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Surveying the relationship between Gly1057Asp polymorphism of IRS-2 gene and susceptibility to type 2 diabetes; a systematic review and meta-analysis study

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a multi-factorial disease in which influenced by several genetic and environmental factors. Insulin receptor substrate 2 (IRS 2) is the main mediator of insulin in the liver which controls insulin sensitivity. Gly1057Asp polymorphism is one of the candidates to increase risk of T2DM. The present study is an attempt to study the relationship of Gly1057Asp polymorphism of IRS-2 and T2DM by a meta-analysis. A systemic search was conducted in English and Persian databases such as Scopus, PubMed, Google Scholar, SID, and other academic databases for studies that have investigated the relationship of Gly1057Asp polymorphism of IRS-2 and T2DM. This association was determined using odds ratios (ORs) with a confidence interval of 95% (CIs). Heterogeneity of the studies was examined by I^2 index. Funnel plots and Egger tests were used to determine bias or publication bias. The collected data was analyzed in STATA through meta-analysis. Nine articles were selected as eligible for further analysis, which represented 3,196 patients with T2DM and 3409 controls subjects without T2DM. The present meta-analysis showed a significant relationship between GA genotype of Gly1057Asp polymorphism and T2DM (OR=0.88; 95% confidence interval, 0.79-0.98), whereas no significant relationship between GG and AA genotype with T2DM was seen; OR for GG and AA genotypes were 1.10 (95% CI, 0.99 -1.22) and 1.13 (95% CI, 0.95- 1.33), respectively. The results of our study show that genotype GA of Gly1057Asp polymorphism of IRS-2 gene plays a protective role and may decrease the risk of T2DM, whereas GG and AA genotypes are considered as a risk factor and related to development of T2DM to some extents.

Implication for health policy/practice/research/medical education:

The present meta-analysis showed a significant relationship between GA genotype of Gly1057Asp polymorphism and type 2 diabetes mellitus (OR=0.88; 95% confidence interval, 0.79-0.98), whereas no significant relationship between GG and AA genotype with type 2 diabetes mellitus was seen; OR for GG and AA genotypes were 1.10 (95% CI, 0.99 -1.22) and 1.13 (95% CI, 0.95-1.33), respectively.

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Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder which manifests a heterogeneous group of metabolic diseases. Glucose intolerance is the common feature of T2DM, and resulting from by at least two pathophysiological defects: impaired insulin signaling and failure of pancreatic β cells to compensate for poor

insulin action through an appropriate increase of insulin secretion (1,2). It has been shown that simultaneous inheritance of genetic variants at multiple loci, and their interaction with environmental factors may contribute to the development of type 2 diabetes (3).

Recent studies speculate that the genetic variants of different molecules involved in intracellular signaling of

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insulin receptors in both liver and pancreatic beta cells, which play a part in underlying pathogenesis of the type 2 diabetes (4,5). The insulin receptor substrate-2 (IRS-2) is one of these molecules and is one of the major substrates of the insulin receptor. Given to its crucial role in the insulin signaling system and in development and/or survival of pancreatic beta cell, it may be an attractive candidate in the pathogenesis of type 2 diabetes (6). It has been shown that IRS-2 protein as a key mediator in insulin signaling plays a central role in insulin-dependent cellular functions such as growth, survival, and metabolism (7).

As well-known, an intracellular signaling cascade begins with the binding of insulin to the extracellular α -subunit of the insulin receptor could lead to the different biological effects in multiple tissues (8,9). One of the most important effects of insulin is to stimulate glucose transport. Upon insulin stimulation, glucose transporter 4 translocates to the plasma membrane, allowing glucose uptake into the cell (10). It has been shown that, the insulin receptor substrates and phosphatidylinositol 3-kinase (PI3K) are two major mediators regulating insulin dependent glucose transport, however, there may be other pathways involved in glucose uptake (11,12). Additionally, there are evidences that show regulatory genes of the proximal insulin signaling pathway may contribute to insulin resistance and could be potential candidates in pathogenesis of type 2 diabetes (13). Phosphorylated IRSs (insulin receptor substrate proteins) act as docking proteins between the insulin receptor and a complex network of intracellular signaling molecules containing Src homology 2 domains, including the p85 subunit of phosphatidylinositol (PI) 3-kinase (7). Under normal circumstances, once insulin binds to its cell surface receptors, the intracellular tyrosine residues of receptor undergo auto-phosphorylation by its self-tyrosine kinase activity and then the downstream cascade of events is started (10-12). In subsequent, other downstream regulatory proteins such as insulin receptor substrate family of IRS-1/2/3/4 and Shc phosphorylated by turn with tyrosine kinase activity of insulin receptor (14). Moreover, insulin messaging may be regulated with activity of phosphotyrosine protein phosphatase (PTPase), via the dephosphorylation of insulin receptor substrate 1/2 and Shc (15). The Shc family of adaptor proteins is a group of proteins that lacks intrinsic enzymatic activity. IRS1 and IRS2 are known as adapter proteins for SH2-domain containing Src messenger proteins including Nck-SHP2-Grb-2-sos complex and lipid kinase regulatory subunit which is known as PI-3-kinase (16). Binding of the IRS to p85, as a regulatory subunit of PI-3-kinase, activate the PI-3-kinase-PKB/AKT pathway that is necessary for fulfillment of the insulin action on glucose transport and construction of glycogen in the liver (17).

Up to now, several SNPs have been identified and reported in the IRS-2 gene in humans (18). One of the most frequent of these is a variant causing a Gly1057Asp substitution. In addition, four other SNPs which rarely

occur have been identified result in variants causing an Ala157Thr substitution, a Leu647Val substitution, a Gly879Ser substitution, along with an AAC insertion (Asn) in the Asn repeat sequence centered on codons of 29–36 (7). Among those variants, the Gly1057Asp substitution has been found to be more associated with increased risk for the T2DM in some populations (16).

IRS2G1057DasareplacementofG(glycine)byD(aspartic acid) takes place at site 1057 of insulin receptor substrate-2 and results from a simple nucleotide substitution or polymorphism (SNP) in IRS2 gene (rs1805097) (19). The association of this polymorphism with type 2 diabetes has been studied in different populations, but the inconsistent results have been reported. Some studies reported an association between Gly1057Asp polymorphism of IRS-2 and susceptibility to T2DM, whereas others have reported controversial data (20-28). To authenticate these studies and as a way of synthesizing their findings, performing a meta-analysis study seemed necessary. In the present study we aimed to investigate and identify the association of these polymorphisms with T2DM by a meta-analysis and literature review.

Search strategy

We searched the PubMed, Scopus, Google Scholar, Web of Science, Embase, and the Cochrane Library databases to identify any articles published in English on the relationship between Gly1057Asp polymorphism of IRS-2 gene with type 2 diabetes. Searching was done using keywords including IRS-2, Type 2 diabetes, Gly1057Asp, rs1805097. The Persian equivalent of these terms and all probable combinations were used to search in Persian databases (i.e., IranMedex, Magiran, SID, and Irandoc). The advanced search was performed with a combination of words or phrases using Boolean operators ('AND', 'OR', 'NOT'). The references list of all related reviews and main articles were examined to identify any further publications that were not retrieved in the online search.

Inclusion and exclusion criteria

In the next stage, the obtained studies of searching process were tested precisely to be included in the study. All case studies and meta-analysis studies on IRS-2 and T2DM were reviewed. Articles that had determined Gly1057Asp polymorphism of IRS-2 gene in type 2 diabetes patients and control subjects without T2DM were considered eligible and included for further analysis. Some studies were out of the realm of the current study and thus were excluded, if they perform on non-human creatures (i.e. animal studies), if they were meta-analyses or systematic reviews, if they presented insufficient data, and those were published in other than English and Persian languages.

Data extraction

The following data and information were extracted from the studies; the name of first writer, study location,

publication year, and sample size and also the number of genotypes GG, GA, AA of Gly1057Asp polymorphism in T2DM patients and control subjects without T2DM. In cases which needed more information, the articles' writers were contacted for supplementary data or further elucidation. All these procedures were conducted by two authors independently and any disagreement was resolved by consensus. The data were entered into data collection forms and entered into Microsoft Excel.

Statistical analysis

The odds ratio (OR) with a confidence interval of 95% was computed as the measuring standard of the relation between Gly1057Asp polymorphism of IRS-2 gene with type 2 diabetes for both individual trials and pooled estimates. To obtain OR and combined ORs, the Peto odds ratio method was utilized. Heterogeneity of the articles was examined using Q and I^2 Cochran statistics. While the results of studies were heterogeneous, random effects models were used in the meta-analysis. Additionally, when there was no heterogeneity for the outcome, the fix effects model was applied to pool analysis and verses. The findings are described in forest plots (the point estimations and their 95% CI). Meta-regression was used to survey the relationship between year of study and OR value. Funnel plots and Egger test were used to examine publication bias. Values of $P < 0.05$ were considered as valid for heterogeneity tests. The data was analyzed with software R (version 2.15.1) and STATA (version 11.2).

Results

In the search process, 27 potential articles were identified; 6 of them were review and repetitive studies which were removed from analysis, thus abstracts of 21 articles were

remained. In the next step, 10 articles were excluded based on unrelated titles and abstracts. We also removed two studies from the list after screening of full text. Eventually, 9 articles were selected for the final analysis (Figure 1).

All these studies were case-control studies and published from 1999 to 2012. Studies were conducted in different countries; two in Italy (24,27) and one for each in Finland (23), Iran (20), India (21), Germany (26), Netherlands (25), Japan (22), Denmark and Sweden (28). The total sample size was 6605 participants containing 3196 T2DM patients and 3409 control subjects without T2DM; including 1573 cases and 1620 controls with GG genotype, 1275 cases and 1,451 controls with genotype GA, and 348 cases and 338 controls with AA genotype. The characteristics of the eligible studies are listed in Table 1.

In the current meta-analysis, OR for genotype GG based on fixed effects model was 1.10 (confidence interval of 95% from 0.99 to 1.22). We found no evidence of heterogeneity ($I^2 = 15.6\%$, $P = 0.304$; Figure 2). This shows that this polymorphism is related to development of T2DM to some extents and it is considered as a risk factor ($P = 0.05$).

Figure 3 presents the Begg's funnel plot related to GG genotype and T2DM for detecting publication bias; According to this figure, the effect of bias was not significant ($P = 0.504$). Additionally, Egger's regression asymmetry test revealed no evidence of publication bias ($P = 0.156$).

The result indicated that there was a significant relationship between GA genotype and T2DM. The odds ratio for genotype GA based on fixed effects model was 0.88 (CI: 95%, 0.79-0.98; Figure 4). Taking into account that, the confidence interval does not include 1 for total OR, it can be said that the gene plays a protective role

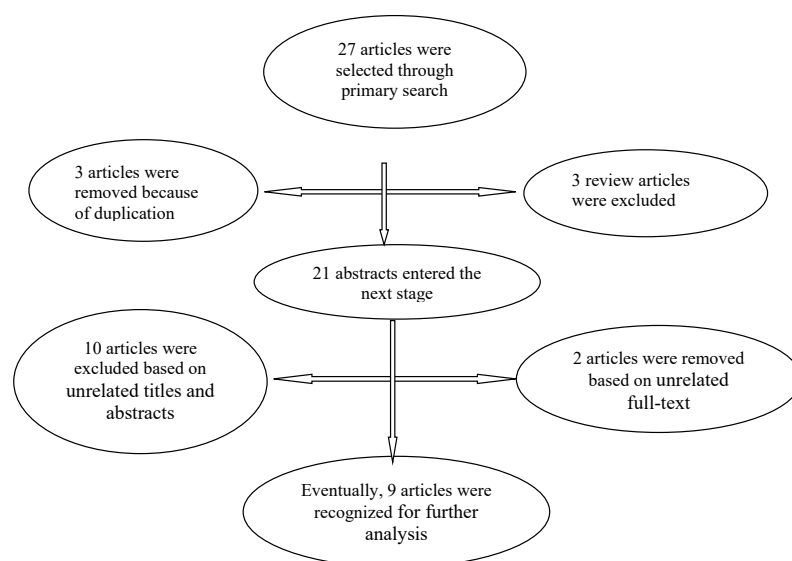


Figure 1. Flowchart of selecting relevant studies for meta-analysis.

Table 1. Study characteristics

First Author/ References	Published Year	Country	Total sample (case)	Total sample (control)	OR (95% CI)		
					GG	GA	AA
Haghani K (20)	2012	Iran	336	341	0.59	1.56	1.70
Bodhini D (21)	2007	India	1018	1193	1.20	0.74	1.43
Okazawa K (22)	2005	Japan	123	260	0.99	0.99	1.03
Laukkanen O (23)	2004	Finland	248	242	1.01	0.99	1.01
D'Alfonso R (24)	2003	Italy	240	186	1.16	0.94	0.82
Leen M (25)	2002	Netherlands	94	64	0.64	1.37	1.44
Fritsche A (26)	2001	Germany	77	318	0.79	1.33	0.85
Mammarella S (27)	2000	Italy	193	206	1.23	0.91	0.73
Almind K (28)	1999	Denmark and Sweden	228	363	1.37	0.67	1.21
Almind K (28)	1999	Denmark and Sweden	639	236	0.90	1.18	0.87

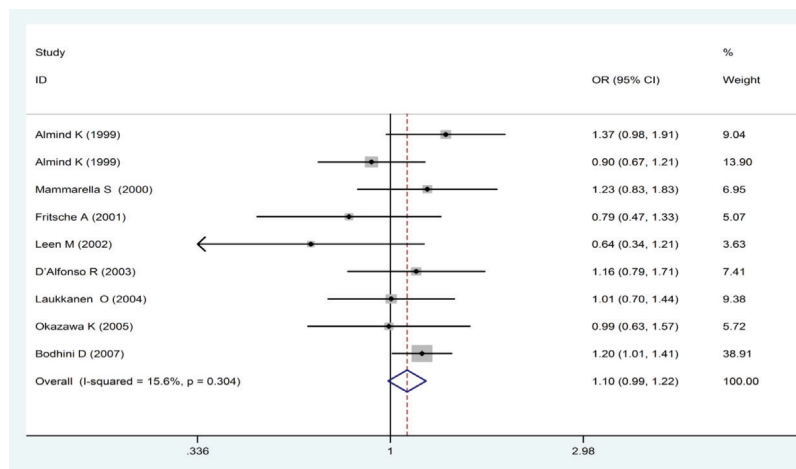


Figure 2. Relationship between Gly1057Asp polymorphism of IRS-2 gene (GG genotype) and susceptibility to diabetes type II based on fixed effects model. Midpoint of each segment is the estimate of prevalence and segment lengths shows the 95% confidence intervals for each study. The diamond mark shows the prevalence in the whole country for all studies.

and having this polymorphism may decrease the risk of T2DM. Given I^2 index, the results of different studies are homogeneous ($I^2 = 46.6\%$, $P = 0.049$; Figure 4). Based on Figure 5, there is a bias in publication.

Our meta-analysis based on fixed effects model found no significant relationship between genotype AA and

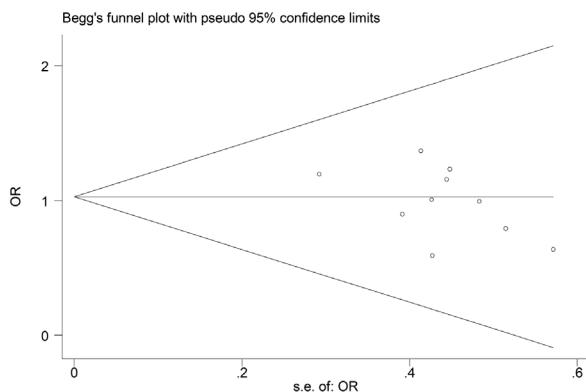


Figure 3. Begg's funnel plot for publication bias (GG genotype).

T2DM; OR was 1.13 (CI: 95%; 0.96-1.33). However, the genotype still is considered as a risk factor of the disease. That is, OR of T2DM in individuals with this genotype is 1.13 times of individuals without this genotype. The difference, however, is not significant.

The included studies showed limited evidence of heterogeneity ($I^2 = 1.2\%$, $P = 0.427$; Figure 6).

Funnel plot and Egger tests showed no evidence of publication bias ($P = 0.541$ for Egger; $P = 0.858$ for Begg; Figure 7).

Discussion

The candidate gene approach is a common approach to define contribution of genetic variants as a risk factor in susceptibility to many diseases such as T2DM (29). In regard to T2DM, this approach tries to find a relationship between T2DM and sequence of the variants (determined based on physiological performance) within or in vicinity of the candidate gene. In order to find importance of different variants with other close variants, their frequency in T2DM patients and controls are compared (27). Many

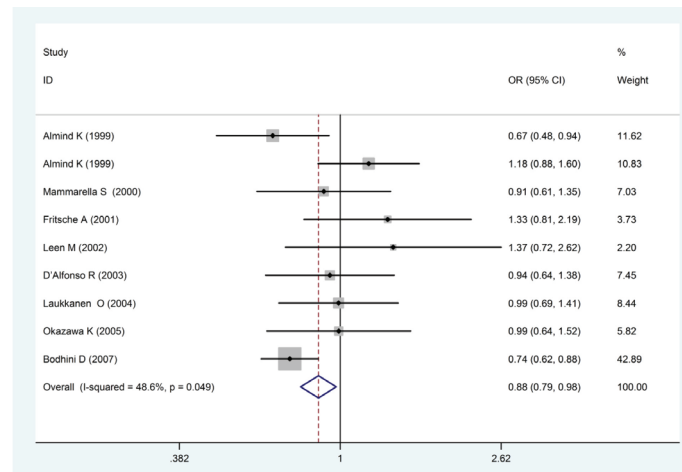


Figure 4. Relationship between Gly1057Asp polymorphism of IRS-2 gene (GA genotype) and susceptibility to diabetes type II based on fixed effects model. Midpoint of each segment is the estimate of prevalence and segment lengths shows the 95% confidence intervals for each study. The diamond mark shows the prevalence in the whole country for all studies.

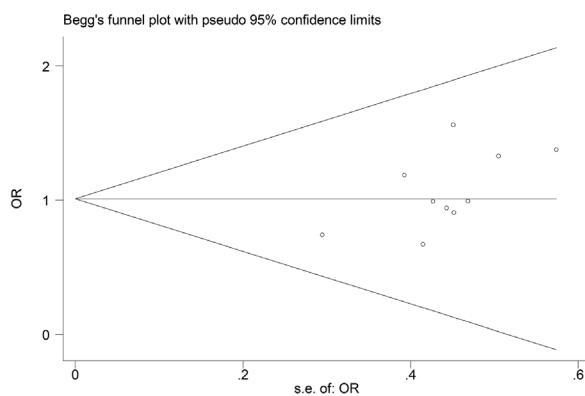


Figure 5. Begg's funnel plot for publication bias (GA genotype).

studies suggest that among several variants of IRS-2 gene, Gly1057Asp polymorphism is an important candidate for development of T2DM (30-32). The present meta-analysis from nine conducted articles did not show a significant relationship between Gly1057Asp polymorphisms and increased risk of T2DM.

There are several studies have been conducted in different populations to find the relationship between Gly1057Asp variant of IRS-2 and T2DM. However, the findings are controversial regarding the effect of these variant on OR of T2DM and relevant metabolic traits (20-28,33). Okazawa et al reported a strong relationship between G1057D variant of IRS-2 and susceptibility to T2DM (22). Additionally, Stefan et al reported that carriers of DD genotype demonstrated low sensitivity to insulin in the liver and pancreatic beta cells (30). However, in contrast, Almind et al reported no relationship between G1257D variant of IRS-2 and T2DM predisposition on white populations (28). Interestingly, D'Alfonso et al showed that the frequency of Gly1057Asp variant of IRS-2

was not related to common form of T2DM. Their results, apparently, indicated that the subjected variant does not influence all clinical and biochemical metrics in T2DM patients and non-T2DM individuals (24). Furthermore, D' Alfonso et al argued that Gly1057Asp variant of IRS-2 is related to low and high prevalence of T2DM in normal and overweight individuals (24). In this regard we found a significant relationship between GA genotype of Gly1057Asp polymorphism and T2DM, whereas no significant relationship between GG and AA genotype with T2DM was observed. These results are inconsistent with D'Alfonso et al and other reports in Danish, German, Dutch, Finn and Chinese populations (25,26,28,34,35), which somehow are consistent with the result of study in the Italian population (27). Another study conducted in Denmark to find the frequency of this polymorphism, however, the results showed no relationship with susceptibility to T2DM (34). The result of study in middle age non-diabetic Danish population with D1057 allele showed decreased levels of serum insulin and C-peptide in oral glucose tolerance test (OGTT) (28). Moreover, the findings of a study in German population showed no relationship between the polymorphism and insulin sensitivity or insulin secretion levels, while the results showed the influence of the polymorphism in the same population on overweight and performance of the pancreatic beta cells (30). In line with these findings, the result of studies in Italy and Japan showed no relationship between this polymorphism and susceptibility to T2DM (24-27,36,37). Thereby, it appears that a considerable difference between the relationship of Gly1057Asp variant of IRS-2 and type 2 diabetes exists.

The underlying molecular mechanisms of how G1057D causes non-protective effect on the improvement insulin performance are still not clear. It is assumed that a charged amino acid (D) was introduced by D1057 variant in place

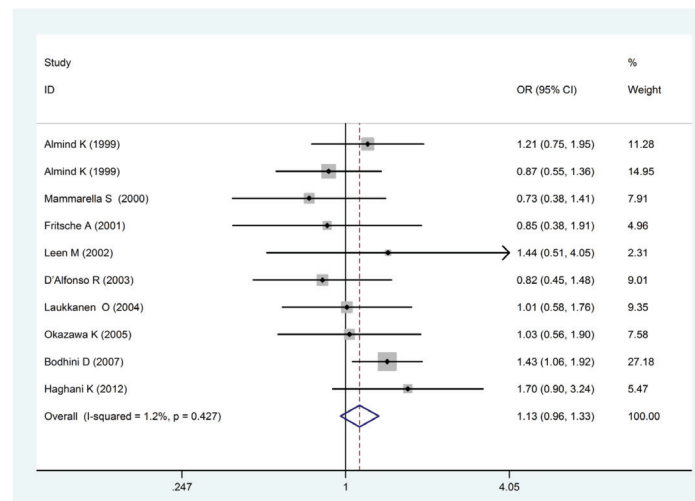


Figure 6. Relationship between Gly1057Asp polymorphism of IRS-2 gene (AA genotype) and susceptibility to diabetes type II based on fixed effects model. Midpoint of each segment is the estimate of prevalence and segment lengths shows the 95% confidence intervals for each study. The diamond mark shows the prevalence in the whole country for all studies.

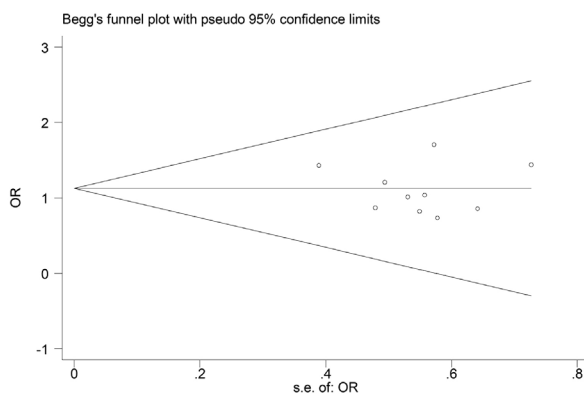


Figure 7. Begg's funnel plot for publication bias (AA genotype).

of natural type of (G) in the domain of IRS-2 molecule between two putative tyrosine phosphorylation sites (1042 and 1072 positions), may cause changes in downstream signals through IRS-2 (27).

The results of our study show that genotype GG and AA genotypes of Gly1057Asp polymorphism of IRS-2 gene are related to development of T2DM to some extents. Most of the reviewed studies in this meta-analysis showed that frequency of DD genotype among patients with T2DM was higher than that of non-diabetic individuals (20-23,25,28). These and other studies have been proven, the presence of a direct relationship between D allele of Gly1057Asp IRS-2 and T2DM (30,32,39,40). Nevertheless, others reported that DD genotype was lower in T2DM patients than the compared group (24,26,27) while, some of them have failed to show the relationship between the subjected polymorphism and susceptibility to T2DM (33-35,38), which are not consistent with our results. Bodhini et al showed that D1057D genotype of IRS-2 among

Asian-Indians interacts with susceptible to diabetes and obesity. Their survey revealed the DD genotype role in susceptibility to T2DM which appears only in the case of obesity and indicated that DD genotype could be used as a genetic indicator for obese individuals who have more susceptibility to T2DM (21). Other researcher argued that D1057 allele is negatively and positively related to T2DM among non-obese and obese patients, respectively. This means that D1057 allele could increase the risk of diabetes among obese persons (27). We combined the obtained results from studies conducted in this regard and observed a mild association between D1057D genotype of IRS-2 and increased risk of T2DM. Hence, it could be considered AA genotypes of Gly1057Asp polymorphism of IRS-2 gene as a risk factor for the development of T2DM.

Our survey also showed that genotype GA of Gly1057Asp polymorphism of IRS-2 gene plays a protective role and may decrease the risk of T2DM. Among included studies, six of them found that frequency of genotype GA of Gly1057Asp polymorphism among non-diabetic individuals was higher than that of patients with T2DM (21-24,27,28). Whereas, others reported that, this genotype was higher in T2DM patients than non-diabetic group (20,25,26). Some studies indicated a direct relationship between genotype GA of Gly1057Asp IRS-2 and decreased risk of T2DM (21,28). These findings suggest that the genotype might act as a protective factor against T2DM, which are consistent with our results. The studies among Japanese and Italian population indicated that IRS-2 gene may act as a modifier of insulin sensitivity among T2DM patients (22,27). D'Alfonso et al examined the effect of IRS-2 variant on cellular function in fibroblasts from carriers of different types of genotypes. They found that Gly1057Asp polymorphism does not change expression level tyrosine phosphorylation of IRS-

2 in response to insulin, it also caused no disturbance in capability of IRS-2 to bind to p85, the regulatory unit of PI 3-kinase (24). These results are in support of the idea that Gly1057Asp variant does not influence IRS-2 performance. Thereby, it could be concluded that Gly1057Asp variant of IRS-2 does not influence insulin secretion levels and insulin sensitivity or does not disturb the performance of IRS-2. Furthermore, Fritsche et al found no proof for the role of Gly1057Asp polymorphism of IRS-2 on functional biodiversity of the beta cells. Their results indicated that capacity of beta cells is not affected by the presence of this polymorphism. They concluded that Gly1057Asp in IRS-2 does not play an independent role in β -cell dysfunction (26). These results are very inconsistent with the idea that IRS-2 polymorphism plays a key role in pathogenesis of T2DM (24,26). Similarly, we found no relationship between Gly1057Asp polymorphism of IRS-2 gene and development of T2DM. Since the Gly1057Asp polymorphism is the most common genetic variant of IRS-2 in human, it does not seem to be probable that this protein acts as a protector of the genetic variant effective on the major way of reduction of insulin secretion and development of T2DM (26).

Conclusion

The present meta-analysis from nine published articles does not find a significant relationship between Gly1057Asp polymorphisms and the increased risk of T2DM. Our study also showed that genotype GA of Gly1057Asp polymorphism of IRS-2 may decrease the risk of T2DM, whereas homozygous genotypes for the Gly1057Asp variant (GG and AA genotypes) were partly associated with development of T2DM. We found a considerable difference between the frequencies of Gly1057Asp polymorphisms on IRS-2 gene in different studies. Geographical differences may partially explain variations in distribution of the genotypes. In addition, differences in body mass index and age of the subjects also explain different results to some extents. Moreover, differences in the methods used to assess T2DM may account for the disparity. It is notable in summary that small number of studies in this field hints necessity of further studies in different populations to examine effects of Gly1057Asp polymorphism on IRS-2 gene and to clarify its relationship with T2DM.

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Authors' contribution

FK, FS, KS and SB search the data and analyzed the paper and prepared the primary draft. NS and AHD edited and finalized the manuscript. All authors read and signed the

final paper.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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