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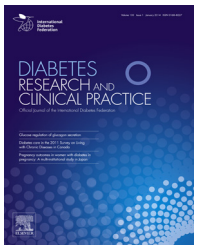

Association of LEPR Gln223Arg polymorphism with T2DM: A meta-analysis

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ABSTRACT

A meta-analysis was conducted to evaluate the association of LEPR Gln223Arg polymorphism with type 2diabetes (T2DM). Sixteen individual studies with 7827 subjects were included into the meta-analysis. Current studies suggest that LEPR Gln223Arg polymorphism may not affect the susceptibility with type 2diabetes (T2DM).

1. Introduction

T2DM (type 2diabetes) is a major public problem in both developed countries and developing countries, and the numbers of diabetes is expected to rise to 592 million by 2035, nearly 1.5 folds of the number of 2013 [1]. As a heterogeneous and polygenic disease, many researches are conducted to find out the genes interacting with the environmental factors that lead to diabetes [2]. Several common polymorphisms of the LEPR (leptin receptor) gene have been demonstrated and evaluated in populations exhibiting different prevalence rates of diabetes. Among those variants, the 668 A to G transition results in change of a glutamine to an arginine at position 223 of the LEPR protein. Moreover, the A223G polymorphism of LEPR gene has been associated with body mass index (BMI), fat mass, leptin levels, and systolic and diastolic blood pressure. Additionally, it was reported that LEPR A223G polymorphism has been associated with impaired glucose tolerance, conversion to T2DM, and insulin resistance. Several studies were published to assess the association between LEPR Gln223Arg polymorphism and T2DM, but they reported controversial results. So we performed a systemic review and meta-analysis to assess the association between LEPR Gln223Arg polymorphism and T2DM.

2. Methods

We performed a systematic search in PubMed, Embase, Web of Science, and Chinese Biomedical Database (CBM) for

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case-control studies on the association of LEPR polymorphism Gln223Arg with T2DM published up to October 20, 2014. We used the following keywords in the literature search: (LEPR, rs1137101, Q223R or Gln223Arg) and (T2DM, diabetes, or diabetic). The references cited in relevant reviews or eligible studies were manually searched to identify additional studies as well. There was no language restrictions imposed to the bibliographic search.

The following inclusion criteria were used to select eligible studies for the meta-analysis: (1) Using case-control design; (2) Evaluating the association of LEPR polymorphism Gln223Arg with the T2DM; (3) Cases were patients with T2DM; and (4) Providing the frequencies of genotypes for LEPR polymorphism Gln223Arg for estimating odds ratio (OR) with its corresponding 95% confidence interval (95% CI). If studies had the same or overlapping data, only the largest study was included in the meta-analysis. The exclusion criteria were as following: (1) Duplication of previous publications; (2) Comment, review and editorial; (3) Family-based studies of pedigrees; (4) Study with no detailed genotype data. Study selection was performed by two investigators independently, according to the inclusion and exclusion criteria by screening the title, abstract and full-text. Any dispute was solved by discussion.

Data extraction was conducted independently by two investigators, and consensus was finally reached on all items by all authors. The following data were extracted from each study: name of first author, year of publication, country of origin, ethnicity, study design, source of controls, genotyping method, numbers of cases and controls, and frequencies of alleles and genotypes in both cases and controls. Ethnicity was categorized as Caucasians, Asians, and others.

We used the pooled OR with 95%CI to assess the associations. The pooled ORs were calculated for the allele model (A vs. G), the additive model (ArgArg vs. GlnGln), the recessive model (ArgArg/ArgGln vs. GlnGln) and the dominant model (ArgArg vs. GlnGln/ArgGln), respectively. Between-study heterogeneity was assessed by calculating Q statistic and quantified by using the I^2 statistic method which described the percentage of variation across studies due to heterogeneity. For low heterogeneity, the pooled ORs were calculated by the fixed-effect model (Mantel–Haenszel's method) [3]. Otherwise, the random effect model (DerSimoni an and Laird's method) was used to calculate the pooled ORs [4]. Subgroup analysis was performed by ethnicity. The publication bias was diagnosed using the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot a symmetry was further assessed using the method of Egger's linear regression test ($P < 0.05$ was considered as a significant publication bias). All of the statistical analyses used in our meta-analysis were performed by Stata version 11.0 (Stata, College Station, TX, USA).

3. Results

Sixteen individual studies with 7827subjects from 14 publications were finally included into the meta-analysis [5–18]. Among those 16 studies, six studies were performed in Caucasian countries, while the other 10 studies were performed in Asians (Table 1). Among nine of those 16 studies, the genotype distributions in the controls of all included studies were in HWE.

As the I^2 was 90.9% (Fig. 1), we excluded seven studies which were not according to HWE, and the I^2 was reduced to 47.9% (Fig. 2) [6,7,9,10,14,15]. Sixteen individual studies with 7827 subjects were finally included into the meta-analysis. There was no association between LEPR Gln223Arg polymorphism and type 2 diabetes mellitus (Fig. 1: G vs. A, OR = 1.12, 95% CI 0.83 to 1.51, P = 0.457; Table 2: AA vs. GG, OR = 0.74, 95% CI 0.39 to 1.43, P = 0.375; AA + AG vs. GG, OR = 0.91, 95% CI 0.62 to 1.32, P = 0.612; AA vs. GG + GA, OR = 0.78, 95% CI 0.50 to 1.20, P = 0.254). After adjusting for heterogeneity by excluding seven studies which were not according to HWE, the result was not change either (G vs. A, OR = 0.99, 95% CI 0.84 to 1.17, P = 0.909).

Table 1 – Characteristics of the studies included in the meta-analysis..

Study	Cases			Control			P_{HWE}	Ethiciy	Country	Diagnostic criteria
	GG	GA	AA	GG	GA	AA				
Park et al. [5]	578	177	11	523	148	13	0.505	Asians	Koreans	ADA1997
Zhao et al. [7]	105	94	80	38	19	15	0.0004	Asians	China	WHO1999
Zhao et al. [6]	85	156	195	91	30	39	2.05E − 13	Asians	China	WHO1999
Ying et al. [8]	158	66	1	89	21	1	0.845	Asians	China	WHO1999
Murugesan et al. [9]	53	67	30	22	55	73	0.036	Caucasians	India	Not mention
Zhang et al. [10]	128	40	4	100	63	1	0.007	Asians	China	WHO1999
Shi et al. [12]	283	49	1	310	80	5	0.949	Asians	China	WHO1999
Gan et al. [11]	200	83	18	121	47	4	0.821	Asians	China	Not mention
Liao et al. [13]	796	194	8	36	8	1	0.502	Asians	Taiwan	ADA2007
Etemad et al. [15]	42	86	17	22	92	19	9.41E − 06	Asians	Malay	IDF
Etemad et al. [15]	13	36	0	7	59	5	2.08E − 08	Asians	China	IDF
Etemad et al. [15]	37	45	8	23	39	15	0.833	Caucasians	India	IDF
Al-Harithy et al. [17]	8	50	92	12	40	78	0.051	Caucasians	Saudi Arabia	Not mention
Mohammadzadeh et al. [16]	5	59	80	5	62	80	0.088	Caucasians	Iranian	ADA1997
Roszkowska-Gancarz [18]	44	98	48	188	374	206	0.479	Caucasians	Poland	Not mention
Swellam et al. [14]	13	18	12	9	14	54	8.53E − 05	Caucasians	Egypt	WHO1999

HWE: Hardy–Weinberg equilibrium.