Research Article

Yunyi Liang, Yi Shu, Haizhao Luo, Riqiu Chen, Zhifu Zeng*

Correlation between CDKAL1 rs10946398C>A single nucleotide polymorphism and type 2 diabetes mellitus susceptibility: A meta-analysis

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Abstract: **Objective** The purpose of this meta-analysis was to assess the correlation between CDKAL1 rs10946398C>A single nucleotide polymorphism (SNP) and type 2 diabetes mellitus (T2DM) susceptibility by pooling the open published studies. **Method** Electronic searching of PubMed, EMBASE, Medline, Cochrane, China Biology Medicine disc (CBM) and China National Knowledge Infrastructure (CNKI) databases were performed by two reviewers independently to collect the open published studies related to CDKAL1 rs10946398C>A single nucleotide polymorphism and T2DM susceptibility. The association between CDKAL1 rs10946398C>A single nucleotide polymorphism and T2DM susceptibility was expressed by odds ratio (OR) and the corresponding 95% confidence interval (95%CI). **Results** Thirteen studies with a total of 13,966 T2DM and 14,274 controls were finally included for analysis in this meta-analysis. Of the included 13 publications, 2 studies were carried out in Europe, 8 in Asia, 2 in Africa and 1 in Latin America. Being significant statistical heterogeneity, the data was pooled through random effect model. In a dominant genetic model, there was significant correlation between CDKAL1 rs10946398C>A SNP and T2DM risk (OR=1.22, $P<0.05$). In a dominant genetic model people with CC or CA genotype had increased risk of developing T2DM; Because of statistical heterogeneity for the included studies in a recessive genetic model (AA+CA vs CC), the data was calculated by random effect method. The combined data

showed people with AA or CA genotype had decreased risk of developing T2DM compared to CC genotype (OR=0.83, $P<0.05$); For a homozygous genetic model (CC vs AA), the OR was calculated through random effect model for statistical heterogeneity among the included 13 studies. The combined OR was 1.33 which indicated people with CC genotype had increased risk of developing T2DM. **Conclusion** According to the present results, CDKAL1 rs10946398C>A single nucleotide polymorphism had correlation with the susceptibility of type 2 diabetes mellitus.

Keywords: type 2 diabetes mellitus; CDKAL1 gene; susceptibility; polymorphism; meta-analysis.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by insufficient insulin secretion or insulin resistance [1,2]. Epidemiological studies have suggested that T2DM is a multifactor genetically heterogeneous disease that involves in the effects of multiple genes and environmental factors [3,4]; thus, its pathogenesis is complex and the cause of this disease has not yet been fully elucidated. CDKAL1 is a newly identified gene that is relevant to T2DM pathogenesis [5,6]. However, research on the relationship between CDKAL1 gene rs10946398 site polymorphism and T2DM is inconclusive [7-9]. Wu *et al.* [10] evaluated the correlation between common variants of CDKAL1 gene and type 2 diabetes. The authors found in Chinese Hans, the common variants of rs10946398C>A single nucleotide polymorphism was associated with the susceptibility of type 2 diabetes mellitus. However, Cruz [9] didn't find the correlations in all genetic models. In this study, a meta-analysis has been conducted to comprehensively and quantitatively evaluate previous study results to obtain medical evidence on the relationship

*Corresponding author: Zhifu Zeng, Department of Endocrinology, Lishui People's Hospital, Lishui Zhejiang Province, 323000 PR China. No.15 Dazhong Road, Liandu District Lishui City Zhejiang Province, 323000 PR China, E-mail: lanj8386@163.com

Yunyi Liang, Yi Shu, Haizhao Luo, Department of Endocrinology, Nanhai People's Hospital of Foshan City 528200 China

Riqiu Chen, Department of Endocrinology, Lishui People's Hospital, Lishui Zhejiang Province, 323000 PR China

between CDKAL1 gene rs10946398 polymorphism and T2DM susceptibility.

2 Methods

2.1 Publication searching

Electronic searching of PubMed, EMBASE Medline, Cochrane, China Biology Medicine disc (CBM) and China National Knowledge Infrastructure (CNKI) databases was performed by two reviewers (Yunyi Liang and Yi Shu) independently to collect the open published studies related to CDKAL1 rs10946398C>A SNP and T2DM susceptibility. The electronic searching words were described as follows: CDKAL1 gene, T2DM, susceptibility, rs10946398 and genetic polymorphism. The studies searching process was done by two reviewers (Yunyi Liang and Yi Shu) and cross checked. The references of included publications were also reviewed to find additional suitable studies.

2.2 Publication inclusion and exclusion criteria

The study inclusion criteria were: ① Open published studies about CDKAL1 rs10946398C>A SNP and T2DM susceptibility with the language restriction of English and Chinese; ② The study was restrict to case-control or cohort study; ③ The study should provide the genotype distribution; ④ The T2DM patients had confirmed diagnosis according to WHO DM diagnostic criteria; ⑤ Subjects in the control group did not have family history of DM. The publication exclusion criteria were: ① Duplicated publications; ② Case report or review study type; ③ Studies published in other language; ④ The original study did not provided genotype distribution or enough data to calculate the OR.

2.3 Data extraction

Two reviewers (Haizhao Luo and Riqiu Chen) independently reviewed the whole paper to extract the necessary information and data. The general characteristics of the included studies such as first and corresponding authors, the paper publication year, and the race of subjects were extracted and cross checked by the two reviewers. The data of genotype distribution

(CC, CA and AA) for CDKAL1 rs10946398 from each included studies were also extracted. The data was cross examined by the two reviewers to make consensus. A third reviewer (Fuzhi Zeng) was consulted if disagreement was encountered.

2.4 Statistical analysis

Stata 11.0 (for meta-analysis) was used to deal with the data analysis. Firstly, the data extracted from each included publication was tested for statistical heterogeneity through chi-square test [11] and the inconsistency was calculated by I² [12]. If significant statistical heterogeneity existed among the included studies, the data was pooled by random effect method otherwise the data was calculated by fixed effect methods. The odds ratio (OR) was used to demonstrate the correlation between DKAL1 rs10946398C>A single nucleotide polymorphism and T2DM susceptibility. The publication bias was evaluated by Begg's funnel plot and Egger's line regression test. Two tail $p \leq 0.05$ was considered statistical significance.

3 Results

3.1 General characteristics of the included thirteen studies

After searching the electronic databases, 364 publications were initially identified. After reading the title, abstract and full text paper, 351 studies were did not meet the inclusion criteria and were excluded. 13 studies [7-10, 13-21] with a total of 13966 T2DM and 14274 controls were finally included for analysis in this meta-analysis, Figure 1. Of the included 13 publications, 2 studies were carried out in Europe, 8 in Asia, 2 in Africa and 1 in Latin America. The detailed information for the included studies were showed in Table 1.

3.2 Genotype distribution

The median CC, CA and AA genotype distribution frequency for T2DM group were 0.22, 0.49 and 0.28. And for control group, the median distribution frequency CC, CA and AA genotype were 0.18, 0.48 and 0.34 respectively. There was no statistical difference for the CC, CA and AA genotype distribution between the two groups ($P > 0.05$), Figure 2.

Figure 1. Publication inclusion flow-chart of this meta-analysis

Table 1. General information for the included studies

Authors	Year	Region	Race	Case			Control		
				CC	CA	AA	CC	CA	AA
Garup [13]	2007	Europe	Caucasus	184	424	244	159	422	281
Scott [7]	2007	Europe	Caucasus	171	549	440	150	539	486
Lewis [14]	2008	Africa	African	353	442	138	357	513	185
Wu [10]	2008	Asia	East Asian	106	212	106	319	922	666
Hu [8]	2009	Asia	East Asian	360	912	578	306	866	613
Cruz [9]	2010	Latin America	America	52	225	242	51	224	244
Han [15]	2010	Asia	East Asian	227	498	273	177	484	330
Lin [16]	2010	Asia	East Asian	310	757	463	195	666	567
Wen [17]	2010	Asia	East Asian	226	574	365	175	542	420
Cooke [18]	2012	Africa	African	968	1269	416	453	683	258
Chen [19]	2013	Asia	East Asian	97	221	125	296	559	264
Al-Sinani [20]	2015	Asia	Europa	401	460	131	140	126	28
Sun [21]	2015	Asia	East Asian	108	231	108	99	294	215

3.3 Statistical heterogeneity evaluation

The statistical heterogeneity for the included studies were evaluate by I^2 test. In the dominant genetic model (CC+CA vs AA), the $I^2=71.4\%$ indicating significant statistical heterogeneity was existed. For the recessive genetic model (AA +CC vs CC), the statistical heterogeneity was significant with $I^2=73.0\%$. Significant heterogeneity also found in homozygous genetic model (CC vs AA) with the $I^2=79.7\%$.

3.4 Dominant genetic model (CC+CA vs AA)

For significant heterogeneity, the data was pooled through random effect model. In dominant genetic model, there was significant correlation between CDKAL1 rs10946398C>A single nucleotide polymorphism (OR=1.22, $P<0.05$). In dominant genetic model people with CC or CA genotype had increased risk of developing DM (Figure 3).

Figure 2. Scatter plot of genotype distribution in DM and control group (a: CC genotype distribution; b: CA genotype distribution; c: AA genotype distribution).

Figure 3. Forest plot of OR with a random-effects model for evaluation of CDKAL1 rs10946398C>A single nucleotide polymorphism and type 2 diabetes mellitus susceptibility in dominant genetic model (CC+CA vs AA)

3.5 Recessive genetic model (AA+CA vs CC)

Because of statistical heterogeneity across the studies in recessive genetic model (AA+CA vs CC), the data was calculated by random effect model. The combined data showed people with AA or CA genotype had decreased risk of developing T2DM compared to CC genotype (OR=0.83, P<0.05), Figure 4.

3.6 Homozygous genetic model (CC vs AA)

For homozygous genetic model (CC vs AA), the OR was calculated through random effect model because of statistical heterogeneity among the included 13 studies. The combined OR was 1.33 which indicated people with CC genotype had increased of developing T2DM, Figure 5.

3.7 Publications bias

The publication bias of this meta-analysis was evaluated by both Begg’s funnel plot and Egger’s line regression

test. For dominant genetic model (CC+CA vs AA). The Begg’s funnel plot was upper and lower symmetry (Figure 6). Egger’s line regression test indicated no publications bias (P=0.34). In recessive (AA+CA vs CC), (Figure 7) and homozygous (CC vs AA), (Figure 8) genetic model the Begg’s funnel plot was seemingly asymmetry. However, the Egger’s line regression test demonstrated no publication bias (P=0.72, P=0.36).

4 Discussion

Insulin resistance is the major pathogenesis of T2DM in humans [22,23]. As a multifactor genetically heterogeneous disease, the pathogenesis and prognosis of T2DM are caused by a combination of inherited and acquired risk factors. Literature on the screening of candidate genes related to T2DM have shown that the variation in some genes related to insulin secretion and blood sugar metabolism is certainly correlated with the occurrence and development of T2DM [24].

A number of case-control studies have revealed that single-nucleotide polymorphisms in multiple loci

Figure 4. Forest plot of OR with a random-effects model for evaluation of CDKAL1 rs10946398C>A single nucleotide polymorphism and type 2 diabetes mellitus susceptibility in recessive genetic model (AA+CA vs CC)

Figure 5. Forest plot of OR with a random-effects model for evaluation of CDKAL1 rs10946398 C>A single nucleotide polymorphism and type 2 diab

Figure 6. The Begg's funnel plot for evaluation publication bias in dominant genetic model (CC+CA vs AA)

Figure 7. The Begg's funnel plot for evaluation publication bias in recessive genetic model (AA+CA vs CC)

Figure 8. The Begg's funnel plot for evaluation publication bias in Homozygous genetic model (CC vs AA)

of CDKAL1 gene are related to T2DM pathogenesis[9, 13, 16]. The risk that the population with a specific genotype suffers from T2DM is significantly increased. However, some studies have reported that the single-nucleotide polymorphism of CDKAL1 genes is not associated with susceptibility to T2DM[9]. CDKAL1 gene is located on the short arm of chromosome 6, with a full length of 697948bp, encoding a 65ku protein. The changes in CDKAL1 gene expression can lead to the decrease in ATP and cause a K_{ATP} channel response induced by glucose to weaken. The activity of Ca^{2+} channel is then impaired, and first-phase insulin secretion is decreased. Studies have also shown that CDKAL1 can inhibit the activity of pancreatic β cells CDK5 under high glucose toxicity and prevent the decline in insulin gene caused by sugar toxicity[25]. Thus, insulin secretion is decreased, and the insulin secretion of people with rs10946398 dangerous allele after glucose load is also decreased. CDKAL1 gene influencing the secretion function of pancreatic β cells is related to insufficient insulin secretion but not to insulin resistance[26].

In this study, meta-analysis is conducted for 13 studies of CDKAL1 rs10946398C>A SNP from different regions. Results showed that population carrying C allele has a significantly increasing risk of suffering from T2DM. Thereafter, CDKAL1 rs10946398C>A single nucleotide polymorphism had correlation with the susceptibility of type 2 diabetes mellitus.

However, meta-analysis also has limitations. First, statistical heterogeneity exists among the included various studies. The presence of statistical heterogeneity reduces the stability of conclusions. Second, meta-analysis is only conducted for one of CDKAL1 gene SNP loci, but the interaction among polymorphic loci has not been explored yet.

Ethical approval: The conducted research is not related to either human or animals use.

Conflict of interest: Authors state no conflict of interest

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