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Peroxisome proliferator-activated receptor Pro12Ala polymorphism and the risks of gestational diabetes mellitus

An updated meta-analysis of 12 studies

Lihong Wang, MD, PhD[a,*], Wenting Xu, MD, MSc[a], Xu Wang, PhD[b]

Abstract

Background: Peroxisome proliferator-activated receptors-λ (PPAR-λ) is a member of nuclear receptor superfamily and acts as a ligand-dependent transcription factor often found in the adrenal gland, the spleen, and adipose tissue. The Pro12Ala polymorphism of PPAR-λ has been associated with the risks of gestational diabetes mellitus (GDM); however, association studies have provided conflicting results. The aim of this Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) compliant meta-analysis is to reach a more up-to-date and accurate estimation of the relationship between Pro12Ala genetic polymorphisms and the risks of GDM.

Methods: Eligible studies were retrieved by searching PubMed, EMBASE, Web of Science, Ovid, WanFang, and Chinese National Knowledge Databases and selected according to a pre-defined inclusion criterion. The risk of bias was assessed using the Newcastle-Ottawa quality assessment scale. The per-allele odds ratio (OR) of risk allele proline (Pro) was compared between cases and controls in each study to describe the association between the Pro allele and an individual's risk of GDM. The ORs were pooled using both the random-effects model (the DerSimonian and Laird method) and the fixed effects model (the Mantel-Haenszel method) and the 95% confidence interval (95% CI) was calculated using Woolf method.

Results: The final meta-analysis included a total of 11 articles of 12 data sets consisting of 7054 controls and 2980 GDM cases. Our results demonstrate that the Pro allele is not associated with GDM [OR: across multiple populations, 95% CI: 0.98–1.24; $P(Z)=0.01$; $P(Q)=0.003$]. In the stratified analysis by ethnicity, significantly increased risks were found for the Chinese (OR = 2.36; 95% CI: 1.47–3.78) and Korean (OR = 1.39; 95% CI: 1.00–1.93) populations.

Conclusion: These data suggest the potential role of Pro allele in the pathogenesis of GDM in Asian populations. Although the funnel plot of included studies showed assymetry, the results using the "trim and fill" method did not alter the conclusion of this study.

Abbreviations: Ala = alanine, BMI = body mass index, CI = confidence Interval, GDM = gestational diabetes mellitus, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PPAR-λ = peroxisome proliferator-activated receptors-λ, Pro = Proline.

Keywords: genetic polymorphism, gestational diabetes mellitus, gestational diabetes, meta-analysis, peroxisome proliferator-activated receptors, Pro12Ala

1. Introduction

Gestational diabetes mellitus (GDM) is defined as the intolerance of glucose that was not present or detected before preganacy[1] and often occurs when a woman's pancreatic function is not sufficient to overcome the diabetogenic environment of pregnancy.[2] GDM is the most common metabolic disorder during pregnancy,[3] and its frequency has further increased in the past decade, with increases ranging from 10% to 100% in different groups of patients and ethnicities.[4–6] Recent trends such as the decrease in physical activity,[7] epidemic of obesity,[8] and adoption of unhealthy lifestyles may all contribute to the increasing prevalence of GDM.[9]

Although the exact disease etiology of GDM is still very much unknown, evidence to date suggests that it is a careful interplay between environmental factors and genetic background.[10] Considerable research has been devoted to identifying potential genetic factors that contribute to GDM, and many genome-wide association studies have been conducted.[11,12] The list of variants associated includes polymorphism within genes such as *CDKAL1*, *IGF2BP2*, *KCNQ1*, *KCNF11*, *MTR1B*, *TCF7L2*, *PPAR*, etc.[13–18]

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[a] Zhangjiagang Hospital of Chinese Medicine, Zhangjiagang, [b] The First Clinical College, Nanjing University of Chinese Medicine, Nanjing, People's Republic of China.

[*] Correspondence: Lihong Wang, Zhangjiagang Hospital of Chinese Medicine, Zhangjiagang, Jiangsu, 215600, People's Republic of China (e-mail: wanglihong8008@163.com).

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Table 1

The Newcastle–Ottawa quality assessment scale for studies included in this meta-analysis.

Ref.	Adequacy of case definition	Representative of the cases	Selection of controls	Definition of controls	Comparability of cases/controls	Ascertainment of exposure	Same method of ascertainment
Cheng et al[35]	*	*	*	*		*	NA
Cho et al[38]	*	*	*	*		*	
Chon et al[39]	*	*	*	*		*	*
Du et al[36]	*	*		*	*	*	NA
Heude et al[40]	*	*	*			*	*
Lauenborg et al[14]	*	*	*	*		*	*
Pappa et al[41]	*	*	*			*	*
Shaat et al[43]	*	*	*	*		*	*
Shaat et al[43]	*	*	*	*		*	*
Shaat et al[42]	*	*	*	*		*	*
Tok et al[44]	*	*	*	*	*	*	*
Zhu et al[37]	*	*	*		*	*	

dependent transcription factor often found in the adrenal gland, the spleen, and adipose tissue.[19–21] PPAR-λ forms heterodimers with the retinoid X receptors and regulates various genes involved in metabolism and adipocyte differentiation.[22,23] Furthermore, PPAR-λ has been shown to have diverse functions such as negatively regulates macrophage activation,[24] inhibits the production of monocytes inflammatory cytokines,[25] adipogenesis, and insulin desensitization.[26] Mutations in the *PPAR-λ* gene have been associated with obesity and diabetes-related phenotypes, such as improved insulin sensitivity and plasma leptin levels.[27–29] The polymorphism of a proline (Pro) substituted with an alanine (Ala) at Amino acid 12 is a common polymorphism. The Ala allele is associated with reduced activity of PPAR-λ.[27] The Pro12Ala has been heavily researched for its role in obesity and type 2 diabetes and is considered one of the most common genetic risk factors for human diabetes.[30–32] However, studies have found conflicting results in Pro12Ala's role in GDM. For example, some studies have reported such a correlation, while other studies have found otherwise. To clarify the in-conflict findings reported so far as well as heterogeneity and publication bias that exists between studies, we have conducted a meta-analysis of genetic association studies of the PPAR-λ Pro12Ala polymorphism to assess its effect on the risk of GDM.

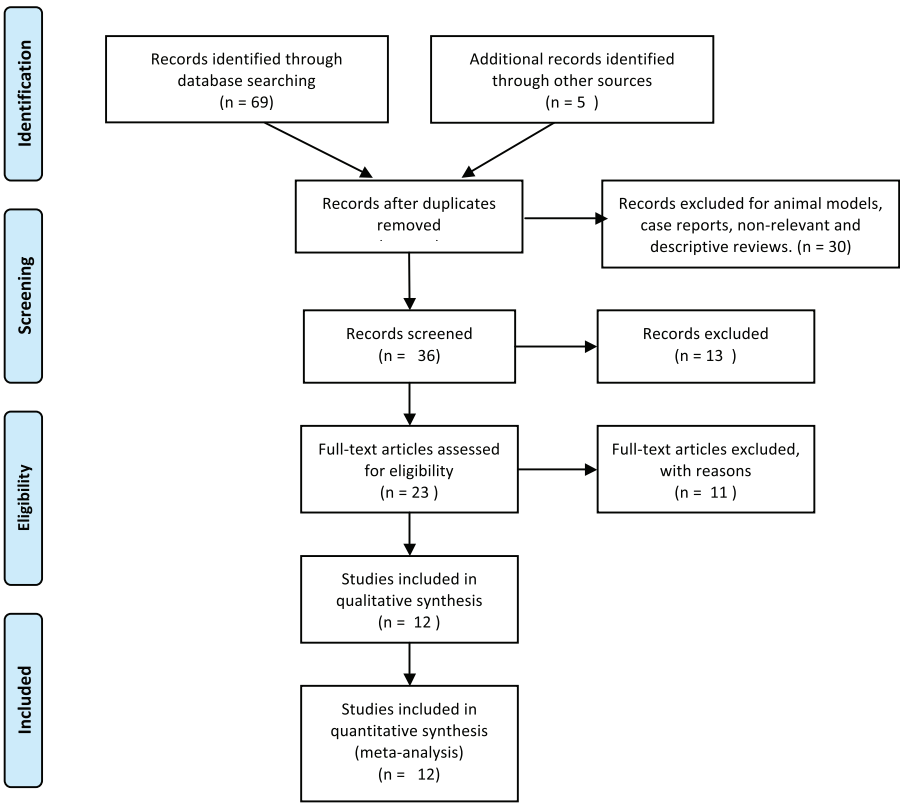

Figure 1. PRISMA flowchart of study selection.

Table 2

Characteristics of included studies.

Ref.	Year	Ethnicity	Genotyping method	Diagnostic criteria	Control	Number of cases/control	Genotype distribution		Mean age of case/control	Mean BMI of case/control	P (HWE) for controls
							Case	Control			
Cheng[38]	2010	Chinese	PCR-RFLP	OGTT confirmed	Normal glucose tolerant	55/173	52/3/0	157/16/0	27.0/29.6	NA/NA	0.5237
Cho[41]	2009	Korean	TaqMan	OGTT confirmed	Normal fasting glucose	865/632	793/71/1	567/63/2	32.0/64.7	23.1/23.3	0.8589
Chon[42]	2013	Korean	PCR-RFLP	OGTT confirmed	Non-diabetic participant	94/41	89/5/0	34/7/0	32.61/34.28	26.77/29.20	0.5501
Du[39]	2012	Chinese	PCR-RFLP	GDM per WHO criteria	Non-diabetic participant	66/69	59/7/0	57/12/0	29.24/28.29	NA/NA	0.4289
Heude[43]	2011	French	TaqMan	OGTT confirmed	Normal glucose tolerant	109/1587	92/17/0	1265/305/17	NA/NA	NA/NA	0.7715
Lauenborg[14]	2009	Dane	TaqMan	OGTT confirmed	Normal glucose tolerant	265/2383	201/60/4	1790/542/51	43.1/45.2	28.9/25.0	0.1892
Pappa[44]	2010	Greek	PCR-RFLP	GDM per IGDW criteria	Normal glucose tolerant	148/107	143/5/0	100/7/0	32.5/26.7	26.0/24.3	0.7265
Shaat[46]	2004	Arabian	PCR-RFLP	OGTT confirmed	Normal glucose tolerant	100/122	91/9/0	106/15/1	31.9/NA	30.9/NA	0.569
Shaat[46]	2004	Scandinavian	TaqMan	OGTT confirmed	Normal glucose tolerant	400/428	286/111/3	317/105/6	32.4/NA	28.9/NA	0.4136
Shaat[45]	2007	Swedish	TaqMan	OGTT confirmed	Nondiabetic participants	637/1232	468/158/11	918/298/16	32.3/30.5	NA/NA	0.1342
Tok[47]	2006	Turkish	PCR-RFLP	OGTT confirmed	Normal glucose tolerant	62/100	50/12/0	84/16/0	33.5/31.6	26.6/23.0	0.3845
Zhu[40]	2009	Chinese	PCR-RFLP	GDM patients	Nondiabetic participants	179/180	165/14/0	155/20/5	28.1/27.4	24.6/23.4	0.0003

OGTT = oral glucose tolerance testing, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.

2. Methods

2.1. Search strategy and inclusion criteria

We searched the literature hosted on PubMed, EMBASE, Web of Science, Ovid, WanFang, and Chinese National Knowledge Databases with keywords related to disease (e.g., "gestational diabetes mellitus," "GDM") and the gene of interest (e.g., "peroxisomal proliferator-activated receptor gamma," "PPAR-λ," or "PPARG"). Genetic association studies published before May 2016 were retrieved, and their references were checked to identify other relevant publications. No earlier date limit was applied. The search was conducted without any restrictions on the language used but focused on human subjects. We did not define a minimum number of patients as a criterion for a study's inclusion in this meta-analysis.

All retrieved study were screened, and all eligible studies included needed to satisfy each point of the following criteria: original papers containing independent data, pathological confirmation of GDM, case–control or cohort study, and genotype distribution information or odds ratio (OR) with its 95% confidence interval (CI) and *P* value. The major reasons for exclusion of studies were overlapping data; review articles, case-only studies, and family-based studies.

2.2. Ethic approval

Ethic approval was deemed unneccesary, as this study is a systematic-review.

2.3. Data extraction

Data extraction was performed independently by 2 reviewers (WL, XP). All data were checked for internal consistency and disagreements were resolved through careful discussion between all authors. For each study, the following were extracted from each article: first author's name, publication year, diagnostic criterion, definition and numbers of cases and controls, frequency of genotypes, genotyping method, source of controls, Hardy–-Weinberg equilibrium (HWE), age, body mass index (BMI), and ethnicity. Studies with different ethnic groups were considered as individual studies for our analyses.

2.4. Risks of bias between individual studies

The Newcastle–Ottawa Scale (NOS) was used for quality assessment. The 3 parameters assessed by NOS in case–control studies are selection, comparability, and exposure; stars were assigned to each parameter according to criteria in the NOS manual.[33,34] Selection is evaluated by the definition and assignment of cases and controls (see Table 1).[35–44] The comparability of the article focuses on the design and analysis of the study. Potential of bias was determined by the method of ascertainment of both cases and controls. The risk of bias is considered high if a study obtained 1 or 0 stars for selection, comparability, and exposure. Two stars for selection, 1 star for compatibility, and 2 stars for exposure are the minimum requirement for a study to be considered having a medium risk. Finally, the risk of bias is recognized as low if a study was awarded 4 stars for selection, 2 stars for comparability, and 3 stars for the ascertainment of exposure.

2.5. Statistical analysis

The association strength between PPAR-λ Pro12Ala polymorphism and GDM was assessed by calculating OR with 95% CI.

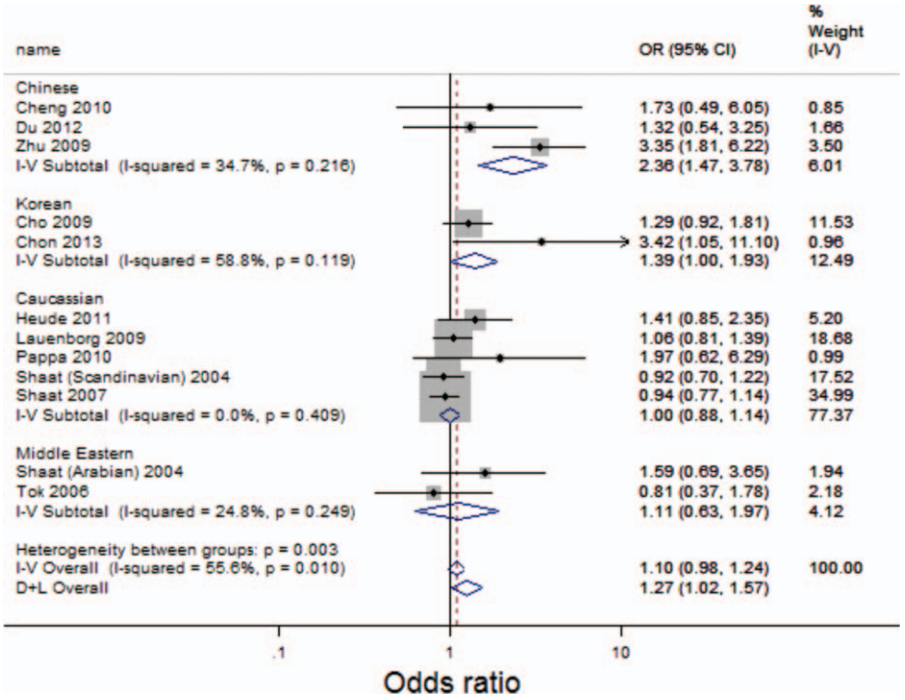

Figure 2. Forest plot of GDM risk associated with the Pro allele at amino acid position 12. CI = confidence interval, D + L = DerSimonian and Laird method, I-V = inverse variance, OR = odds ratio.

The χ^2 test was used to evaluate whether there is a significant deviation from HWE among the control subjects of the study. The per-allele OR of risk allele proline (Pro) was compared between cases and controls in each study to quantitatively describe the presence of the Pro allele and an individual's risk of GDM. The ORs were pooled using both the random-effects model (the DerSimonian and Laird method) and the fixed effects model (the Mantel–Haenszel method) as previously described,[45,46] and 95% CI was calculated using Woolf method.[47] The results of the random effects model were reported in this article because it takes into consideration the variation between studies. A prespecified stratified analysis was conducted to explain the heterogeneity between each study and to investigate the relationship present in a subgroup. Stratified analysis was performed for ethnicity (Caucasian, Chinese, Korean, and Middle Eastern).

Heterogeneity across individual studies was examined using Cochran χ^2 Q test.[48] Q test was also performed to detect the heterogeneity within each subgroup. Publication bias was assessed using the linear regression approach to measure funnel plot asymmetry on the natural logarithm of OR, as described by Egger et al.[49] All statistical analysis were carried out with Stata statistical software version 13.0 (Stata Corporation, College Station, TX). Type I error rate was set at 0.05, and all *P* values were for 2-sided analysis.

3. Results

3.1. Study characteristics

The search yielded a combined 69 references. Study selection process is shown in Fig. 1. The final meta-analysis included a total of 11 articles of 12 data sets.[14,35–44] The 12 data sets included 7054 controls and 2980 GDM cases. The detailed characteristics of included studies are summarized in Table 2. Of the GDM cases, 300 were Chinese, 959 were Korean, 1559 were Caucasian, and 162 were Middle Eastern.

3.2. Meta-analysis results

Overall, there was no evidence of an association between the Pro12Ala variant and increased risks of GDM when all data sets

Table 3

Meta analysis of the PPAR-λ Pro12Ala polymorphism and the risks of GDM.

Total/Subgroup	Number of data sets	Number of cases/controls	Pro Allele		
			OR (95% CI)	*P* (Z)	*P* (Q)
Total	12	2980/7054	1.10 (0.98–1.24)	0.10	0.003
Chinese	3	300/422	2.36 (1.47–3.79)	0.01	0.22
Korean	2	959/673	1.39 (1.00–1.93)	0.05	0.12
Caucasian	5	1559/5737	1.00 (0.88–1.14)	0.99	0.41
Middle Eastern	2	162/222	1.11 (0.63–1.97)	0.71	0.25

95% CI = 95% confidence interval, OR = odds ratio.

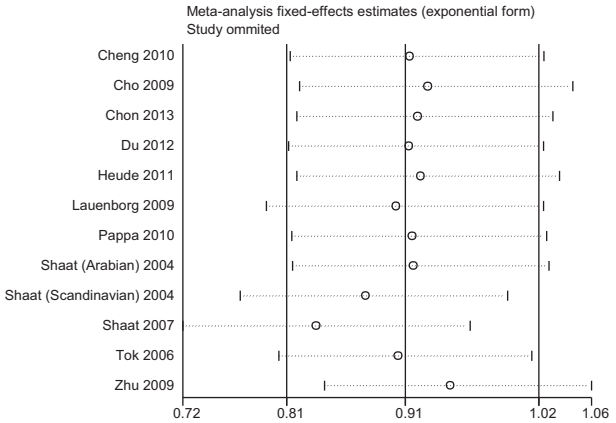

Figure 3. Sensitivity analysis of the Pro12Ala polymorphism and the risk of GDM.

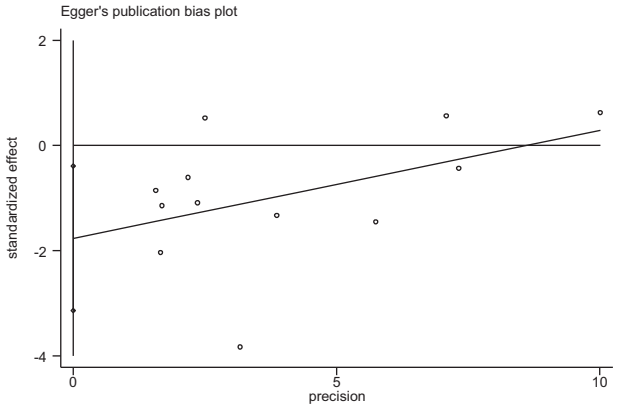

Figure 5. Egger's test of the Pro12Ala polymorphism ($P=0.005$). Ala = alanine, Pro = proline.

were pooled together. The per-allele OR of Pro using the random effects models was 1.10 [95% CI: 0.98–1.24; $P(Z)=0.01$; $P(Q)=0.003$; Fig. 2]. The main results of the meta-analysis are listed in Table 3.

In the stratified analysis by ethnicity, significantly increased risks were found for the Chinese (OR = 2.36; 95% CI: 1.47–3.78) and Korean (OR = 1.39; 95% CI: 1.00–1.93) population (See Fig. 2). However, no significant associations were detected for the Caucasian (OR = 1.00; 95% CI: 0.88–1.14) and Middle Eastern (OR = 1.11; 95% CI: 0.63–1.97) populations.

3.3. Sensitivity analysis

Sensitivity analyses using single-study omission demonstrated that this meta-analysis was stable (Fig. 3). Statistical significance of the summary ORs was not modified (data not shown). Therefore, the results of this study are stable.

3.4. Publication bias

Begger's and Eggar's funnel plots were constructed using the standard error and compared against the OR of each study (Figs. 4 and 5). The plots suggest the possibility of publication bias toward positive findings in smaller studies. The Duval and Tweedie nonparametric "trim and fill" method was utilized to adjust for publication bias[50] and its results did show different conclusions (data not shown). Thus, this indicates that this meta-analysis is statistically robust.

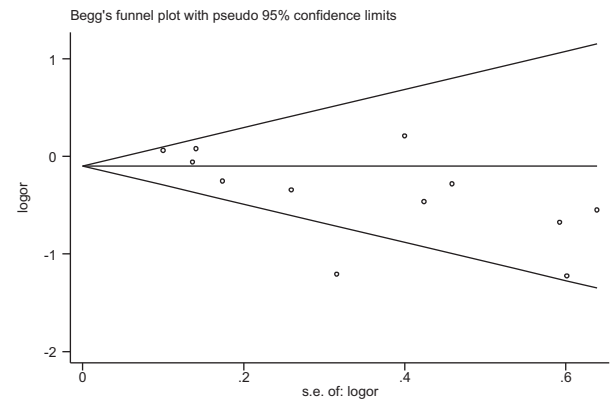

Figure 4. Funnel plot of the Pro12Ala polymorphism shows a possible excess of smaller studies with positive findings beyond the 95% CI. Ala = alanine, CI = confidence interval, logor = log odds ratio, Pro = proline, s.e = standard error.

4. Discussion

PPAR-λ is a ligand-dependent transcription factor involved in many body functions, including adipogenesis and also regulates immune responses.[20,25] The substitution of a Pro to Ala at site 12 is associated with reduced PPAR-λ activities[27] and has been identified as a possible polymorphism involved obesity and type 2 diabetes.[30–32]

Our up-to-date meta-analysis summarizes the evidence to date regarding the association between PPAR-λ Pro12Ala and GDM using a total of 7054 controls and 2980 GDM cases. Our study suggests that Pro12Ala is not associated with the risks of GDM.

In our stratified analysis by ethnicity, a strong association was observed for both the Chinese (OR: 2.36, 95% CI: 1.47–3.78) and Korean (OR: 1.39, 95% CI: 1.00–1.93) population but not for the Caucasian (OR = 1.00, 95% CI = 0.88–1.14) and Middle Eastern (OR = 1.11, 95% CI = 0.63–1.97) populations. These results indicate that the association of the polymorphism has a genetic and possibly environmental background factor in contributing to the pathology of GDM. Other factors such as differences in matching criteria and selection bias could also play a role in the difference between ethnic groups. It should also be noted that the analysis only included 3 Chinese studies and 2 Korean studies. This suggests the possibility that the observed differences may be due to chance. Thus, additional studies are required to increase the statistical power and validate the racial difference of the Pro12Ala polymorphism and GDM risk.

The preferential publication of studies with positive results is a significant source of bias in many meta-analyses. However, the included studies in our meta-analysis also consist of studies with negative conclusions. Although our funnel plots showed asymmetry, the results using the "trim and fill" method did not alter the conclusion of this study. This suggests that the bias may not be caused by publication bias but by potential heterogeneity between each study's population, language bias, citation bias, or simply by chance.

Several limitations should be noted in interpreting our results. We were not able to adjust for potential confounding effects conferred by gender, environmental factors, and lifestyle due to the lack of data. Our results were based on unadjusted estimates —a more precise analysis could be conducted if all raw data were available. The lack of individual health and metabolic data, such as fasting plasma glucose levels, β-cell function, and indices for insulin sensitivity also forbid us from performing a more sensitive analysis.

In conclusion, the pooled results of our meta-analysis indicate that Pro12Ala is not associated with the risks of GDM. However, in the Chinese and Korean populations, the Pro allele is strongly associated with the risks for GDM. Larger association studies with strict selection criteria are required to validate this result.

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