Original Article Association of rs7754840 G/C polymorphisms in CDKAL1 with type 2 diabetes: a meta-analysis of 70141 subjects

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Abstract: The reported association of the CDKAL1 rs7754840 G/C gene polymorphism with T2DM susceptibility remains controversial. In this study, this association was further investigated using a meta-analysis of 33,149 patients and 36,992 controls from 32 independent studies. The random-effect models were used in order to evaluate the pooled odds ratios (ORs) and their 95% confidence intervals (Cls). A significant relationship between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was observed under allelic (OR: 1.37, 95% Cl: 1.22, 1.55, P < 0.001), recessive (OR: 1.58, 95% Cl: 1.20-2.08, P < 0.001), dominant (OR: 1.13, 95% Cl: 1.21-1.33, P = 0.01), and homozygous (OR: 1.27, 95% Cl: 1.21-1.33, P < 0.001), and heterozygous (OR: 0.83, 95% Cl: 0.75-0.93, P < 0.001). Overall, the CDKAL1 rs7754840 G/C gene polymorphism was found to be significantly associated with an increased T2DM risk; the C allele of the CDKAL1 rs7754840 G/C gene polymorphism may confer susceptibility to T2DM.

Keywords: CDKAL1, polymorphism, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a complex multifactorial metabolic disease characterized by hyperglycemia, with a varying degree of insulin resistance, impaired insulin secretion and increased hepatic glucose production [1]. Using data from the International Diabetes Federation (IDF) it is speculated that the number of patients with diabetes mellitus will continually increase, reaching up to 552 million by 2030, of which 90-95% will be due to T2DM [2]. In China, it is estimated that the number of patients with diabetes will increase from 20.8 million in 2000 to 42.3 million in 2030 [3]. The large increase coincides with a higher prevalence of obesity and reduced levels of physical activity.

T2DM is the most common form of diabetes and has been shown to be caused by the interplay of multiple genes as well as environmental factors [4]. The well-established heritability of T2DM has resulted in intense efforts in determining genetic risk factors for this disease. Currently, 91 loci have been reported to be closely associated with T2DM susceptibility [5-16], however, the most commonly reported variants found within these loci account for only a small proportion of the heritability of T2DM and the functional role of the majority of these variants remains unclear. At least 16 candidate loci have been unequivocally associated with T2DM. One of the most reproducible risk genes for diabetes identified across different ethnic populations is Cyclin dependent kinase 5 (CDK). which regulates protein subunit 1 homolog 1 (CDKAL1) [17]. The CDK gene spans approximately 37 kb on chromosome 6p22.3 and encodes for 579 amino acids. CDKAL1 has been shown to have enzymatic activity and catalyzes the ms2t6A modification in tRNALys (UUU) in mammalian cells [18]. The functional loss of CDKAL1 affects the accuracy of protein translation, causing the synthesis of abnormal insulin which triggers endoplasmic reticulum stress in ß cells.

In 2007, using the results obtained from the GWA studies of the Diabetes Genetic Initiative

		Study		Source of			T2DM			Contro		-
Author	Year	design	Subgroup	controls	NOS Score	GG	GC	CC	GG	GC	CC	Case/control
Scott [20]	2007	Case-control	Caucasian	PB	7	867	1094	344	957	1078	304	2305/2339
Saxena [21]ª	2007	Case-control	Caucasian	PB	8	1237	1231	307	1616	1496	346	2775/3458
Saxena [21] ^b	2007	Case-control	Caucasian	PB	8	542	520	124	534	515	125	1186/1174
Saxena [21]°	2007	Case-control	Caucasian	PB	8	409	445	120	443	436	108	974/987
Zeggini [25]ª	2007	Case-control	Caucasian	PB	6	399	1439	1304	345	1523	1690	3142/3558
Zeggini [25] ^b	2007	Case-control	Caucasian	PB	6	118	414	368	96	426	399	900/921
Zeggini [25]°	2007	Case-control	Caucasian	PB	6	41	169	197	66	290	322	407/678
Zeggini [25] ^d	2007	Case-control	Caucasian	PB	6	87	247	179	54	205	199	513/458
Herder [26]	2008	Case-control	Caucasian	PB	5	177	200	56	746	611	126	433/1483
Horikawa [27]	2008	Case-control	Asian	HB	5	543	881	446	538	781	262	1861/1581
Lee [28]	2008	Case-control	Asian	HB	6	221	402	262	170	260	70	885/500
Lewis [29]	2008	Case-control	African	PB	6	155	499	400	161	453	319	933/1054
Liu [30]	2008	Case-control	Asian	PB	6	574	862	402	720	923	314	1838/1957
Ng [31] ^a	2008	Case-control	Asian	PB	5	498	722	261	631	703	196	1481/1530
Ng [31] ^b	2008	Case-control	Asian	PB	5	176	380	205	182	314	136	761/632
Ng [31]°	2008	Case-control	Asian	PB	5	177	398	224	429	755	332	799/1516
Sanghera [32]	2008	Case-control	Asian	PB	6	281	196	46	203	134	31	523/368
Wu [33]	2008	Case-control	Asian	PB	6	106	212	106	316	921	671	424/1908
van Hoek [34]	2008	Case-control	Caucasian	PB	6	1533	958	149	1592	960	144	2640/2696
Kirchhoff [35]	2008	Case-control	Caucasian	HB	7	13	17	6	397	370	87	36/854
Hu [36]	2009	Case-control	Asian	PB	6	358	911	580	302	864	619	1849/1785
Rong [37]	2009	Case-control	Asian	PB	7	750	495	132	959	660	116	1377/1735
Tabara [38]	2009	Case-control	Asian	PB	7	149	225	117	137	203	57	491/397
Takeuchi [39]ª	2009	Case-control	Asian	PB	6	96	180	86	181	238	78	362/497
Takeuchi [39] ^b	2009	Case-contro	Asian	PB	6	279	504	228	425	546	175	1011/1146
Ren [40]	2009	Case-control	Asian	PB	5	116	182	102	113	132	55	264/300
Chidambaram [41]	2010	Case-control	Asian	PB	8	408	279	45	420	229	25	732/674
Cruz [42]	2010	Case-control	Mexican	PB	6	243	224	52	267	230	50	519/547
Bao [43]	2012	Case-control	Asian	PB	6	239	354	167	184	194	54	761/433
Nemr [44]	2012	Case-control	Arabs	PB	7	279	247	104	421	295	76	630/792
Mansoori [45]	2015	Case-control	Arabs	PB	6	19	38	83	12	74	54	140/140
Song [46]	2015	Case-control	Asian	PB	6	15	25	11	30	18	3	51/51

Table 1. Characteristics of the included studies regarding the association of CDKAL1 rs7754840 G/C
gene polymorphism and T2DM

T2DM: type 2 diabetes mellitus; Case: the total number of T2DM cases; control size: the total number of control group; PB: population-based; HB: hospital-based; NOS: Newcastle-Ottawa quality assessment scale.

(DGI) [19], Finland-United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics (FUSION) [20], Wellcome Trust Case Control Consortium (WTCCC), and the United Kingdom Type 2 Diabetes Genetics Consortium (UKT2D) [21] the rs7754840 G/C polymorphism in the CDKAL gene was reported for the first time to be strongly associated with T2DM.

Despite the multiple published studies on the relationship between the CDKAL1 gene rs7754840 G/C polymorphism and T2DM, the results remain controversial. Replicate studies reproducibly evaluated the association in multiple European and Asian populations. In the

present study, a meta-analysis including European, Asian, African, Arab and Mexican population studies was performed in an effort to strengthen the association between T2DM and the rs7754840 SNP within the CDKAL1 gene.

Materials and methods

Publication search and inclusion criteria

A systematic search of electronic databases including Pub Med, Embase, Web of Science, China National Knowledge Infrastructure, and China Biological Medicine Database was done

Genetic model	Pooled OR (95% CI)	Z value	P value	Study number	T2DM size	Control size	P value for heterogeneity
Allelic genetic model	1.37 [1.22, 1.55]	5.24	< 0.00001	32	33149	36992	< 0.00001
Asia	1.31 [1.24, 1.39]	9.21	< 0.00001	17	15603	16872	< 0.00001
Caucasus	1.37 [1.03, 1.84]	2.14	0.03	11	15324	17060	< 0.00001
Africa	2.29 [2.03, 2.57]	13.83	< 0.00001	1	933	1581	NA
Mexico	1.07 [0.89, 1.29]	0.76	0.45	1	519	547	NA
Arabs	1.44 [1.24, 1.66]	4.91	0.76	2	770	932	0.99
Recessive genetic model	1.58 [1.20, 2.08]	3.27	< 0.00001	32	33149	36992	< 0.00001
Asia	2.18 [1.45, 3.27]	3.74	< 0.00001	17	15603	16872	< 0.00001
Caucasus	0.99 [0.66, 1.47]	0.07	0.94	11	15324	17060	< 0.00001
Africa	1.46 [1.17, 1.82]	3.30	0.001	1	933	1581	NA
Mexico	1.12 [0.74, 1.69]	0.54	0.59	1	519	547	NA
Arabs	2.08 [1.51, 2.86]	4.47	< 0.00001	2	770	932	NA
Dominant genetic model	1.13 [1.03, 1.23]	2.52	0.36	32	33149	36992	0.01
Asia	1.21 [1.04, 1.41]	2.51	0.01	17	15603	16872	< 0.00001
Caucasus	1.01 [0.90, 1.14]	0.16	0.88	11	15324	17060	< 0.00001
Africa	1.21 [0.95, 1.54]	1.55	0.12	1	933	1581	NA
Mexico	1.08 [0.85, 1.38]	0.65	0.52	1	519	547	NA
Arabs	1.00 [0.43, 2.32]	2.84	1.00	2	770	932	0.03
Homozygous genetic model	1.27 [1.21, 1.33]	3.64	0.93	32	33149	36992	< 0.00001
Asia	1.37 [1.16, 1.63]	2.84	0.004	17	15603	16872	< 0.00001
Caucasus	1.40 [1.11, 1.77]	1.85	0.06	11	15324	17060	< 0.00001
Africa	1.34 [0.98, 1.82]	1.95	0.05	1	933	1581	NA
Mexico	1.30 [1.00, 1.70]	0.61	0.54	1	519	547	NA
Arabs	1.14 [0.75, 1.75]	3.94	0.23	2	770	932	0.99
Heterozygous genetic model	0.83 [0.75, 0.93]	3.43	0.01	32	33149	36992	0.0006
Asia	0.78 [0.66, 0.90]	3.23	0.001	17	15603	16872	< 0.00001
Caucasus	1.01 [0.90, 1.13]	0.17	0.87	11	15324	17060	0.007
Africa	0.88 [0.72, 1.07]	1.31	0.19	1	933	1581	NA
Mexico	0.94 [0.61, 1.44]	0.30	0.76	1	519	547	NA
Arabs	0.47 [0.26, 0.84]	4.65	0.01	2	770	932	0.06

Table 2. Summary of the meta-analysis of the association of the CDKAL1 gene rs7754840 G>C polymorphism and type 2 diabetes mellitus

T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval; T2DM size: the total number of T2DM cases; control size: the total number of the control group; Allelic genetic model: C allele distribution frequency; recessive genetic model: CC versus GC + GG; Dominant genetic model: GG versus GC + CC; Homozygous genetic model: CC versus GG. Heterozygous genetic mode: GC versus AA.

in order to find potential studies. The following terms were used: 'CDKAL1', 'rs7754840', 'T2DM' and 'polymorphism', with the date of publication ranging from 2007 to March 18, 2015.

Potential studies were only included if they met the following criteria: (1) They included an evaluation of the CDKAL1 rs7754840 G/C gene polymorphism and T2DM; (2) The studies should be case-control or cohort studies published in official journals; (3) A diagnosis of T2DM was made using the World Health Organization and American Diabetes Association fasting plasma criteria, which requires that the fasting plasma glucose levels of patients to be no less than 7.0 mmol/l, or that the 2 hrs plasma glucose level be no less than 11.1 mmol/l; and (4) The studies should be consistent with the HWE.

Data extraction

The data were extracted following a standard protocol. The meta-analysis was done by two

	Case g	roup	Control	aroup		Risk Difference	Risk Difference
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 Asia							
Bao 2012	688	1520	302	864	3.1%	0.10 [0.06, 0.14]	
Chidambaram 2010	369	1464	279	1348	3.2%	0.05 [0.01, 0.08]	
Horikawa 2008	1773	3722	1305	3162	3.3%	0.06 [0.04, 0.09]	-
Hu 2009	1627	3698	1467	3570	3.3%	0.03 [0.01, 0.05]	
Lee 2008	921	1770	400	1000	3.2%	0.12 [0.08, 0.16]	
Liu 2008	1666	3676	1551	3914	3.3%	0.06 [0.03, 0.08]	-
Ng 2008 a	1244	2962	1095	3060	3.3%	0.06 [0.04, 0.09]	
Ng 2008 b	790	1522	586	1264	3.2%	0.06 [0.02, 0.09]	
Ng 2008 c	846	1598	1419	3032	3.2%	0.06 [0.03, 0.09]	
Ren 2010	381	800	242	600	3.0%	0.07 [0.02, 0.13]	
Rong 2009	759	2754	892	3470	3.3%	0.02 [-0.00, 0.04]	
Sanghera 2008	288	1041	196	736	3.1%	0.01 [-0.03, 0.05]	
Song 2015	47	102	24	102	2.0%	0.23 [0.10, 0.35]	
Tabara 2009	459	982	317	794	3.1%	0.07 [0.02, 0.11]	
Takeuchi 2009 a	352	724	394	994	3.1%	0.09 [0.04, 0.14]	
Takeuchi 2009 b	960	2022	788	2018	3.2%	0.08 [0.05, 0.11]	
Wu 2008	425	848	1553	3816	3.2%	0.09 [0.06, 0.13]	
Subtotal (95% CI)		31205		33744	53.1%	0.06 [0.05, 0.08]	•
Total events	13595		12810			2000	
Heterogeneity: Tau ² =				P < 0.00	001); I ^a =	71%	
Test for overall effect:	Z = 8.51 (F	< 0.00	001)				
1.1.2 Caucasus							
1.1.2 Caucasus Herder 2008	312	866	863	2966	3.2%	0.07 10.02 0.111	
Herder 2008 Kirchhoff 2008	312	866	544	1708	2.2%	0.07 [0.03, 0.11] 0.08 [-0.03, 0.20]	
Saxena 2007 a	1845	5550	2188	6916	3.3%		
Saxena 2007 a Saxena 2007 b	768	2372	2188	2348	3.3%	0.02 [-0.00, 0.03]	
Saxena 2007 b Saxena 2007 c	685	1948	625	1974	3.2%	-0.00 [-0.03, 0.02]	
Saxena 2007 c Scott 2007	1782	4610	1686	4678	3.2%	0.04 [0.01, 0.06] 0.03 [0.01, 0.05]	
Van Hoek 2008	1256	5280	1248	5392	3.3%		
	4074	6311	1248	1974	3.3%	0.01 [-0.01, 0.02]	_
Zeggini 2007 a Zeggini 2007 b	1150	1800	1224	1842	3.2%	0.32 [0.29, 0.34] -0.03 [-0.06, 0.01]	
Zeggini 2007 b Zeggini 2007 c	563	814	934	1356	3.1%	0.00 [-0.04, 0.04]	
Zeggini 2007 d	605	1026	863	2966	3.2%	0.30 [0.26, 0.33]	
Subtotal (95% CI)	000	30649	003	34120	34.6%	0.07 [0.01, 0.14]	
Total events	13069	50045	11592	54120	54.070	0.07 [0.01, 0.14]	
Heterogeneity: Tau ² =		- 789 2		/P = 0.0	00011-12-	0.0%	
Test for overall effect: 2				(0.0	0001),1 -		
		,					
1.1.3 Africa							
Lewis 2008	1150	1866	1305	3162	3.2%	0.20 [0.18, 0.23]	-
Subtotal (95% CI)		1866		3162	3.2%	0.20 [0.18, 0.23]	•
Total events	1150		1305				
Heterogeneity: Not ap							
Test for overall effect:	Z = 14.27	(P < 0.0)	0001)				
1.1.4 Mexico							
Cruz 2012	328	1038	329	1094	3.2%	0.02 [-0.02, 0.05]	
Subtotal (95% CI)	320	1038	328	1094	3.2%	0.02 [-0.02, 0.05]	•
Total events	328	1050	329	1034	5.2.70	0.02 [-0.02, 0.05]	T I I I I I I I I I I I I I I I I I I I
Heterogeneity: Not ap			020				
Test for overall effect: 2		e = 0.45					
		5.40,					
1.1.5 Arabs							
Mansoori 2015	204	280	182	280	2.7%	0.08 [0.00, 0.15]	
Nemr 2012	455	1260	447	1584	3.2%	0.08 [0.04, 0.11]	
Subtotal (95% CI)		1540		1864	5.9%	0.08 [0.05, 0.11]	•
Total events	659		629				
Heterogeneity: Tau ² =				= 0.99); P	*= 0%		
Test for overall effect:	Z = 4.91 (F	< 0.00	001)				
T-1-LOFACOD				70004	100.00	0.0010.05.0.103	
Total (95% CI)		66298		73984	100.0%	0.08 [0.05, 0.10]	-
Total events	28801		26665				
Heterogeneity: Tau ² =				(P < 0.0	0001); P=	87%	-0.2 -0.1 0 0.1 0.2
Test for overall effect:				0 - 0 -	00041	- 05 5%	Favours (experimental) Favours (control)
Test for subgroup diffe	mences: C	-nr= 88	.04. ar = 4	• (P < 0.0	10001). P	- 80.0%	

Figure 1. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under the allelic genetic model (distribution of C allelic frequency of CDKAL1 rs7754840 gene).

researchers, two of which independently searched for studies, while the third served as the arbitrator in case disagreements that occurred between the two researchers. The current meta-analysis did not accept studies that were not in accordance with the inclusion criteria, published repeatedly, or supplied insufficient data. If similar data were used in different studies, the data were only included once in this analysis. The following information was collected from each study: the first author's name, publication year, region, number of genotypes, genotyping, study design and the total number of T2DM and control groups.

Statistical analyses

In the present meta-analysis, four genetic models, including the allelic (G allele distribution frequency), recessive (CC vs. GG + GC), dominant (GG + GC vs. CC), homozygous (CC vs. GG), and the heterozygous (GC vs. GG) genetic models were used. The association of the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was compared using the odd ratio (ORs) and their corresponding 95% confidence intervals (CIs). The heterogeneity between the individual studies was calculated using Chi-square-based Q-tests and the significance level was set at P < 0.05 level [22]. If heterogeneity existed, the random-effect model (DerSimonian and Laird method) [23] would be used in order to pooled the OR among the studies. Otherwise, the fixedeffect model was adopted (the Mantel-Haenszel method) [24]. A Z-test was used to determine the pooled OR, with the significance set at P < 0.05 level.

HWE was evaluated using Fisher's exact test with the significance set at P < 0.05 level. Potential publication bias was estimated using a funnel plot. A sensitivity analysis was per-

	Cas	-	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.1 Asia							
Bao 2012	167	593	54	378	3.3%	2.35 [1.68, 3.30]	
Chidambaram 2010	45	687	25	649	3.1%	1.75 [1.06, 2.89]	
Horikawa 2008	446	1327	262	1042	3.4%	1.51 [1.26, 1.81]	
Hu 2009	580	1269	619	1166	3.4%	0.74 [0.63, 0.87]	
Lee 2008	262	623	70	430	3.3%	3.73 [2.76, 5.05]	
Liu 2008	402	1436	314	1643	3.4%	1.65 [1.39, 1.95]	
Ng 2008 a	261	1220 556	196 136	1334 523	3.4%	1.58 [1.29, 1.94]	
Ng 2008 b Ng 2008 c	205 224	575	332	1184	3.4% 3.4%	1.66 [1.28, 2.16] 1.64 [1.33, 2.02]	
Ren 2010	102	298	55	245	3.2%	1.80 [1.22, 2.64]	
Rong 2009	132	1245	116	1619	3.4%	1.54 [1.18, 2.00]	
Sanghera 2008	46	477	31	337	3.1%	1.05 [0.65, 1.70]	
Song 2015	11	40	3	48	1.9%	5.69 [1.46, 22.15]	
Tabara 2009	117	374	57	340	3.3%	2.26 [1.58, 3.24]	
Takeuchi 2009 a	86	276	78	419	3.3%	1.98 [1.39, 2.82]	
Takeuchi 2009 b	228	783	14	11132		326.24 [188.91, 563.40]	•
Wu 2008	101	318	671	1237	3.4%	0.39 (0.30, 0.51)	-
Subtotal (95% CI)		12097		23726	54.6%	2.18 [1.45, 3.27]	-
Total events	3415		3033				
Heterogeneity: Tau ² =				(P < 0.0	0001); I ² =	97%	
Test for overall effect: 2	Z = 3.74 (P	= 0.000	(2)				
2.1.2 Caucasus							
Herder 2008	56	377	126	1357	3.3%	1.70 [1.22, 2.39]	
Kirchhoff 2008	6	30	87	767	2.5%	1.95 (0.78, 4.91)	
Saxena 2007 a	307	2468	346	3112	3.4%	1.14 [0.96, 1.34]	+
Saxena 2007 b	124	1062	125	1049	3.3%	0.98 [0.75, 1.27]	-
Saxena 2007 c	120	854	108	879	3.3%	1.17 [0.88, 1.54]	+
Scott 2007	344	1961	304	2035	3.4%	1.21 [1.02, 1.43]	-
Van Hoek 2008	149	2491	144	2552	3.4%	1.06 [0.84, 1.35]	
Zeggini 2007 a	1304	1838	1690	1868	3.4%	0.26 [0.21, 0.31]	
Zeggini 2007 b	388	532	339	522	3.4%	1.45 [1.12, 1.89]	
Zeggini 2007 c	197	210	322	356	2.9%	1.60 (0.82, 3.11)	
Zeggini 2007 d	179	334 12157	199	259	3.3%	0.35 [0.24, 0.50]	
Subtotal (95% CI) Total events	3174	12157	3790	14756	35.5%	0.99 [0.66, 1.47]	
Heterogeneity: Tau ² = 1		- 262 2		/P ≈ 0 0	00011-12-	96%	
Test for overall effect: 2				(1 - 0.0		30 %	
	.	,					
2.1.3 Africa							
Lewis 2008	400	654	319	614	3.4%	1.46 [1.17, 1.82]	
Subtotal (95% CI)		654		614	3.4%	1.46 [1.17, 1.82]	
Total events	400		319				
Heterogeneity: Not app Test for overall effect: 2	olicable Z = 2 20 /P	- 0.004	0				
lest for overall effect: 2	2 = 3.30 (P	= 0.001	0)				
2.1.4 Mexico							
Cruz 2012	52	467	50	497	3.2%	1.12 [0.74, 1.69]	_ <u>+</u>
Subtotal (95% CI)		467		497	3.2%	1.12 [0.74, 1.69]	*
Total events	52		50				
Heterogeneity: Not app							
Test for overall effect: 2	Z = 0.54 (P	= 0.59)					
2.1.5 Arabs							
Mansoori 2015	83	57	54	86		Not estimable	
Nemr 2012	104	526	76	716	3.3%	2.08 [1.51, 2.86]	
Subtotal (95% CI)		583	. •	802	3.3%	2.08 [1.51, 2.86]	◆
Total events	187		130				
Heterogeneity: Not app							
Test for overall effect: 2	Z=4.47 (P	< 0.000	01)				
Tetal (05% CD		25050		40205	100.0%	1 59 14 20 2 602	
Total (95% CI)	7000	25958	2000	40395	100.0%	1.58 [1.20, 2.08]	-
Total events	7228	- 000 4	7322	(B = C C	00043	0.7%	
Heterogeneity: Tau ² = 1 Test for overall effect: 2				(r ² < 0.0	0001); 1*=	87.70	0.05 0.2 1 5 20
Test for subgroup diffe				1(P = 0)	$(10), I^2 = 7$	0.1%	Favours (experimental) Favours (control)
. control oungroup une				– 0.			

Figure 2. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a recessive genetic model (CC vs. GC + GG).

formed to identify potential outliers. The statistical analyses were performed with Review Manager 5.3 software.

Results

Studies and populations

Three hundred eighty four studies were identified in the literature search. Twenty nine publications were obtained though the retrieval process and among these, twenty four papers that included thirty two studies met the inclusion criteria. Typically, one paper included one study, however, a few publications included multiple studies; such as the paper published by Zegginia et al, which included 4 individual studies. Among the five papers that were excluded, one paper had been published repeatedly, two papers were unrelated to the CDKAL1 gene rs7754840 G/C polymorphism or T2DM, and two papers were excluded for deviating from Hardy-Weinberg equilibrium (HWE). All information was extracted from 33,149 T2DM cases and 36,992 controls (**Table 1**) [21, 22, 25-46]. These populations included Asians, Caucasians, Africans, Mexicans and Arabs. The Caucasian subgroup is comprised of 11 studies, the Asian subgroup is comprised of 17 studies, both the African and the Mexican subgroups are comprised of only 1 study, and the Arab subgroup is comprised of 2 studies.

Pooled analyses

In the whole population, a significant relationship between the CDKAL1 rs7754840 G/C

CDKAL1 polymorphisms and type 2 diabetes

	Case		Cont			Odds Ratio	Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
.1.1 Asia							
ao 2012	521	760	248	432	3.2%	1.62 [1.27, 2.07]	
hidambaram 2010	324	732	254	674	3.4%	1.31 (1.06, 1.63)	
lorikawa 2008	1424	1870	1319	1581	3.6%	0.63 [0.54, 0.75]	
lu 2009	1491	1849	1483	1785	3.6%	0.85 [0.72, 1.00]	
ee 2008	664	885	330	500	3.2%	1.55 [1.22, 1.97]	
iu 2008	1264	1838	1237	1957	3.8%	1.28 [1.12, 1.47]	T
lg 2008 a	983	1481	899	1530	3.7%	1.39 (1.19, 1.61)	
lg 2008 b	585	761	450	632	3.2%	1.34 [1.06, 1.71]	
lg 2008 c	622	799	1087	1516	3.4%	1.39 [1.13, 1.70]	-
ten 2010	284	400	187	300	2.8%	1.48 [1.08, 2.03]	
ong 2009	627	1377	776	1735	3.7%	1.03 (0.90, 1.19)	Т
anghera 2008	242	523	165	368	3.1%	1.06 (0.81, 1.39)	T
ong 2015	36	51	22	51	1.0%	3.16 [1.40, 7.17]	
abara 2009	342	491	260	397	3.0%	1.21 [0.91, 1.60]	
akeuchi 2009 a	266	362	316	497	2.9%	1.59 [1.18, 2.13]	
akeuchi 2009 b	732	1011	721	1146	3.5%	1.55 [1.29, 1.86]	-
/u 2008	318	424	1592	1908	3.2%	0.60 [0.46, 0.77]	
ubtotal (95% CI)		15614		17009	54.2%	1.21 [1.04, 1.41]	•
otal events	10725		11346				
eterogeneity: Tau ^a = 0				(P < 0.0	10001); P	= 89%	
est for overall effect: Z	(= 2.51 (P	= 0.01)					
.1.2 Caucasus							
lerder 2008	256	433	737	1483	3.4%	1.46 [1.18, 1.82]	
irchhoff 2008	23	36	457	854	1.2%	1.54 [0.77, 3.07]	
axena 2007 a	782	900	825	921	2.9%	0.77 [0.58, 1.03]	
axena 2007 b	366	407	612	678	2.3%	0.96 [0.64, 1.45]	
axena 2007 c	426	513	404	458	2.5%	0.65 [0.45, 0.94]	
cott 2007	2743	3142	3213	3558	3.7%	0.74 [0.63, 0.86]	-
an Hoek 2008	1107	2640	1104	2696	3.9%	1.04 [0.93, 1.16]	Ť
eggini 2007 a	1438	2305	1382	2339	3.9%	1.15 (1.02, 1.29)	-
eggini 2007 b	1538	2775	1842	3458	3.9%	1.09 [0.99, 1.21]	T T
eggini 2007 c	644	1186	640	1174	3.7%	0.99 [0.84, 1.17]	+
eggini 2007 d	565	974	544	987	3.6%	1.12 [0.94, 1.35]	<u>+</u>
ubtotal (95% CI)		15311		18606	34.9%	1.01 [0.90, 1.14]	•
otal events	9888		11760				
leterogeneity: Tau* = 0			df = 10 (P ≺ 0.00	001); I [×] =	78%	
est for overall effect: Z	= 0.16 (P	= 0.88)					
.1.3 Africa							
ewis 2008	899	1054	772	933	3.2%	1.21 [0.95, 1.54]	
ubtotal (95% CI)		1054		933	3.2%	1.21 [0.95, 1.54]	-
otal events	899		772				
leterogeneity: Not app							
est for overall effect: Z	(= 1.55 (P	= 0.12)					
.1.4 Mexico							
ruz 2012	276	519	280	547	3.2%	1.08 [0.85, 1.38]	T
		519	1001010	547	3.2%	1.08 [0.85, 1.38]	T
ubtotal (95% CI)	12.2272		280				
otal events	276						
ubtotal (95% CI) otal events leterogeneity: Not app	licable						
ubtotal (95% CI) otal events eterogeneity: Not app	licable	= 0.52)					
ubtotal (95% CI) otal events eterogeneity: Not app est for overall effect: Z	licable	= 0.52)					
ubtotal (95% Cl) otal events eterogeneity: Not app est for overall effect: Z 1.5 Arabs	licable = 0.65 (P					0.00/0.00 + 000	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015	licable = 0.65 (P	140	128	140	1.1%	0.60 (0.28, 1.28)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012	licable = 0.65 (P	140 630		792	3.4%	1.43 (1.16, 1.76)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI)	licable := 0.65 (P 121 351	140	128 371				
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI) otal events	licable = 0.65 (P 121 351 472	140 630 770	128 371 499	792 932	3.4% 4.5%	1.43 (1.16, 1.76)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI) otal events leterogeneity: Tau ^a = C	121 351 472 0.30; Chi ^a ;	140 630 770 = 4.65, 6	128 371 499 df=1 (P:	792 932	3.4% 4.5%	1.43 (1.16, 1.76)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI) otal events	121 351 472 0.30; Chi ^a ;	140 630 770 = 4.65, 6	128 371 499 df=1 (P:	792 932	3.4% 4.5%	1.43 (1.16, 1.76)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z 1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI) otal events leterogeneity: Tau ² = C est for overall effect: Z	121 351 472 0.30; Chi ^a ;	140 630 770 = 4.65, 6 = 1.00)	128 371 499 df=1 (P:	792 932 = 0.03); I	3.4% 4.5% = 78%	1.43 (1.16, 1.76) 1.00 [0.43, 2.32]	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lanscori 2015 lemr 2012 ubtotal (95% CI) otal events leterogeneity: Tau ^a = C est for overall effect: Z otal (95% CI)	121 351 472 30,30; Chi ^a 2 0.00 (P	140 630 770 = 4.65, 6	128 371 499 df = 1 (P :	792 932 = 0.03); I	3.4% 4.5%	1.43 (1.16, 1.76)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lansoori 2015 lemr 2012 ubtotal (95% CI) otal events est for overall effect: Z otal (95% CI) otal events	121 351 472 .30; Chi ^a 22260	140 630 770 = 4.65, 0 = 1.00) 33268	128 371 499 df = 1 (P = 24657	792 932 = 0.03); 38027	3.4% 4.5% = 78% 100.0%	1.43 (1.16, 1.76) 1.00 (0.43, 2.32) 1.13 (1.03, 1.23)	
ubtotal (95% CI) otal events leterogeneity: Not app est for overall effect: Z .1.5 Arabs lanscori 2015 lemr 2012 ubtotal (95% CI) otal events leterogeneity: Tau ^a = C est for overall effect: Z otal (95% CI)	11111111111111111111111111111111111111	140 630 770 = 4.65, 1 = 1.00) 33268 = 204.4	128 371 499 df = 1 (P 24657 8, df = 31	792 932 = 0.03); 38027	3.4% 4.5% = 78% 100.0%	1.43 (1.16, 1.76) 1.00 (0.43, 2.32) 1.13 (1.03, 1.23)	

Figure 3. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a dominant genetic model (GC + CC vs. GG).

gene polymorphism and T2DM was observed under the allelic (OR: 1.37, 95% CI: 1.22-1.55, P < 0.001), recessive (OR: 1.58, 95% CI: 1.20-2.08, P < 0.001), dominant (OR: 1.13, 95% CI: 1.21-1.33, P = 0.01), homozygous (OR: 1.27, 95% CI: 1.21-1.33, P < 0.001), or the heterozygous genetic model (OR: 0.83, 95% CI: 0.75-0.93, P < 0.001). In the subgroup analysis, a significant association was found in the Asian population under the allelic (OR: 1.31, 95% CI: 1.24-1.39, P < 0.001), recessive (OR: 2.18, 95% CI: 1.45-3.27, P < 0.001), dominant (OR: 1.21, 95% CI: 1.04-1.41, P = 0.01), homozygous (OR: 1.37, 95% CI: 1.16-1.63, P = 0.004) or the heterozygous genetic model (OR: 0.78, 95% CI: 0.66-0.90, P < 0.001) (Table 2; Figures 1-5).

In the subgroup analysis, there was a significant association between them in Caucasian population under allelic under allelic (OR: 1.37, 95% Cl: 1.03-1.84, P = 0.03). No significant association was found under recessive (OR: 0.99, 95% Cl: 0.66-1.47, P = 0.94), dominant

			-				
Cturks or Cultureum	Case		Cont		Mainht	Odds Ratio	Odds Ratio
Study or Subgroup 4.1.1 Asia	Events	Total	Events	Total	vveight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Bao 2012	167	406	54	238	3.3%	2.38 [1.66, 3.42]	
Chidambaram 2010	45	400	25	427	2.9%	1.77 [1.07, 2.95]	
Horikawa 2008	446	989	262	800	3.7%	1.69 (1.39, 2.05)	-
Hu 2009	580	938	619	921	3.7%	0.79 [0.65, 0.96]	-
Lee 2008	26	247	70	240	2.9%	0.29 [0.17, 0.47]	
Liu 2008	402	976	314	1034	3.7%	1.61 [1.34, 1.93]	-
Ng 2008 a	261	759	196	827	3.6%	1.69 [1.35, 2.10]	
Ng 2008 b	205	381	136	318	3.6%	1.56 (1.15, 2.10)	
Ng 2008 c	224	401	332	761	3.6%	1.64 [1.28, 2.09]	
Ren 2010	102	218	55	168	3.2%	1.81 [1.19, 2.74]	
Rong 2009	132	882	116	1075	3.5%	1.46 [1.11, 1.90]	
Sanghera 2008	46	327	31	234	2.9%	1.07 [0.66, 1.75]	
Song 2015	11	26	3	32	1.1%	7.09 [1.71, 29.35]	
Tabara 2009	117	266	57	194	3.2%	1.89 [1.27, 2.79]	
Takeuchi 2009 a	86	182	78	259	3.2%	2.08 [1.40, 3.08]	
Takeuchi 2009 b	228	507	175	600	3.6%	1.98 [1.55, 2.54]	
Wu 2008	106	212	671	987	3.5%	0.47 (0.35, 0.64)	<u> </u>
Subtotal (95% CI)		8170		9115	55.2%	1.40 [1.11, 1.77]	•
Total events	3184		3194				
Heterogeneity: Tau ^a = 0				P < 0.0	00001); I [»] =	90%	
Test for overall effect: Z	= 2.84 (P	= 0.004))				
4.1.2 Caucasus							
Herder 2008	56	233	126	872	3.3%	1.87 [1.31, 2.67]	
Kirchhoff 2008	6	19	87	484	1.7%	2.11 [0.78, 5.70]	
Saxena 2007 a Saxena 2007 b	307	1544	346	1962 659	3.7%	1.16 [0.98, 1.37]	
Saxena 2007 c	124	529	108	551	3.5%	9.82 [5.68, 16.99]	
Scott 2007	344	1211	304	1261	3.7%	1.20 [0.90, 1.61] 1.25 [1.04, 1.49]	
Van Hoek 2008	149	1682	144	1736	3.6%	1.07 (0.85, 1.37)	
Zeggini 2007 a	1304	1703	1690	2035	3.8%	0.67 [0.57, 0.78]	-
Zeggini 2007 b	368	486	399	495	3.5%	0.75 [0.55, 1.02]	
Zeggini 2007 c	197	238	322	388	3.1%	0.98 [0.64, 1.51]	
Zeggini 2007 d	0	200	õ	0	0.1 %	Not estimable	
Subtotal (95% CI)	•	8311	•	10443	32.7%	1.34 [0.98, 1.82]	•
Total events	2975		3541				
Heterogeneity: Tau ^a = 0		= 117.59		(P < 0.00	0001); I ^a = 9	92%	
Test for overall effect: Z				•			
4.1.3 Africa							
Lewis 2008	400	555	319	480	3.6%	1.30 [1.00, 1.70]	
Subtotal (95% CI)		555		480	3.6%	1.30 [1.00, 1.70]	•
Total events	400		319				
Heterogeneity: Not app							
Test for overall effect: Z	:= 1.95 (P	= 0.05)					
4.1.4 Mexico							
Cruz 2012	52	295	50	317	3.1%	1.14 [0.75, 1.75]	
Subtotal (95% CI)		295		317	3.1%	1.14 [0.75, 1.75]	
Total events	52		50				
Heterogeneity: Not app Test for overall effect: Z		- 0.64					
rest for overall effect. 2	. = 0.61 (P	= 0.54)					
4.1.5 Arabs							
Mansoori 2015	83	102	54	66	2.1%	0.97 [0.44, 2.16]	
Nemr 2012	104	383	76	497	3.4%	2.06 [1.48, 2.88]	
Subtotal (95% CI)	104	485	.0	563	5.5%	1.55 [0.76, 3.18]	
Total events	187		130	000	0.0.0		
Heterogeneity: Tau ² = 0		= 2.92 d		= 0.09)	= 66%		
Test for overall effect: Z				0.00),	0010		
		0.20/					
Total (95% CI)		17816		20918	100.0%	1.37 [1.16, 1.63]	◆
Total events	6798		7234				
Heterogeneity: Tau ^a = 0				(P < 0.0	00001); I ^a =	:91%	0.02 0.1 1 10 50
Test for overall effect: Z	= 3.64 (P	= 0.000	3)				Favours [experimental] Favours [control]
Test for subgroup diffe	rences: C	hi [≇] = 0.88	 df = 4 	(P = 0.9)	3). I≊ = 0%		Favours (experimental) Favours (control)
				1000 C			

Figure 4. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a Homozygous genetic model (CC vs. GG).

(OR: 1.01, 95% CI: 0.90-1.14, P = 0.88), homozygous (OR: 1.40, 95% CI: 1.11-1.77, P = 0.06), or the heterozygous genetic model (OR: 1.01, 95% CI: 0.90-1.13, P = 0.87). In the African subgroup, a significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was identified under the allelic (OR: 2.29, 95% CI: 2.03-2.57, P < 0.001), recessive (OR: 1.46, 95% CI: 1.17-1.82, P < 0.001). No significant association was found under dominant (OR: 1.21, 95% CI: 0.95-1.54, P = 0.12), homozygous (OR: 1.30, 95% CI: 1.00-1.70, P = 0.05), or the heterozygous genetic model (OR: 0.88, 95% CI: 0.72-1.07, P = 0.19). In the Mexican subgroup. No significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM in the Mexican subgroup was identified under the allelic (OR: 1.07, 95% CI: 0.89-1.29, P = 0.45), recessive (OR: 1.12, 95% CI: 0.74-1.69, P = 0.59), dominant (OR: 1.08, 95% CI: 0.85-1.38, P = 0.52), homozygous (OR: 1.14, 95% CI: 0.75-1.75, P = 0.54), or the heterozygous genetic model (OR: 0.94, 95% CI: 0.61-1.44, P = 0.76). In the Arab subgroup, there was a significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was identified under the allelic (OR: 1.44, 95% CI: 1.24-1.66, P < 0.001), dominant (OR: 1.34, 95% CI: 1.09-1.64, P = 0.005), recessive (OR: 2.08, 95% CI: 1.51-2.86, P < 0.001), homozygous (OR: 1.84, 95% CI: 1.36-2.50, P < 0.001), and the heterozygous genetic model (OR: 0.51, 95% CI: 0.38-0.68, P < 0.001).

Significant heterogeneity was observed in every subgroup for each genetic model (P < 0.05). In order to identify the source of this observed

CDKAL1 polymorphisms and type 2 diabetes

	Case		Cont	ol		Odds Ratio	Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
.1.1 Asia							
3ao 2012	354	521	194	248	3.0%	0.59 [0.41, 0.84]	
hidambaram 2010	279	324	229	254	2.1%	0.68 [0.40, 1.14]	
lorikawa 2008	881	1424	781	1319	4.2%	1.12 (0.96, 1.30)	+
lu 2009	911	1491	864	1483	4.2%	1.13 [0.97, 1.30]	-
ee 2008	402	664	260	330	3.3%	0.41 [0.30, 0.56]	<u> </u>
lu 2008	862	1264	923	1237	4.1%	0.73 [0.61, 0.87]	-
lg 2008 a	722	983	703	899	3.8%	0.77 [0.62, 0.95]	-
g 2008 b	380	585	314	450	3.5%	0.80 [0.62, 1.04]	
g 2008 c	398	622	755	1087	3.9%	0.78 [0.63, 0.96]	-
en 2010	182	284	132	187	2.7%	0.74 [0.50, 1.11]	
ong 2009	495	627	660	776	3.5%	0.66 [0.50, 0.87]	
anghera 2008	196	242	134	165	2.2%	0.99 [0.59, 1.63]	
abara 2009	225	342	203	260	2.9%	0.54 [0.37, 0.78]	
abara 2009 akeuchi 2009 a	180	266	203	316	2.9%		
					3.7%	0.69 [0.48, 0.99]	-
akeuchi 2009 b	504	732	546	721		0.71 [0.56, 0.89]	
/u 2008	212	318	921	1592	3.6%	1.46 [1.13, 1.88]	•
ubtotal (95% CI)		10689		11324	53.7%	0.78 [0.66, 0.90]	•
otal events	7183		7857				
eterogeneity: Tau ⁼ = 0 est for overall effect: Z				P ≺ 0.00	001); ==	83%	
.1.2 Caucasus				-			
lerder 2008	200	256	611	737	3.0%	0.74 [0.52, 1.05]	
irchhoff 2008	17	23	370	457	0.9%	0.67 [0.26, 1.74]	
axena 2007 a	414	782	426	825	3.9%	1.05 [0.87, 1.28]	Т
axena 2007 b	169	366	290	612	3.6%	0.95 [0.73, 1.23]	
axena 2007 c	247	426	205	404	3.5%	1.34 [1.02, 1.76]	
cott 2007	1439	2743	1523	3213	4.4%	1.22 [1.11, 1.36]	-
an Hoek 2008	958	1107	960	1104	3.6%	0.96 [0.75, 1.23]	-
eggini 2007 a	1094	1438	1078	1382	4.1%	0.90 [0.75, 1.07]	-
eggini 2007 b	1231	1538	1496	1842	4.1%	0.93 [0.78, 1.10]	-
eggini 2007 c	520	644	515	640	3.5%	1.02 [0.77, 1.34]	+
eggini 2007 d	0	0	0	0		Not estimable	
ubtotal (95% CI)		9323		11216	34.5%	1.01 [0.90, 1.13]	•
otal events	6289		7474				
leterogeneity: Tau ⁼ = 0 est for overall effect: Z				= 0.007); I≖ = 609	, o	
.1.3 Africa							
ewis 2008	499	899	453	772	3.9%	0.88 [0.72, 1.07]	-
ubtotal (95% CI)		899		772	3.9%	0.88 [0.72, 1.07]	•
otal events	499		453				
eterogeneity: Not appl							
est for overall effect: Z		= 0.19)					
1.4 Mexico							
	224	276	230	280	2.6%	0.94 [0.61, 1.44]	
ruz 2012		0740		280	2.6%	0.94 [0.61, 1.44]	•
	224	276					
ubtotal (95% CI)	224	276	230				
ubtotal (95% CI) otal events eterogeneity: Not app	224 licable						
ubtotal (95% CI) otal events eterogeneity: Not appl	224 licable						
ubtotal (95% Cl) otal events eterogeneity: Not app est for overall effect: Z 1.5 Arabs	224 licable = 0.30 (P	= 0.76)		420	240	0.00.00.00.00.00	
ubtotal (95% CI) otal events eterogeneity: Not app est for overall effect: Z 1.5 Arabs ansoori 2015	224 licable = 0.30 (P 38	= 0.76) 121	74	128	2.1%	0.33 (0.20, 0.56)	
ubtotal (95% CI) otal events eterogeneity: Not app est for overall effect: Z 1.5 Arabs ansoori 2015 emr 2012	224 licable = 0.30 (P	= 0.78) 121 351		371	3.1%	0.61 [0.44, 0.86]	
ubtotal (95% CI) otal events eterogeneity: Not appi est for overall effect: Z 1.5 Arabs ansoori 2015 emr 2012 ubtotal (95% CI)	224 licable = 0.30 (P 38 247	= 0.76) 121	74 295				
ubtotal (95% CI) stal events eterogeneity: Not appi est for overall effect: Z 1.5 Arabs ansoori 2015 emr 2012 ubtotal (95% CI) stal events	224 licable = 0.30 (P 38 247 285	= 0.78) 121 351 472	74 295 369	371 499	3.1% 5.2%	0.61 [0.44, 0.86]	 •
ubtotal (95% CI) otal events eterogeneity: Not appi est for overall effect: Z 1.5 Arabs ansoori 2015 emr 2012 ubtotal (95% CI) otal events eterogeneity: Tau ² = 0	224 licable = 0.30 (P 38 247 285 0.13; Chi ⁼ :	= 0.76) 121 351 472 = 3.64,	74 295 369 df = 1 (P =	371 499	3.1% 5.2%	0.61 [0.44, 0.86]	
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Figure 5. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a heterozygous genetic model (GC vs. GG).

heterogeneity, a subsequent meta-regression was performed using the Asian population data. Under the allelic, recessive, and the homozygous genetic models, the CC genotype number in the T2DM group was verified to be the main confounding factor behind the source of the heterogeneity (P < 0.05).

Diagnostics bias

Funnel plots were performed in order to determine if there was a publication bias in the literature. Funnel plots were performed under the allelic genetic model (shown in **Figure 6**). Visual inspection of the funnel plots indicated an asymmetry. The asymmetry of the funnel plot may be due to an insufficient number of case (which may lead to a small-study effect) and significant statistical heterogeneity in the current meta-analysis.

Discussion

The association between the CDKAL1 rs7754840 SNP and T2DM has been investigated using different populations; however, the results of these studies are in disagreement. In this meta-analysis involving 33,149 T2DM patients and 36,992 controls from 21 independent studies, the relationship of the CDKAL1

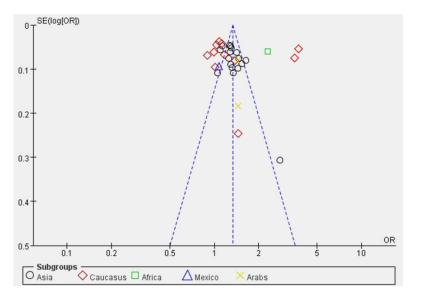


Figure 6. Funnel plots for the CDKAL1 gene G/C polymorphism and T2DM risk in the allelic genetic model.

gene rs7754840 G/C polymorphism with T2DM was investigated. Overall, our data indicated that a significant association exists between the CDKAL1 gene rs7754840 A/G polymorphism and T2DM under the allelic (OR: 1.37), recessive (OR: 1.58), dominant (OR: 1.13), homozygous (OR: 1.27), and the heterozygous genetic models (OR: 0.83).

Considering the possibility that different ethnic backgrounds may influence the results, a subgroup analysis stratified by the different ethnic backgrounds was also performed in the current meta-analysis. A significant association was shown to exist in the Asian and Arab subgroups (P < 0.05), while no significant association was detected in the Caucasian, African and Mexican subgroups (P > 0.05). In conclusion, the C allele of the CDKAL1 gene rs7754840 G/C polymorphism may increase susceptibility to developing T2DM, except in the Caucasian, African and Mexican populations. The results for the population as a whole and the Asian, Arab subgroups were genome-wide significant under most of the genetic models. In the Caucasian subgroup, the results reached genome-wide significance under the allelic genetic models. The negative results found for both the African and Mexican populations were perhaps not only associated with ethnic differences, but could also be a result of small sample sizes; only one research study with 933 T2DM subjects and one with 519 T2DM subjects were included for the

African and Mexican subgroups. In comparison to the 6,798 and 6,535 research subjects used in the analysis for the Asian and Caucasian studies, the sample size for the Mexican and African studies was relatively small. Therefore, the results should be further verified using more studies with larger sample sizes for the African and Mexican subgroups.

Cyclin-dependent kinase 5 (CDK5) has been shown to blunt insulin secretion in response to glucose and to play a permissive role in the decrease of insulin gene expression, especially in

high glucose environments [47]. Ubeda et al suggested that CDKAL1 plays a role in the inhibition of CDK5 activity in pancreatic ß cell expression, which prevents a decrease in insulin gene expression resulting from glucotoxicity [48]. As mutations accumulate in the CDKAL1 gene, the inhibition of CDK5 activity would decrease and β cell function, being the secretion of insulin, would be compromised. It has been reported that in relation to β cell function, the CDKAL1 gene has been significantly associated with insulin resistance, however, not the lack of insulin secretion. The rs7754840 C allele located in the CDKAL1 gene is a single nucleotide polymorphism associated with a genetic susceptibility towards type 2 diabetes. The mutation has two alleles, G and C; where G is the wild-type allele and C is the mutant. When the $G \rightarrow C$ mutation occurs, the β cells become degenerated and insulin secretion is inhibited; thus the CDKAL1 gene rs7754840 G/C mutation most likely leads to an increased risk of type 2 diabetes [49, 50].

In 2013, Peng et al [51] performed a metaanalysis regarding the relationship between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM. They concluded that the CDKAL1 rs7754840 C allele increased the risk of T2DM. Despite the similarity between these results and the results performed in this study, the current meta-analysis was far superior in comparison. The previous study was published in 2012, whereas the current meta-analysis included literature published from 2010 up to the present. Additionally, only basic data extraction was done and there was no use of any genetic models in Peng's work, whereas the present metaanalysis utilized five different genetic models, including the allelic, recessive, dominant, homozygous, and the heterozygous genetic models. Thus, the conclusions drawn from this study are more objective and scientifically validated than theirs.

As a result, in the current meta-analysis, the CDKAL1 gene rs7754840 G/C polymorphism was found to be significantly associated with T2DM susceptibility, particularly in the Asian and Arab populations. People with the G allele in the CDKAL1 gene rs7754840 G/C polymorphism may be predisposed to developing T2DM. This conclusion may lead to the formulation of new methods for T2DM therapies. Taking the limitations discussed above into consideration, more large-scale studies focusing on the association of the CDKAL1 gene rs7754840 G/C polymorphism and T2DM should be done to further validate the conclusion.

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Disclosure of conflict of interest

None.

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