Tohoku J. Exp. Med., 2025, **266**, 19-28

Review

Correlation Between *ENPP1* Gene rs1044498 Polymorphism with the Risk of Type 2 Diabetes Mellitus: A Meta-analysis

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As a common metabolic disease, type 2 diabetes mellitus (T2DM) is regulated by the ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (ENPP1). A functional polymorphism of ENPP1 (rs1044498, K121Q) has been found to contribute to T2DM susceptibility. This study aims to analyze the combined association of ENPP1 rs1044498 polymorphism with T2DM risk. We searched for publications in Embase, Medline, EBSCO, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang databases from January 2010 to December 2023. Pooled association strength was analyzed using either a random-effects or fixed-effects model, and expressed as combined odds ratios (ORs) with 95% confidence intervals (CIs). Data analysis was performed by STAT 12.0. Due to high heterogeneity, a random-effects model was used for the calculation. In the total population, ENPP1 rs1044498 was evidently related to an increased susceptibility to T2DM under the following models: Q vs. K (OR = 1.405, 95% CI = 1.059-1.863), KQ + QQ vs. KK (OR = 1.475, 95% CI = 1.075-2.023), QQ vs. KK + KQ (OR = 2.355, 95% CI = 1.302-4.262), QQ vs. KK (OR = 3.096, 95% CI = 1.393-6.882) and KQ vs. KK (OR = 1.399, 95% CI = 1.038-1.885). In ethnic subgroups, rs1044498 was associated with T2DM risk in Asians under the following models: Q vs. K (OR = 1.480, 95% CI = 1.017-2.154), KQ + QQ vs. KK (OR = 1.578, 95% CI = 1.047-2.379), QQ vs. KK+ KQ (OR = 3.709, 95% CI = 1.727-7.967), QQ vs. KK (OR = 5.049, 95% CI = 1.784-16.397) and KQ vs. KK (OR = 1.478, 95% CI = 1.008-2.167). The distinct association between rs1044498 and T2DM risk was discovered in the diagnostic criteria not shown subgroup and plasma subgroup. This study demonstrated high sensitivity with minimal publication bias. The ENPP1 121Q allele is a risk factor for T2DM, particularly in the Asian population.

Keywords: *ENPP1*; meta-analysis; rs1044498; type 2 diabetes mellitus
Tohoku J. Exp. Med., 2025 May, **266** (1), 19-28.
doi: 10.1620/tjem.2024.J057

Introduction

Diabetes mellitus (DM) is a metabolic disease featured by high blood glucose (Burnett et al. 2024). It's caused by insufficient insulin secretion and/or impaired biological function of insulin. DM is categorized into type 1 DM (T1DM) and type 2 DM (T2DM), while T2DM is the more common and has a high incidence rate that has been increasing in recent years (Wang et al. 2021). The exact causes of T2DM remain unknown. However, several studies have identified environmental risk factors such as aging, lifestyle, overnutrition, and obesity, all of which contribute to the development of T2DM (Lambrinou et al. 2019; Olm et al. 2020; Zhang et al. 2020). The onset of T2DM shows significant genetic heterogeneity (Redondo et al. 2020; Shi et al. 2021). Variations and polymorphisms in many genes, which alter the expression or function of the gene, may play a role in the mechanism of T2DM (Sayed and Nabi 2021).

Ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (ENPP1), also known as plasma cell membrane glycoprotein 1 (PC-1), is a type II transmembrane glycoprotein with pyrophosphatase and phosphodiesterase activities outside cells. Its activity depends on Ca^{2+} and Zn^{2+}, and is involved in the progression of hormones, nerves, immunity, and so on (Ruiz-Fernandez de Cordoba et al. 2023). ENPP1 is widely expressed in different tissues, and its dys-

Received March 19, 2024; revised and accepted June 22, 2024; J-STAGE Advance online publication July 4, 2024
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regulation can contribute to various diseases (Roberts et al. 2019). Overexpression of the ENPP1 protein can lead to insulin resistance and hyperglycemia by directly interacting with the subunit of the insulin receptor (Grarup et al. 2006; Roberts et al. 2021). Polymorphisms of *ENPP1* gene are associated with disease susceptibility (Chen et al. 2017; Di et al. 2018; Marchenko et al. 2018b; Sortica et al. 2019; Wong et al. 2022). Both rs7754586 and rs55725924 polymorphisms were closely related to T2DM susceptibility (Chen et al. 2017). The Q121 allele of *ENPP1* can affect the glucose and insulin levels during fasting (Arianti et al. 2021). *ENPP1* gene K121Q (rs1044498) polymorphism is widely explored in T2DM development. Albegali et al. (2019) found that rs1044498 was obviously related to T2DM risk under a dominant model in a Pakistan population. Conversely, Yako et al. (2015) indicated that rs1044498 had no obvious association with T2DM susceptibility. Marchenko et al. (2018a) indicated that the 121Q allele was positively correlated with T2DM susceptibility. However, results vary among different studies.

Therefore, the current meta-analysis study aimed to collect relevant articles to examine the cumulative association of ENPP1 rs1044498 polymorphism with T2DM risk.

Materials and methods

Publication search

Eligible studies were searched from Embase, Medline, EBSCO, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang databases. Present meta-analysis selected *ENPP1* gene rs1044498 (K121Q) polymorphism. Search terms for this study were [(diabetes mellitus OR diabetes OR DM OR T2DM) AND (rs1044498 OR *ENPP1* K121Q OR *ENPP1* Lys121Gln OR *ENPP1* K173Q OR *ENPP1* Lys173Gln OR *ENPP1* polymorphisms OR PC-1 polymorphisms)]. To identify other relevant articles, a manual search of eligible papers was also performed.

Inclusion and exclusion criteria

This study includes papers that meet the following criteria: (1) the paper is a case-control study that includes a T2DM group and a normal glucose group; (2) it provides sufficient data on *ENPP1* gene rs1044498 genotypes; (3) there are no restrictions on baseline features. Papers are excluded from this study if they meet the following criteria: (1) genotype distribution in control group does not conform to the Hardy-Weinberg equilibrium (HWE) test; (2) they do not provide sufficient data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs); (3) they are letters, reviews, case reports, abstracts, or editorials; (4) they do not focus on *ENPP1* polymorphisms in T2DM. If multiple articles are written by the same authors, only the most recent one is included. Eligible studies are assessed by two independent authors, and any differences are resolved through discussion.

Data extraction and analysis

The following data were extracted from each article: first author's name, publication year, ethnicity, genotype distribution, number of cases and controls, age, gender, and genotype method. Newcastle-Ottawa Scale (NOS) score (Stang 2010) was used to evaluate the quality of each eligible study. NOS scores range from 0 to 9, with scores ≥ 5 considered high-quality and included in this study. STATA 12.0 was used for the meta-analysis. The Cochran Q test

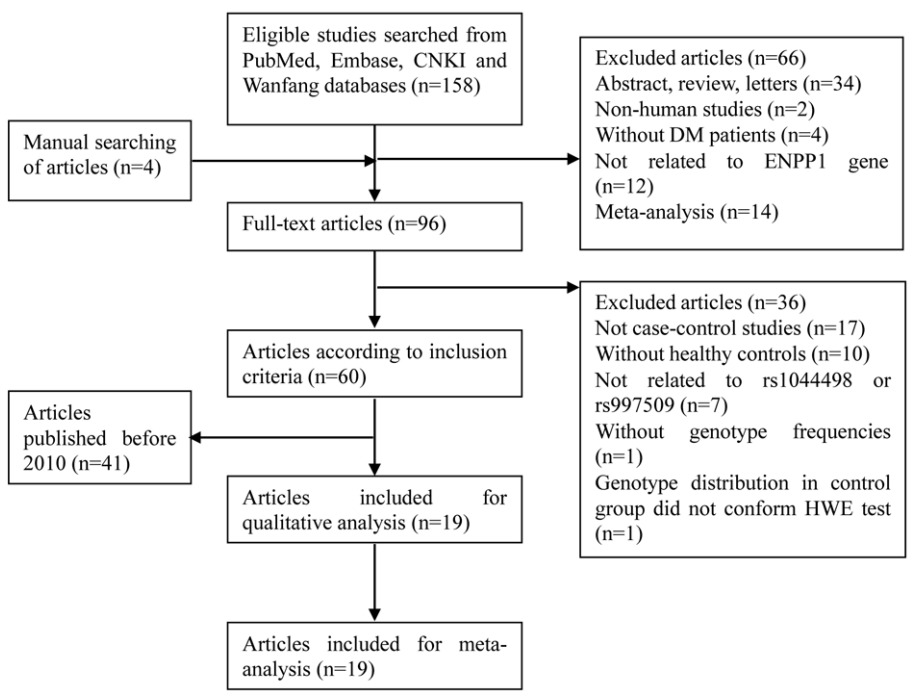

Fig. 1. Flowchart of the meta-analysis.

Table 1. Characteristics of eligible studies in this meta-analysis.

First author	Year	Ethnicity (Country)	Diagnostic criteria	Case		Control		Control source	P_{HWE} of control	Genotyping method	Samples	NOS score
				No. (male/female)	Age	No. (male/female)	Age					
Zhang	2010	Asian (China)	ADA	100 (52/48)	56.40 ± 12.1	150 (78/72)	55.20 ± 15.1	HB	0.723	PCR-RFLP	plasma	6
Lan	2010	Asian (China)	WHO	50 (22/28)	55	48 (23/25)	50	PB	0.42	PCR-RFLP	plasma	8
Bhatti	2010	Asian (India)	ADA	328 (174/154)	58.7 ± 10.3	326 (143/183)	55.1 ± 14.0	PB	0.201	PCR-RFLP	leukocytes	8
Lee	2010	Asian (Korea)	ADA	269 (128/141)	56.7 ± 13.7	195 (86/109)	64.2 ± 2.7	HB	0.658	PCR	plasma	8
Shi	2011	Asian (China)	ADA	639 (321/318)	69.20 ± 6.30	885 (496/389)	67.80 ± 5.69	PB	0.141	PCR-RFLP	plasma	7
Zhao	2011	Asian (China)	WHO	1879 (752/1127)	63.80 ± 9.00	2014 (968/1046)	58.10 ± 9.00	HB	0.447	PCR-RFLP	plasma	8
Luo	2011	Asian (China)	WHO	147	-	83	-	-	0.518	PCR-RFLP	-	6
Saberi	2011	Caucasian (Iran)	WHO	155	-	377	-	PB	0.006	PCR-RFLP	plasma	6
Wang	2012	Asian (China)	WHO	88 (43/45)	56.73 ± 9.23	245 (135/110)	53.92 ± 5.92	HB	0.091	PCR-RFLP	plasma	9
Wang	2012	Asian (China)	-	416 (206/211)	57.28 ± 9.74	188 (77/111)	57.25 ± 10.53	HB	0.087	TaqMan	plasma	9
Zhang	2014	Asian (China)	ADA	146 (81/65)	53.9 ± 19.5	238 (53/185)	36.11 ± 10.8	PB	0.053	PCR-RFLP	plasma	8
Zou	2015	Asian (China)	WHO	56 (24/32)	60.4 ± 9.3	52 (24/28)	61.2 ± 7.5	HB	0.159	PCR-RFLP	leukocytes	9
Yako	2015	African (South Africa)	WHO	152 (34/118)	60.1 ± 11.8	319 (18/310)	53.2 ± 13.5	PB	0.219	TaqMan	plasma	8
Hsiao	2016	Asian (China)	-	553 (292/261)	62.2 ± 8.9	960 (457/503)	61.7 ± 4.6	PB	0.324	TaqMan	plasma	8
Sumi	2017	Asian (India)	-	160	55.4 ± 10.7	271	45.32 ± 12.99	HB	0.274	PCR-RFLP	plasma	7
Sharafshah	2018	Caucasian (Iran)	WHO	537 (151/386)	52.31 ± 9.09	441 (180/261)	56.74 ± 12.44	HB	0.1	TaqMan	leukocytes	7
Marchenko	2018	Caucasian (Ukraine)	-	317	-	302	-	-	0.598	PCR-RFLP	plasma	7
Albegali	2019	Asian (Pakistan)	-	161 (82/79)	-	161 (82/79)	-	HB	0.791	PCR-RFLP	plasma	7
Zhang	2021	Asian (China)	-	138	-	405	-	HB	0.488	PCR-RFLP	plasma	8

HB, hospital-based; PB, population--based; P_{HWE}, *P* value for Hardy-Weinberg Equilibrium; -, not shown; ADA, American Diabetes Association; WHO, World Health Organization.

Table 2. Genotype and allele distributions of *ENPP1* polymorphisms in subjects.

First author	Year	Ethnicity	Case						Control					
			No.	KK	KQ	QQ	K	Q	No.	KK	KQ	QQ	K	Q
Zhang	2010	Asian	100	89	11	0	189	11	150	131	19	0	281	19
Lan	2010	Asian	50	41	9	0	91	9	48	38	10	0	86	10
Bhatti	2010	Asian	328	199	129	0	527	129	326	195	131	0	521	131
Lee	2010	Asian	269	224	45	0	493	45	195	183	12	0	378	12
Shi	2011	Asian	639	508	123	8	1139	139	885	701	178	6	1580	190
Zhao	2011	Asian	1879	1463	393	23	3319	439	2014	1610	385	19	3605	423
Luo	2011	Asian	147	37	76	34	150	144	83	72	11	0	155	11
Saberi	2011	Caucasian	155	109	45	1	263	47	377	255	119	3	629	125
Wang	2012	Asian	88	68	18	2	154	22	245	184	60	1	428	62
Wang	2012	Asian	416	256	129	31	641	191	188	149	34	5	332	44
Zhang	2014	Asian	146	115	20	1	250	22	238	213	25	0	451	25
Zou	2015	Asian	56	41	7	0	89	7	52	35	17	0	87	17
Yako	2015	African	152	38	73	41	149	155	319	72	175	81	319	337
Hsiao	2016	Asian	553	368	153	32	889	217	960	754	197	9	1705	215
Sumi	2017	Asian	160	16	104	40	136	184	271	200	63	8	463	79
Sharafshah	2018	Caucasian	537	301	215	17	817	249	441	296	121	20	713	161
Marchenko	2018	Caucasian	317	188	108	21	484	150	302	205	86	11	496	108
Albegali	2019	Asian	161	153	7	1	313	9	161	130	29	2	289	33
Zhang	2021	Asian	138	102	36	0	240	36	405	312	93	0	717	93

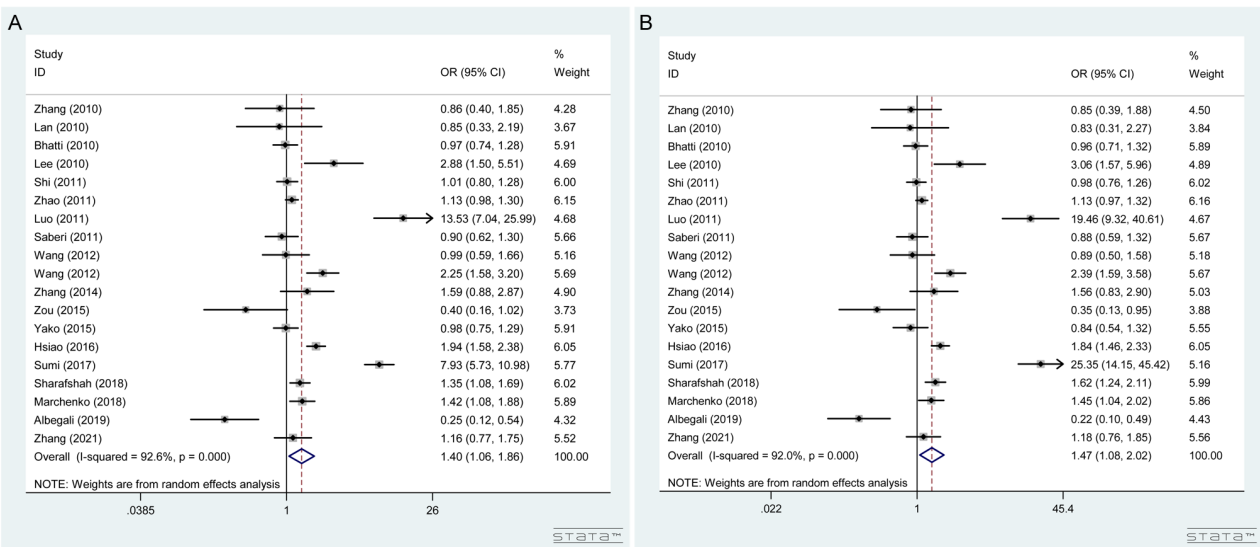

Fig. 2. Forest plot for pooled odds ratios (ORs) and 95% confidence intervals (CIs) for *ENPP1* rs1044498 genotype using a random-effects model.
A, Forest plot for all eligible studies under Q vs. K model; B, Forest plot for all eligible studies under KQ + QQ vs. KK model.

and I^2 statistical test were performed to conduct the heterogeneity (Zintzaras and Ioannidis 2005). $P < 0.05$ or $I^2 > 50\%$ were defined as obvious heterogeneity, then the random-effects mode was used to estimate pooled effects (DerSimonian and Laird 2015). Elsewise, a fixed-effects model was performed (Mantel and Haenszel 1959). Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were evaluated using the Z test. The potential source of heterogeneity was investigated by subgroup analysis via binary data. Publication bias was evaluated by Begg's test (Begg and Mazumdar 1994).

Results

Characteristics of eligible studies

Initially, 158 articles were collected from Medline, EBSCO, PubMed, Embase, CNKI, and Wanfang databases.

Table 3. Meta-analysis of association between *ENPP1* polymorphisms and diabetes mellitus risk.

Polymorphism	Association		Heterogeneity			Bias
	OR (95%CI)	*P*	Q	*P*	I^2	*P*
Q vs. K						
All	1.405 (1.059-1.863)	0.018	244.34	0.000	92.6%	0.576
Asian	1.480 (1.017-2.154)	0.041	231.70	0.000	94.4%	
Caucasian	1.239 (0.973-1.577)	0.082	4.37	0.112	54.3%	
African	0.985 (0.750-1.293)	0.912	0.00	-	-	
HB	1.301 (0.803-2.108)	0.285	160.34	0.000	94.4%	
PB	1.146 (0.869-1.513)	0.334	30.88	0.000	80.26%	
non	4.304 (0.453-40.929)	0.204	40.34	0.000	97.5%	
ADA	1.229 (0.889-1.698)	0.211	11.5	0.022	65.2%	
WHO	1.276 (0.875-1.860)	0.205	66.1	0.000	89.4%	
-	1.643 (0.870-3.101)	0.126	110.66	0.000	95.5%	
plasma	1.345 (0.985-1.836)	0.062	183.79	0.000	92.4%	
leukocytes	0.988 (0.649-1.505)	0.956	8.35	0.015	76.0%	
-	13.527 (7.041-25.988)	0.000	0.00	-	-	
KQ+QQ vs. KK						
All	1.475 (1.075-2.023)	0.016	226.00	0.000	92.0%	0.834
Asian	1.578 (1.047-2.379)	0.029	215.75	0.000	93.5%	
Caucasian	1.311 (0.940-1.830)	0.111	6.14	0.046	67.4%	
African	0.844 (0.538-1.324)	0.460	0.00	-	-	
HB	1.436 (0.836-2.467)	0.190	148.10	0.000	93.9%	
PB	1.105 (0.833-1.464)	0.488	22.74	0.001	73.6%	
non	5.199 (0.403-67.097)	0.206	40.27	0.000	97.5%	
ADA	1.236 (0.864-1.769)	0.247	12.14	0.016	67.0%	
WHO	1.293 (0.809-2.066)	0.283	72.8	0.000	90.4%	
-	1.909 (0.878-4.148)	0.103	111.78	0.000	95.5%	
plasma	1.395 (0.992-1.961)	0.056	161.56	0.000	91.3%	
leukocytes	0.975 (0.539-1.763)	0.933	12.62	0.002	84.1%	
-	19.459 (9.324-40.613)	0.000	0.00	-	-	
QQ vs. KK+KQ						
All	2.355 (1.302-4.262)	0.005	55.98	0.000	78.6%	0.304
Asian	3.709 (1.727-7.967)	0.001	29.19	0.000	72.6%	
Caucasian	1.075 (0.493-2.343)	0.856	3.96	0.138	49.6%	
African	1.126 (0.727-1.744)	0.594	0.00	-	-	
HB	2.136 (0.770-5.928)	0.145	32.67	0.000	84.7%	
PB	2.176 (0.824-5.744)	0.117	16.66	0.002	76.0%	
non	7.999 (0.168-381.219)	0.292	7.19	0.0077	86.1%	
ADA	2.060 (0.751-5.652)	0.161	0.37	0.544	0.0%	
WHO	1.317 (0.696-2.495)	0.398	12.99	0.023	61.5%	
-	3.738 (1.650-8.466)	0.002	14.97	0.005	73.3%	
plasma	2.456 (1.359-4.437)	0.003	39.71	0.00	74.8%	
leukocytes	0.687 (0.355-1.328)	0.264	0.00	-	-	
-	50.762 (3.068-839.860)	0.006	0.00	-	-	
QQ vs. KK						
All	3.096 (1.393-6.882)	0.006	95.772	0.000	87.5%	0.244
Asian	5.409 (1.784-16.397)	0.003	61.46	0.000	87.0%	
Caucasian	1.230 (0.608-2.488)	0.564	3.31	0.191	39.5%	
African	0.959 (0.557-1.652)	0.880	0.00	-	-	
HB	3.053 (0.708-13.160)	0.134	65.33	0.000	92.3%	
PB	2.163 (0.721-6.490)	0.169	19.53	0.001	79.5%	

non	14.194 (0.108-1860.062)	0.286	11.23	0.001	91.1%	
ADA	2.053 (0.747-5.638)	0.163	0.41	0.522	0.0%	
WHO	1.553 (0.700-3.446)	0.279	17.85	0.003	72.0%	
-	5.138 (1.328-19.885)	0.018	38.77	0.000	89.7%	
plasma	2.947 (1.261-6.886)	0.013	74.46	0.000	86.9%	
leukocytes	0.836 (0.429-1.627)	0.598	0.00	-	-	
-	133.400 (7.955-2236.956)	0.001	0.00	-	-	
KQ vs. KK						
All	1.399 (1.038-1.885)	0.027	188.83	0.000	90.5%	0.484
Asian	1.478 (1.008-2.167)	0.046	176.88	0.000	92.1%	
Caucasian	1.316 (0.903-1.917)	0.153	7.34	0.025	72.7%	
African	0.790 (0.490-1.275)	0.335	0.00	-	-	
HB	1.392 (0.826-2.348)	0.214	129.86	0.000	93.1%	
PB	1.062 (0.843-1.339)	0.609	14.63	0.023	59.0%	
non	4.186 (0.443-39.594)	0.212	29.87	0.000	0.000	
ADA	1.217 (0.848-1.746)	0.287	12.15	0.016	67.1%	
WHO	1.228 (0.787-1.918)	0.366	61.39	0.000	88.6%	
-	1.751 (0.827-3.708)	0.144	96.30	0.000	94.8%	
plasma	1.327 (0.960-1.833)	0.087	135.88	0.000	89.7%	
leukocytes	0.985 (0.517-1.877)	0.963	14.62	0.001	86.3%	
-	13.445 (6.374-28.357)	0.000	0.00	-	-	
QQ+KK vs. KQ						
All	0.779 (0.605-1.002)	0.052	139.04	0.000	87.1%	0.529
Asian	0.757 (0.549-1.042)	0.088	125.12	0.000	88.8%	
Caucasian	0.771 (0.525-1.131)	0.183	7.76	0.021	74.2%	
African	1.238 (0.842-1.819)	0.278	0.00	-	-	
HB	0.793 (0.511-1.231)	0.301	96.28	0.000	90.7%	
PB	0.959 (0.782-1.175)	0.685	12.22	0.057	50.9%	
non	0.342 (0.065-1.795)	0.205	17.68	0.000	94.3%	
ADA	0.825 (0.574-1.184)	0.296	12.19	0.016	67.2%	
WHO	0.866 (0.593-1.265)	0.457	46.50	0.000	84.9%	
-	0.694 (0.387-1.245)	0.221	64.08	0.000	92.2%	
plasma	0.812 (0.617-1.067)	0.135	101.39	0.000	86.2%	
leukocytes	1.013 (0.528-1.944)	0.969	15.07	0.001	86.7%	
-	0.143 (0.070-0.291)	0.000	0.00	-	-	

OR, odds ratio; 95% CI, 95% confidence interval; bias, Publication bias; HB, hospital-based; PB, population-based; non, not described; -, not shown; ADA, American Diabetes Association; WHO, World Health Organization.

These articles, related to ENPP1 rs1044498 polymorphism and T2DM, were published between January 2010 and December 2023. After reviewing the abstracts, 66 articles were excluded from this study (34 were abstracts, reviews, or letters; 2 were not related to humans; 4 lacked DM patients, and 12 were not related to the *ENPP1* gene). Upon examining the full text, 36 articles were further excluded. Moreover, 41 articles published before 2010 were removed. Ultimately, 19 articles (including 6,291 cases and 7,660 controls) (Bhatti et al. 2010; Lan 2010; Lee et al. 2010; Zhang et al. 2010; Zhang et al. 2014; Luo et al. 2011; Saberi et al. 2011; Shi et al. 2011; Zhao et al. 2011; Wang et al. 2012a, b; Yako et al. 2015; Zou et al. 2015; Hsiao and Lin 2016; Sumi et al. 2017; Marchenko et al. 2018a; Sharafshah et al. 2018; Albegali et al. 2019; Zhang et al. 2021) were included in this meta-analysis (Fig. 1 and Table 1). Subjects of 3 studies were Caucasians, 15 were Asians, and 1 was Africans. All eligible studies had an NOS score more than 5 (Table 1).

Meta-analysis for association between ENPP1 polymorphisms and T2DM risk

Genotype and allele distributions of *ENPP1* rs1044498 polymorphism are listed in Table 2. Significant heterogeneity was found for rs1044498 under various models, including Q vs. K, KQ + QQ vs. KK, QQ vs. KK + KQ, QQ vs. KK, KQ vs. KK, and QQ + KK vs. KQ ($P < 0.05$, $I^2 > 50\%$, Table 2), requiring the association analysis to be performed

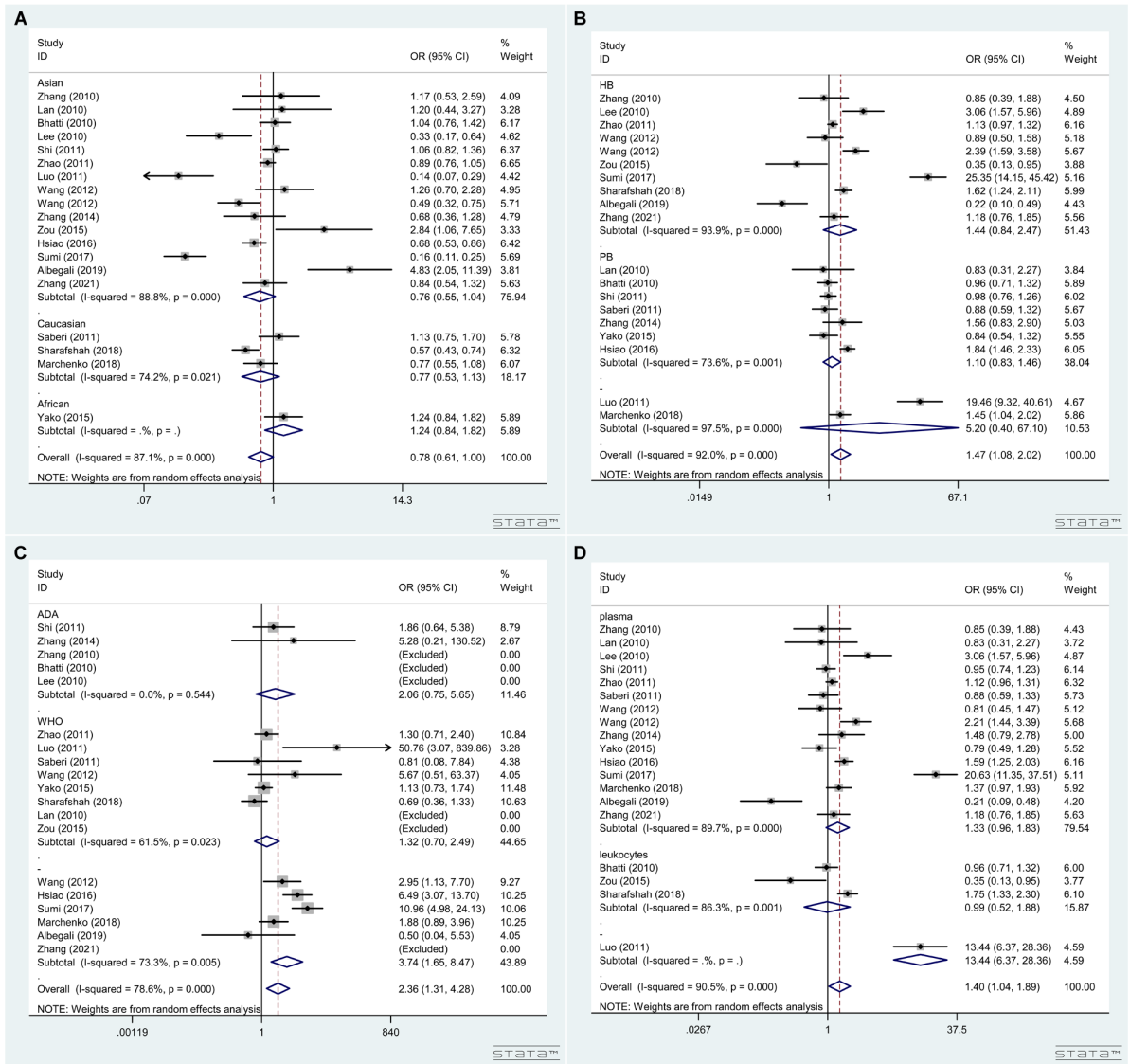

Fig. 3. Subgroup analysis for *ENPP1* rs1044498 polymorphism in T2DM.
A, Forest plot for subgroup analysis based on ethnicity under QQ + KK vs. KQ model; B, Forest plot for subgroup analysis based on control source under KQ+QQ vs. KK model; C, Forest plot for subgroup analysis based on diagnostic criteria under QQ vs. KK + KQ model; D, Forest plot for subgroup analysis based on samples under KQ vs. KK model.

under random-effect model. *ENPP1* rs1044498 was found to be significantly associated with an increased risk of T2DM under Q vs. K (OR = 1.405, 95% CI = 1.059-1.863, Fig. 2A), KQ + QQ vs. KK (OR = 1.475, 95% CI = 1.075-2.023, Fig. 2B), QQ vs. KK + KQ (OR = 2.355, 95% CI = 1.302-4.262), QQ vs. KK (OR = 3.096, 95% CI = 1.393-6.882) and KQ vs. KK (OR = 1.399, 95% CI = 1.038-1.885) models.

Subgroup analysis for association between rs1044498 polymorphism and T2DM risk

Subgroup analysis was also conducted based on ethnicity, control source, diagnostic criteria, and samples under all genetic models to seek the source of heterogeneity (Table 3). According to the subgroup analysis of ethnicity, rs1044498 was significantly associated with T2DM risk in Asians respectively under Q vs. K (OR = 1.480, 95% CI = 1.017-2.154), KQ + QQ vs. KK (OR = 1.578, 95% CI = 1.047-2.379, Fig. 3A), QQ vs. KK + KQ (OR = 3.709, 95% CI = 1.727-7.967), QQ vs. KK (OR = 5.049, 95% CI = 1.784-16.397) and KQ vs. KK (OR = 1.478, 95% CI = 1.008-2.167) models, but not Caucasian and African subgroups. No distinct correlation was discovered between rs1044498 and T2DM susceptibility in non (not described), PB (population-based), and HB (hospital-based) subgroups (Fig. 3B). Subgroup analysis based on diagnostic criteria indicated that rs1044498 was significantly correlated with T2DM susceptibility under QQ vs. KK + KQ (OR = 3.738, 95% CI = 1.650-8.466, Fig. 3C), QQ vs. KK (OR = 5.138, 95% CI = 1.328-19.885) is not shown subgroup. Significant

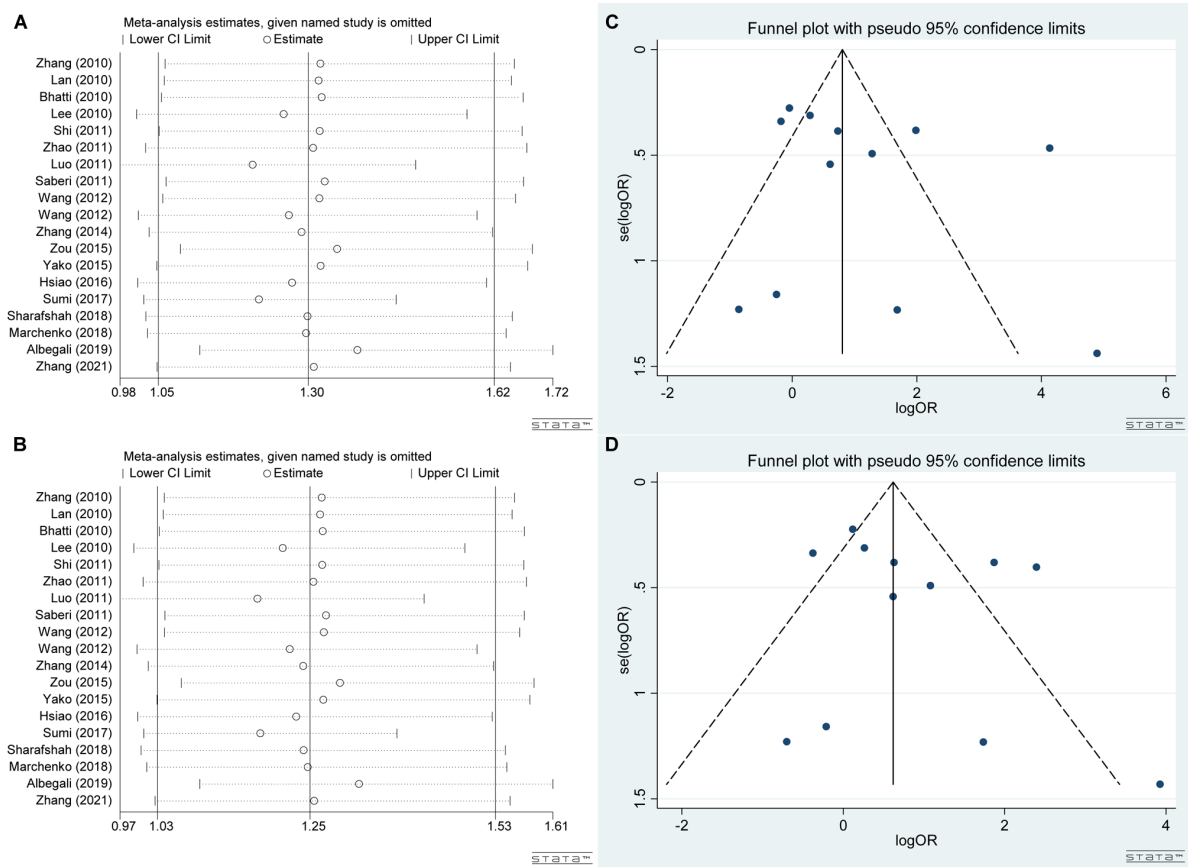

Fig. 4. Sensitivity analysis and publication bias analysis for *ENPP1* rs1044498 polymorphism.
A, for Q vs. K model; B, for KQ + QQ vs. KK model. C, for QQ vs. KK model, Begg's test $P = 0.244$; D, for QQ vs. KK + KQ mode, Begg's test $P = 0.304$.

association also has been discovered between rs1044498 and T2DM susceptibility in subgroup analysis based on samples under QQ vs. KK + KQ (OR = 2.456, 95% CI = 1.359-4.437), QQ vs. KK (OR = 2.947, 95% CI = 1.261-6.886) in plasma subgroup. Only one article did not show the samples for DNA extraction, the association between rs1044498 and T2DM risk was significant under all genetic models in this subgroup (Fig. 3D). Further subgroup analysis under other genetic models is shown in Table 3. High heterogeneity was discovered in all subgroup analyses, suggesting ethnicity, control source, diagnostic criteria, and samples might be the source of heterogeneity.

Sensitivity analysis and publication bias

We used the one-by-one elimination method to assess the sensitivity among all eligible articles. We found that the pooled ORs of rs1044498 did not significantly change (Fig. 4A,B). Symmetric funnel plots for all eligible rs1044498 studies showed no noticeable publication bias in any genetic models (Begg's test: $P > 0.05$, Fig. 4C,D).

Discussion

In recent years, due to the aging population, the global incidence rate of T2DM has increased. Prior analyses suggest that genetic factors play a crucial role in T2DM development (Redondo et al. 2020; Shi et al. 2021). More specifically, the ENPP1 protein regulates insulin receptors, decreasing their tyrosine kinase activity, which results in insulin resistance (Bhatti et al. 2010). Furthermore, overexpression of ENPP1 suppresses insulin resistance signaling by reducing its β-subunit phosphorylation (Lee et al. 2010). *ENPP1* rs1044498 polymorphism, a missense variant in exon 4 (c.517A > C) of *ENPP1* gene, results in an amino acid change from lysine (K) 121 to glutamine (Q) and alters the protein's function (Bhatti et al. 2010). This polymorphism has been found to stabilize insulin receptor interaction and inhibit insulin signaling more in rs1044498 C allele carriers than in A allele carriers (Hsiao and Lin 2016). However, there were no previous studies focused on the effects of rs1044498 on *ENPP1* expression. Previous studies have identified rs1044498 as a risk factor for insulin resistance (Roberts et al. 2021), T2DM (Hsiao and Lin 2016), and obesity (Grarup et al. 2006) in various backgrounds. Numerous meta-analyses have also indicated that rs1044498 is a risk factor for T2DM in Caucasians and Asians (Abate et al. 2005; Li 2012; Tang et al. 2014).

Our meta-analysis included studies published between 2010 and 2023, unlike previous meta-analyses that only

enrolled studies published before 2013. The NOS score of all eligible studies was higher than 5, suggesting these articles were of high quality for meta-analysis. The heterogeneity analysis for rs1044498 was significantly higher, so we analyzed the pooled association using a random-effects model. Our findings indicated a clear correlation between the 121Q allele and an elevated T2DM risk, with increases of 1.405, 1.475, 2.355, 3.096, and 1.399 times. Subgroup analysis showed that rs1044498 was significantly associated with increased T2DM susceptibility in Asian populations, but not in Caucasian and African subgroups. Subgroup analysis based on the control source revealed no significant association between rs1044498 and T2DM risk under 6 genetic models. Subgroup analysis based on diagnostic criteria suggested that rs1044498 was positively correlated with T2DM risk in articles not show diagnostic criteria, but not in American Diabetes Association (ADA) and World Health Organization (WHO) subgroups. An obvious correlation between rs1044498 and T2DM susceptibility was discovered in the plasma subgroup. High heterogeneity existed in all subgroups, indicating control source, diagnostic criteria, and samples were the source of heterogeneity. Sensitivity analysis demonstrated that our results were highly robust. Symmetric funnel plots indicated that there was no obvious publication bias in the eligible studies.

Present results are consistent with previous meta-analyses. Wang et al. (2010) conducted a meta-analysis involving 10 Chinese studies, finding that the 121Q allele was significantly associated with an increased risk of T2DM in the Chinese Han population. Li's meta-analysis also found similar results within the Chinese population (Li 2012). Abate et al. (2005) analyzed four papers published before 2010. Their collective results suggested that the 121Q allele was negatively correlated with T2DM risk. Tang et al. (2014) collected 40 studies published before 2013 for their meta-analysis. They found that the K121Q polymorphism was positively associated with T2DM risk in all populations, specifically the Caucasian and Asian populations (Wang et al. 2010). These results were also stable. However, they noted a larger publication bias than our study under the Q vs. K model. These discrepancies could be due to the different studies included. In our meta-analysis, only three studies focused on Caucasians and one on Africans, which is less than in previous meta-analyses.

Despite the good robustness and lower publication bias observed in the current meta-analysis, its limitations should not be overlooked. Firstly, articles published before 2010 that met the inclusion criteria were not included in this study. Secondly, a subgroup analysis based on other types of DM, such as T1DM and gestational diabetes mellitus (GDM), was not conducted, due to a lack of original articles. Thirdly, the study did not consider gene-environment interactions or the effects of the genotyping method used for association analysis. Lastly, all polymorphisms in the ENPP1 gene were not examined, meaning the mechanism of ENPP1 in Diabetes Mellitus development remains unexplored.

In summary, the current study found that individuals carrying 121Q allele had a significantly higher susceptibility to T2DM, especially in the Asian population. A larger meta-analysis, incorporating all related research, should be conducted in the future to explore the association of rs1044498 with DM susceptibility among all DM subtypes.

Conflict of Interest

The authors declare no conflict of interest.

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