabetes mellitus (DM) is aggravating year by year all over the world, especially in developing countries [1, 2]. As one of severe complications, diabetic retinopathy (DR) has become an important cause of irreversible visual impairment and blindness in DM patients, which ranks first in fundus lesions [3]. The incidence and blindness rates of DR are higher in patients with type 1 DM (T1DM) than in those with type 2 DM (T2DM) [4, 5]. At present, the exact etiology of DR is still beyond totally known [6]. It has been widely recognized that hyperglycemia and long duration of diabetes along with hypertension are the main risk factors for the development of DR [7]. However, these factors can not explain all of the DR cases, and accumulated evidence has indicated that genetic factors may play a significant role in the pathogenic mechanism of this disease [8]. Multiple candidate genes have been proposed to have certain effects on DR risk, such as methylenetetrahydrofolatereductase (MTHFR) gene [9], nitric oxide synthase (NOS) gene [10], aldo-keto reductase family 1, member B1 (*AKR1B1*) gene [11], vaseular endothelial growth factor (VEGF) gene [12], and angiotensin-converting enzyme (ACE) gene [13].

AKR1B1, also known as aldose reductase (AR), exists widely in human tissues including retinal capillary pericytes. *AKR1B1* gene is located on chromosome 7q35, containing 10 exons and 9 introns. Genome-wide association studies have suggested that genes on chromosome 7q31-34 are closely associated with diabetic microangiopathy. So it is hypothesized that *AKR1B1* gene may be affect the incidence of DR. The polymorphism rs759853 located at the promoter of the *AKR1B1* gene has been reported to be implicated in the onset risk of DR in Caucasian and Asian patients with T1DM and T2DM [14, 15]. However, some other studies failed to replicate this finding [16, 17]. Considering that previous results about the relationship between DR occurrence and *AKR1B1* rs759853 polymorphism are conflicting and inconclusive, we gathered all related studies from electronic databases and performed the present meta-analysis to further explore this issue.

Materials and methods

Search strategy

The online databases of PubMed, EMBASE, Cochrane Library, BIOSIS and CNKI were searched for all potentially relevant publications on the relationship between *AKR1B1* rs759853 polymorphism and DR risk. The combination of the following keywords and terms were used for searching: “aldose reductase or *AR* or *AKR1B1*”, “diabetic retinopathy or DR”, and “polymorphism or polymorphisms”. Furthermore, a manual search was performed to scan the bibliographies of all included articles in case of missing any related reports. No language restriction was imposed in literature search.

Selection criteria

The studies embraced in this meta-analysis had to satisfy the following inclusion criteria: a) exploring the effect of *AKR1B1* rs759853 polymorphism on DR risk; b) with case and control groups; c) giving sufficient information for the calculation of odds ratios (ORs) and their 95% confidence intervals (95% CIs); d) with human beings as study subjects. Studies were removed if they met any one of the following conditions: a) reviews; b) not case-control studies; c) inadequate data on genotype frequencies; and d) not involving the role of *AKR1B1* rs759853 polymorphism in DR pathogenesis.

Data extraction

Essential information was extracted from each eligible study and then recorded in a standard data-collection form by two reviewers independently. These data consisted of the first author’s name, publication year, original country, ethnic descent, genotyping method, DM type, numbers of cases and controls, genotype and/or allele frequencies in case and control groups, and *P* value for Hardy-Weinberg equilibrium (HWE) in controls. A cross-check was conducted to examine the accuracy of all extracted data, and discrepancies over these information were solved through discussion between the two reviewers until consensus was reached on all items.

Statistical analysis

In order to investigate the association between *AKR1B1* rs759853 polymorphism and DR risk, crude ORs and their corresponding 95% CIs were computed under the contrasts of TT

vs. CC, TT+CT vs. CC, TT vs. CC+CT, T vs. C and CT vs. CC, respectively. The χ^2 test was employed to check whether genotype frequencies in controls conformed to HWE. Stratified analyses by ethnicity and DM type were performed to discover specific relationship between the polymorphism and the disease risk. Q-statistic was applied to examine between-study heterogeneity. Fixed-effects model was selected to calculate summary ORs and 95% CIs when statistically significant heterogeneity was absent (P>0.05); or else, random-effects model was more appropriate. Sensitivity analysis was accomplished to inspect the influences of individual studies on final estimates. Begg's funnel plots and Egger's regression test were both assumed to evaluate potential publication bias. All data syntheses in this meta-analysis were completed with STATA 12.0 software (Stata Corp, College Station, TX, USA) and the cutoff of statistical significance was set at P<0.05.

Results

Characteristics of identified studies

As outlined in **Figure 1**, initial database searching yielded a total of 120 potentially relevant articles. Then 71 of them were removed for unrelated titles and abstracts. Through reading full texts, 27 more reports were further excluded due to reviews (6), not involving *AKR1B1* rs759853 polymorphism (8), not case-control studies (9), and the absence of genotype frequencies (5). Consequently, 21 eligible articles [14-34] published between 1999 and 2016 were eventually included in our meta-analysis, containing 22 case-control studies with 4,173 cases and 4,880 controls. Among these studies, 4 were on Caucasians, 16 on Asians, and 1 on mixed populations. The genotype distribution of the controls in six studies [15, 19, 22, 25, 28, 33] significantly deviated from HWE in this meta-analysis (P<0.05). The principal characteristics of identified studies are outlined in **Table 1**.

Meta-analysis results

In overall analysis, no significant association was found between *AKR1B1* polymorphism rs759853 and the risk of DR under any one of genetic models [TT vs. CC: OR=0.92, 95% CI=0.69-1.21 (**Figure 2**); TT + CT vs. CC: OR=0.90, 95% CI=0.74-1.09; TT vs. CC + CT: OR=0.96, 95% CI=0.76-1.21; allele T vs. allele C: OR=0.93, 95% CI=0.80-1.09; CT vs. CC:

OR=0.88, 95% CI=0.72-1.07]; neither was in stratification analysis based on ethnicity or HWE (**Table 2**). Nevertheless, after subgroup analysis by DM type, we observed that the polymorphism significantly decreased the disease risk in patients with T1DM [TT vs. CC: OR=0.33, 95% CI=0.17-0.67 (**Figure 2**); TT + CT vs. CC: OR=0.49, 95% CI=0.36-0.68; TT vs. CC + CT: OR=0.48, 95% CI=0.28-0.83; allele T vs. allele C: OR=0.56, 95% CI=0.44-0.72; CT vs. CC: OR=0.52, 95% CI=0.37-0.74]. Furthermore, subgroup analysis by genotyping method suggested that rs759853 genotyped using MassARRAY assay was significantly correlated with decreased risk of DR under dominate model (TT + CT vs. CC: OR=0.71, 95%CI=0.52-0.96).

Heterogeneity analysis

Table 2 demonstrated great inter-study heterogeneity under TT vs. CC, TT + CT vs. CC, T vs. C, and CT vs. CC models (P_Q<0.05), so the random-effects model was utilized to estimate the ORs for these four contrasts. Conversely, the fixed-effects model was employed in TT vs. CC + CT contrast due to the absence of significant heterogeneity (P_Q>0.05).

Sensitivity analysis

The results of sensitivity analysis showed that pooled ORs were not substantially changed after sequentially omitting each individual study (data not shown), which reflected that our estimates were stable and robust.

Publication bias

Potential publication bias was evaluated by both Begg's funnel plot and Egger's test. The funnel plots seemed symmetrical (**Figure 3**), which was statistically testified by Egger's test (P=0.160), suggesting publication bias between selected studies was negligible in this meta-analysis.

Discussion

DR is one of the most severe microvascular complications of DM, and may result in

blindness among the patients. Since the incidence rate of DM has increased rapidly over the past several decades, the morbidity rate of this complication also sees an upward trend [35]. The pathogenesis of DR is reportedly multifactorial, involving interactions between environmental and genetic risk factors [36]. Substantial evidence has demonstrated that DR occurrence can be affected not only by the duration of diabetes and blood glucose level but also by genetic predisposition. For instance, some patients with poorly controlled diabetes or a long duration of diabetes may not develop retinopathy, whereas some others with relatively fine glycemic control may suffer advanced retinopathy. All of these phenomenons suggest that genetic factors may exert significant impacts on the initiation and progression of DR.

AKR1B1 is a rate-limiting enzyme in the polyol pathway. Researches have observed its increased enzyme activity and expression in patients with diabetic microvascular complications. The gene *AKR1B1* has thus been considered as one of potential candidate genes for individual susceptibility to diabetic microangiopathy. Investigators both at home and abroad have reported a significant association between *AKR1B1* polymorphism rs759853 and DR susceptibility. For example, a study by Katakami et al. [14] reported that the C allele of *AKR1B1* gene polymorphism rs759853 was a susceptibility allele for DR incidence in Japanese patients with T2DM. In addition, Ren et al. [23] indicated that the rs polymorphism759853 could lower the risk of DR in patients with T2DM as well. However, Deng et al. [16] recruited 268 Chinese patients with T2DM and concluded that this polymorphism might not be significantly correlated with the DR initiation.

In light of the aforementioned conflicting conclusions, we undertook the present meta-analysis to systematically appraise the genetic association of *AKR1B1* polymorphism rs759853 with DR risk based on previously published articles. In accordance with search strategy and selection criteria, 22 literatures published between 1999 and 2016 were finally incorporated in the current meta-analysis, containing a total of 23 independent studies with 4,267 cases and 4,919 controls. Among the studies, 4 were on Caucasians, 17 on Asians and 1 on mixed populations. The results of meta-analysis indicated that *AKR1B1* polymorphism rs759853 had no significant effect on developing DR under all contrasts in overall analysis; nevertheless, this polymorphism was significantly related to a decreased risk of DR in patients with T1DM after subgroup analysis by DM type. Moreover, sensitivity

analysis verified the credibility and robustness of our results.

Nonetheless, the findings of this meta-analysis should be interpreted prudently in consideration of the following limitations. Firstly, only openly published articles were incorporated in the meta-analysis. Hence, unpublished relevant papers detecting the roles of the polymorphism rs759853 in DR risk were missed, leading to certain publication bias though not detected even with Egger's test. Secondly, significant between-study heterogeneity was uncovered among included studies, which might impact the accuracy of final estimates. Thirdly, the majority of included studies concerned on Caucasian and Asian populations, so our findings might be less applicable for other ethnic groups. Finally, the effects of gene-gene and gene-environment interactions on DR susceptibility was neglected in this article owing to the lack of necessary information from original papers. Further investigations are still required to address the functional roles of *AKR1B1* gene in etiology of DR, as well as other vasculopathies.

In short, the current meta-analysis provides statistical evidence supporting that *AKR1B1* rs759853 polymorphism may be an independent protective factor against the generation of DR in patients with T1DM, but not in those with T2DM or in total DM cases. Considering the above mentioned shortcomings in our analysis, more researches involving different ethnic populations are recommended to further ascertain the influence of *AKR1B1* polymorphism rs759853 on DR etiology in future.

References

[1] Gwatidzo SD and Stewart Williams J. Diabetes mellitus medication use and catastrophic healthcare expenditure among adults aged 50+ years in China and India: results from the WHO study on global AGEing and adult health (SAGE). BMC Geriatr 2017; 17: 14.

[2] Unnikrishnan R, Anjana RM and Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol 2016; 12: 357-370.

[3] Lin S, Gupta B, James N and Ling RH. Visual impairment certification due to diabetic retinopathy in North and Eastern Devon. Acta Ophthalmol 2017;

[4] Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L and Douglas I. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ Open 2017; 7: e014444.

[5] Mozetic V, Freitas CG and Riera R. Statins and Fibrates for Diabetic Retinopathy: Protocol for a Systematic Review. JMIR Res Protoc 2017; 6: e30.

[6] Cai X and McGinnis JF. Diabetic Retinopathy: Animal Models, Therapies, and Perspectives. J Diabetes Res 2016; 2016: 3789217.

[7] Vyas U, Khandekar R, Trivedi N, Desai T and Danayak P. Magnitude and determinants of ocular morbidities among persons with diabetes in a project in Ahmedabad, India. Diabetes Technol Ther 2009; 11: 601-607.

[8] Mishra B, Swaroop A and Kandpal RP. Genetic components in diabetic retinopathy. Indian J Ophthalmol 2016; 64: 55-61.

[9] Luo S, Wang F, Shi C and Wu Z. A Meta-Analysis of Association between Methylenetetrahydrofolate Reductase Gene (MTHFR) 677C/T Polymorphism and Diabetic Retinopathy. Int J Environ Res Public Health 2016; 13:

[10] Bazzaz JT, Amoli MM, Pravica V, Chandrasecaran R, Boulton AJ, Larijani B and Hutchinson IV. eNOS gene polymorphism association with retinopathy in type 1 diabetes. Ophthalmic Genet 2010; 31: 103-107.

[11] Zhou M, Zhang P, Xu X and Sun X. The Relationship Between Aldose Reductase C106T Polymorphism and Diabetic Retinopathy: An Updated Meta-Analysis. Invest

Ophthalmol Vis Sci 2015; 56: 2279-2289.

[12] Xie XJ, Yang YM, Jiang JK and Lu YQ. Association between the vascular endothelial growth factor single nucleotide polymorphisms and diabetic retinopathy risk: A meta-analysis. J Diabetes 2016;

[13] Luo S, Shi C, Wang F and Wu Z. Association between the Angiotensin-Converting Enzyme (ACE) Genetic Polymorphism and Diabetic Retinopathy-A Meta-Analysis Comprising 10,168 Subjects. Int J Environ Res Public Health 2016; 13:

[14] Katakami N, Kaneto H, Takahara M, Matsuoka TA, Imamura K, Ishibashi F, Kanda T, Kawai K, Osonoi T, Matsuhisa M, Kashiwagi A, Kawamori R, Shimomura I and Yamasaki Y. Aldose reductase C-106T gene polymorphism is associated with diabetic retinopathy in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2011; 92: e57-60.

[15] dos Santos KG, Canani LH, Gross JL, Tschiedel B, Souto KE and Roisenberg I. The -106CC genotype of the aldose reductase gene is associated with an increased risk of proliferative diabetic retinopathy in Caucasian-Brazilians with type 2 diabetes. Mol Genet Metab 2006; 88: 280-284.

[16] Deng Y, Yang XF, Gu H, Lim A, Ulziibat M, Snellingen T, Xu J, Ma K and Liu NP. Association of C(-106)T polymorphism in aldose reductase gene with diabetic retinopathy in Chinese patients with type 2 diabetes mellitus. Chin Med Sci J 2014; 29: 1-6.

[17] Yang X, Deng Y, Gu H, Ren X, Li N, Lim A, Snellingen T, Liu X, Wang N and Liu N. Candidate gene association study for diabetic retinopathy in Chinese patients with type 2 diabetes. Mol Vis 2014; 20: 200-214.

[18] Richeti F, Noronha RM, Waetge RT, de Vasconcellos JP, de Souza OF, Kneipp B, Assis N, Rocha MN, Calliari LE, Longui CA, Monte O and de Melo MB. Evaluation of AC(n) and C(-106)T polymorphisms of the aldose reductase gene in Brazilian patients with DM1 and susceptibility to diabetic retinopathy. Mol Vis 2007; 13: 740-745.

[19] Santos KG, Tschiedel B, Schneider J, Souto K and Roisenberg I. Diabetic retinopathy in Euro-Brazilian type 2 diabetic patients: relationship with polymorphisms in the aldose reductase, the plasminogen activator inhibitor-1 and

the methylenetetrahydrofolate reductase genes. Diabetes Res Clin Pract 2003; 61: 133-136.

[20] Araki S, Koya D, Makiishi T, Sugimoto T, Isono M, Kikkawa R, Kashiwagi A and Haneda M. APOE polymorphism and the progression of diabetic nephropathy in Japanese subjects with type 2 diabetes: results of a prospective observational follow-up study. Diabetes Care 2003; 26: 2416-2420.

[21] Demaine A, Cross D and Millward A. Polymorphisms of the aldose reductase gene and susceptibility to retinopathy in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci 2000; 41: 4064-4068.

[22] Kao YL, Donaghue K, Chan A, Knight J and Silink M. A novel polymorphism in the aldose reductase gene promoter region is strongly associated with diabetic retinopathy in adolescents with type 1 diabetes. Diabetes 1999; 48: 1338-1340.

[23] Ren M, Zhao LL, Zhang Y, Shi Y, Mao YM and Qi XY. Relationship between polymorphisms of aldose reductase gene and type 2 diabetic retinopathy. Shandong Medical Journal 2014; 54: 20-22.

[24] Wang WL, Yu DM, Liu DM and Xie Y. The Relationship between the C(-106)T Polymorphisms of Aldose Reductase Gene Promoter Region and Diabetic Retinopathy. Chin J Prev Contr Chron Non-commu Dis 2006; 14: 238-240.

[25] Zou XM, Ma FL and Lu JM. The study on the relationship between the C-106T polymorphism in adose reductase gene promoter region and the susceptibility of retinopathy in type 2 diabetes mellitus. . Chin J Diabetes 2003; 11: 200-203.

[26] Yin H, Zhang YL, Q. CH, Xin Y, Fu HL, Sun B and Wang JM. Association of C(-106)T polymorphism of the aldose reductase gene with susceptibility to diabetic retinopathy. Chin J Clinicians (Electronic Edition) 2010; 4: 1881-1884.

[27] Delbaere A, Sidis Y and Schneyer AL. Differential response to exogenous and endogenous activin in a human ovarian teratocarcinoma-derived cell line (PA-1): regulation by cell surface follistatin. Endocrinology 1999; 140: 2463-2470.

[28] Zhang JL. Correlative study of diabetic retinopathy and a C(-106)T polymorphism of aldose reductase gene promoter region. Journal of Shandong Medical College 2014; 36: 276-278.

[29] Zhang YH and Xiao Q. A preliminary study of the relationship between the(C-106T)

single nucleotide polymorphism in the aldose reductase gene promoter region and tIle susceptibility of retinopathy in type 2 diabetes mellitus. J Fourth Mil Med Univ 2003; 24: 2091-2093.

[30] Wang HF and Yu Q. The correlative between diabetic retinopathy and polymorphism of aldose reductase. Chin J Pract Ophthalmol, 2004; 22: 422-424.

[31] Liang S, Guan HJ, Chen H and Hu JY. Relationship between C(-106)T Polymorphism of Aldose Reductase Promoter Region and Diabetic Retinopathy. Progress in Modern Biomedicine 2009; 9: 77-79.

[32] Yin H, Zhang YL, Xin Y, Chen HQ and Pu HL. The difference of C(-106)T polymorphism of the Aldose Reductase gene between diabetic retinopathy in Han and Hui population. China Modern Medicine 2011; 18: 30-32.

[33] Kaur N and Vanita V. Association of aldose reductase gene (AKR1B1) polymorphism with diabetic retinopathy. Diabetes Res Clin Pract 2016; 121: 41-48.

[34] Rezaee MR, Amiri AA, Hashemi-Soteh MB, Daneshvar F, Emady-Jamaly R, Jafari R, Soleimani B and Haghiaminjan H. Aldose reductase C-106T gene polymorphism in type 2 diabetics with microangiopathy in Iranian individuals. Indian J Endocrinol Metab 2015; 19: 95-99.

[35] Bastawrous A, Mathenge W, Wing K, Bastawrous M, Rono H, Weiss HA, Macleod D, Foster A, Peto T, Blows P, Burton M and Kuper H. The incidence of diabetes mellitus and diabetic retinopathy in a population-based cohort study of people age 50 years and over in Nakuru, Kenya. BMC Endocr Disord 2017; 17: 19.

[36] Tang ZH, Wang L, Zeng F and Zhang K. Human genetics of diabetic retinopathy. J Endocrinol Invest 2014; 37: 1165-1174.

Table 1. Principal characteristics of the studies included in the meta-analysis

First author	Year	Country	Ethnicity	Genotyping method	DM type	diabetic retinopathy						without diabetic retinopathy						HWE
						Sample size	CC	CT	TT	C	T	Sample size	CC	CT	TT	C	T	
Kao	1999	Australia	Caucasian	PCR	T1DM	67	39	16	12	94	40	97	35	35	27	105	89	0.007
Demaine	2000	UK	Caucasian	PCR	T1DM	105	49	53	3	151	59	36	9	22	5	40	32	0.154
Cheng	2013	China	Asian	PCR	T1DM	164	113	45	6	271	57	158	91	59	8	241	75	0.692
Richeti	2007	Brazil	Mixed	PCR-RFLP	T1DM	29	15	13	1	43	15	33	10	18	5	38	28	0.503
Yin	2010	China	Asian	PCR-RFLP	T2DM	36	16	13	7	45	27	31	20	9	2	49	13	0.490
Yin	2011	China	Asian	PCR-RFLP	T2DM	46	24	17	5	65	27	35	21	12	2	54	16	0.869
Zhang	2003	China	Asian	PCR-RFLP	T2DM	54	28	17	9	73	35	76	24	34	18	82	70	0.385
Santos	2003	Brazil	Caucasian	PCR	T2DM	99	32	46	21	110	88	110	47	39	24	133	87	0.007
Zou	2003	China	Asian	PCR-RFLP	T2DM	50	32	15	3	79	21	66	29	36	1	94	38	0.007
Liang	2009	China	Asian	PCR-RFLP	T2DM	82	42	30	10	114	50	63	41	18	4	100	26	0.311
Wang	2003	China	Asian	PCR-RFLP	T2DM	66	44	19	3	107	25	392	273	94	25	640	144	0.752
Wang	2004	China	Asian	PCR-RFLP	T2DM	100	50	33	17	133	67	78	46	27	5	119	37	0.702
Santos	2006	Brazil	African	PCR-RFLP	T2DM	100	51	36	13	138	62	55	30	18	7	78	32	0.125
Rezaee	2015	Iran	Asian	PCR-RFLP	T2DM	109	58	39	12	155	63	97	37	47	13	121	73	0.751
Zhang	2014	China	Asian	PCR-RFLP	T2DM	125	67	48	10	182	68	115	77	30	8	184	46	0.048
Ren	2014	China	Asian	PCR-RFLP	T2DM	161	86	57	18	229	93	213	85	102	26	272	154	0.586
Wang	2006	China	Asian	PCR-RFLP	T2DM	168	90	68	10	248	88	152	111	34	7	256	48	0.050
Deng	2014	China	Asian	MassARRAY	T2DM	128	92	31	5	215	41	139	90	44	5	224	54	0.895
Santos	2006	Brazil	Caucasian	PCR-RFLP	T2DM	287	103	132	52	338	236	137	52	55	30	159	115	0.040
Yang	2014	China	Asian	MassARRAY	T2DM	205	145	54	6	344	66	266	167	91	8	425	107	0.292
Kaur	2016	India	Asian	PCR	T2DM	487	210	158	119	578	396	439	188	172	79	548	330	0.001
Katakami	2011	Japan	Asian	PCR	T2DM	1505	1087	380	38	2554	456	2092	1416	596	80	3428	756	0.084

Notes: T1DM, Type 1 Diabetes Mellitus; T1DM, Type 2 Diabetes Mellitus; PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium.

Table 2. *AKR1B1* rs759853 polymorphism and the risk of diabetic retinopathy

Genetic comparison	Group/Subgroup		OR (95%CI)	*Ph*
TT vs. CC	Ethnicity	Caucasian	0.59 (0.27, 1.27)	0.018
		Asian	1.04 (0.76, 1.42)	0.024
		other	0.49 (0.07, 3.69)	0.098
	DM type	T1DM	0.33 (0.17, 0.67)	0.290
		T2DM	1.05 (0.81, 1.36)	0.051
	HWE	*P*≥0.05	0.87 (0.60, 1.25)	0.013
		P<0.05	1.04 (0.70, 1.54)	0.113
	Genotyping method	PCR	0.68 (0.39, 1.17)	0.001
		PCR+RFLP	1.08 (0.75, 1.57)	0.065
		MassARRAY	0.91 (0.40, 2.08)	0.884
		Total	0.92 (0.69, 1.21)	0.004
TT + CT vs. CC	Ethnicity	Caucasian	0.75 (0.39, 1.44)	0.002
		Asian	0.93 (0.75, 1.16)	0.000
		other	0.74 (0.27, 2.04)	0.097
	DM type	T1DM	0.49 (0.36, 0.68)	0.631
		T2DM	1.01 (0.82, 1.23)	0.000
	HWE	*P*≥0.05	0.87 (0.69, 1.11)	0.000
		P<0.05	0.95 (0.64, 1.40)	0.002
	Genotyping method	PCR	0.77 (0.58, 1.02)	0.006
		PCR+RFLP	1.02 (0.75, 1.41)	0.000
		MassARRAY	0.71 (0.52, 0.96)	0.930
		Total	0.90 (0.74, 1.09)	0.000
TT vs. CC + CT	Ethnicity	Caucasian	0.72 (0.51, 1.01)	0.209
		Asian	1.09 (0.84, 1.42)	0.111
		other	0.72 (0.31, 1.69)	0.182
	DM type	T1DM	0.48 (0.28, 0.83)	0.404
		T2DM	1.05 (0.84, 1.31)	0.157
	HWE	*P*≥0.05	0.92 (0.69, 1.23)	0.149
		P<0.05	1.03 (0.71, 1.48)	0.102
	Genotyping method	PCR	0.76 (0.47, 1.23)	0.004
		PCR+RFLP	1.05 (0.79, 1.39)	0.321
		MassARRAY	1.02 (0.45, 2.31)	0.893
		Total	0.96 (0.76, 1.21)	0.051
T vs. C	Ethnicity	Caucasian	0.76 (0.50, 1.16)	0.005
		Asian	1.00 (0.83, 1.19)	0.000
		other	0.76 (0.33, 1.71)	0.073
	DM type	T1DM	0.56 (0.44, 0.72)	0.672
		T2DM	1.03 (0.88, 1.21)	0.000
	HWE	*P*≥0.05	0.95 (0.75, 1.27)	0.006
		P<0.05	0.92 (0.76, 1.12)	0.000
	Genotyping method	PCR	0.80 (0.62, 1.03)	0.000
		PCR+RFLP	1.06 (0.84, 1.33)	0.000
		MassARRAY	0.77 (0.59, 1.01)	0.896

		Total	0.93 (0.80, 1.09)	0.000
CT vs. CC	Ethnicity	Caucasian	0.83 (0.43, 1.62)	0.006
		Asian	0.89 (0.71, 1.11)	0.000
		other	0.82 (0.35, 1.94)	0.176
	DM type	T1DM	0.52 (0.37, 0.74)	0.799
		T2DM	0.97 (0.79, 1.20)	0.000
	HWE	*P*≥0.05	0.86 (0.68, 1.08)	0.000
		P<0.05	0.93 (0.60, 1.46)	0.001
	Genotyping method	PCR	0.77 (0.59, 1.01)	0.032
		PCR+RFLP	1.00 (0.72, 1.38)	0.000
		MassARRAY	0.69 (0.50, 0.95)	0.981
		Total	0.88 (0.72, 1.07)	0.000

Notes: T1DM, Type 1 Diabetes Mellitus; T1DM, Type 2 Diabetes Mellitus; *Ph*, *P*-value of heterogeneity test.

Figure legends

Figure 1. Flow diagram of selecting studies.

Figure 2. Forest plot of diabetic retinopathy risk associated with *AKR1B1* rs759853 polymorphism under TT vs. CC model after stratified analysis by DM type. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Figure 3. Begg's funnel plot for publication bias under the model TT vs. CC + CT. Each point represents a separate study for the indicated association. Log(OR), natural logarithm of OR. Horizontal line, mean effect size.

Figure 1

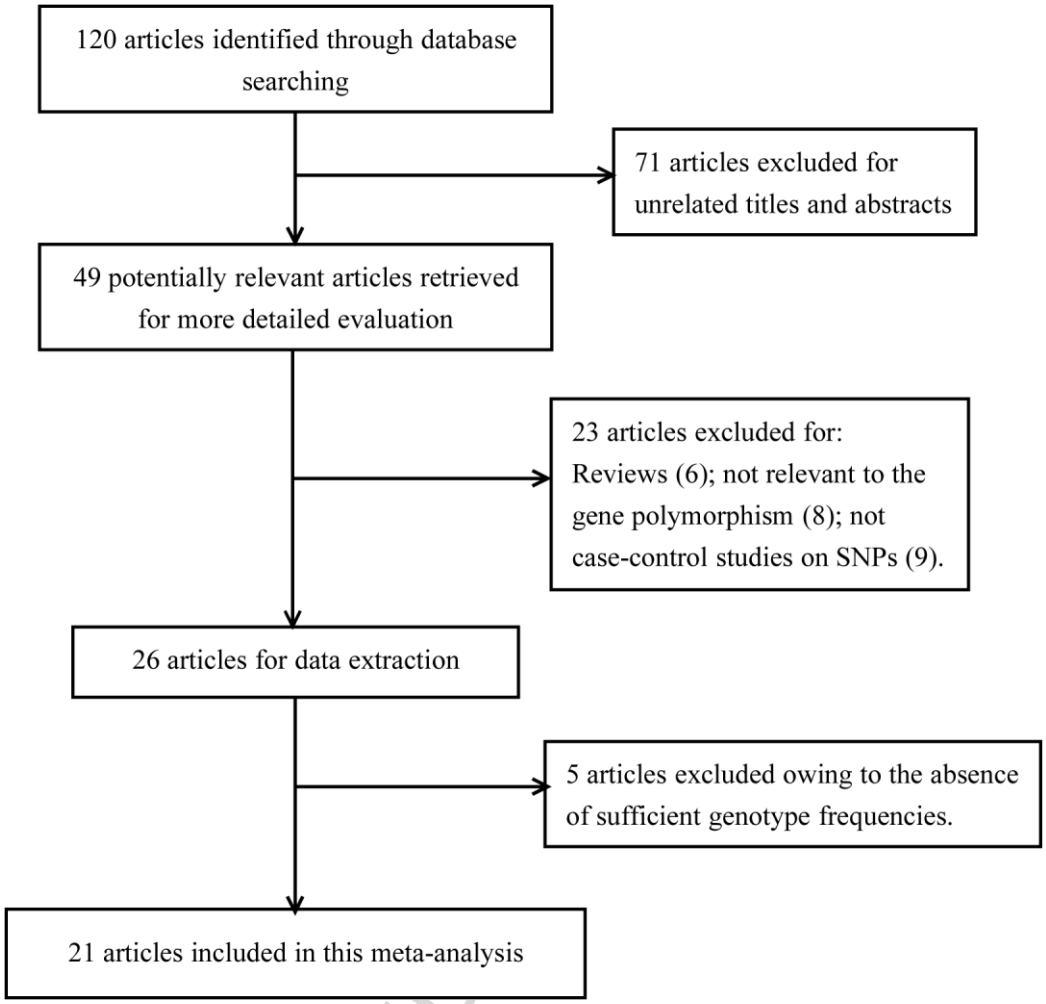


Figure 2

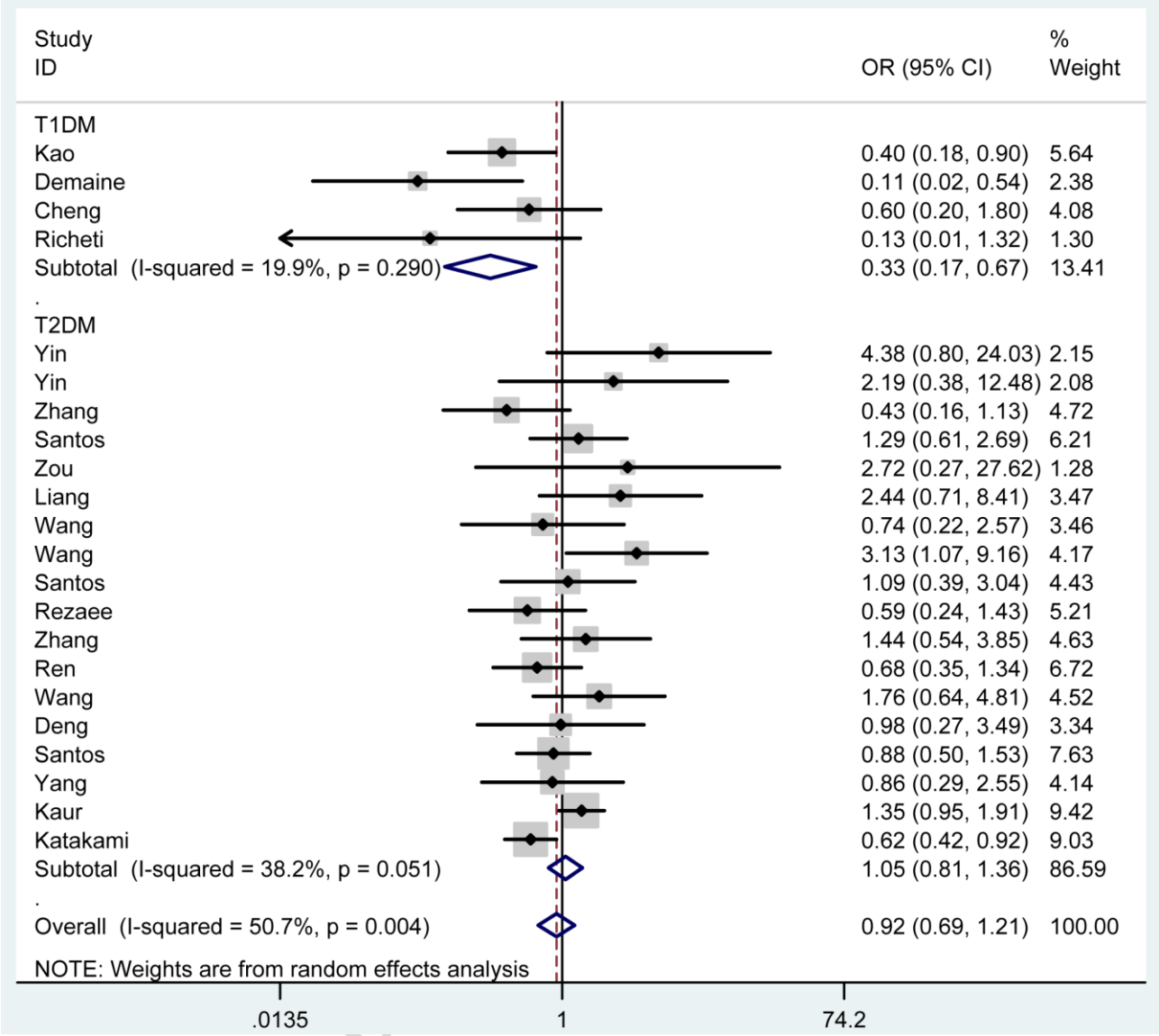
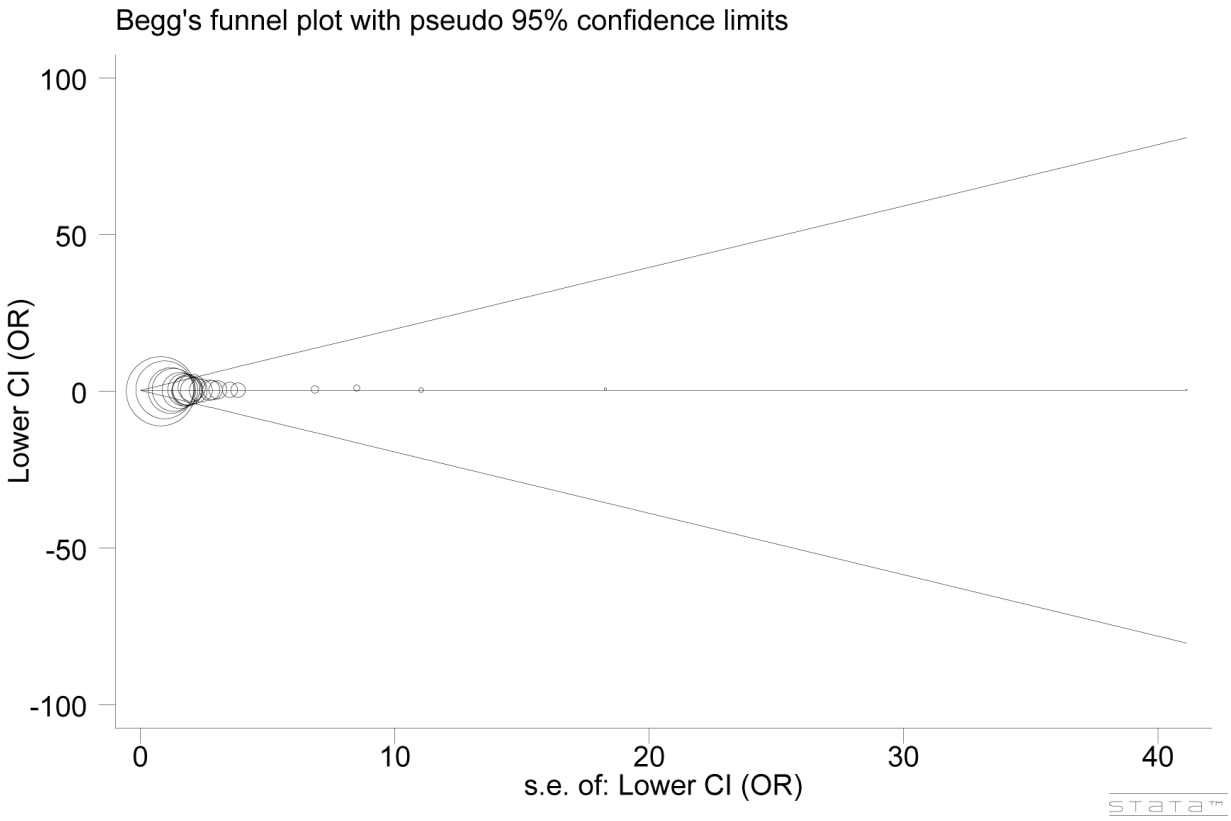


Figure 3



Highlights

1) A meta-analysis was performed to investigate the genetic association of AKR1B1 rs759853 polymorphism with diabetic retinopathy (DR) risk.

2) Rs759853 polymorphism might reduce risk of DR in patients with type 1 DM.

3) Rs759853 genotyped using MassARRAY assay was significantly correlated with decreased risk of DR under dominate model.