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Meta-Analysis

Meta-analysis of insights into *HHEX* (rs1111875) and *SLC30A8* (rs13266634) gene variants and type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is aggravated by inherited factors, peripheral insulin resistance and environmental factors. Genome wide association studies (GWAS) revealed more than 400 genetic loci to be associated with T2DM. The function of *HHEX* gene rs1111875 variant and the insulin secretion response after a glucose load might impact the risk of T2DM mainly via altering pancreatic β-cell activity. The *Solute Carrier Family 30, Member 8* (*SLC30A8*) is primarily expressed in pancreatic β-cells and may play a key role in insulin secretory pathway. This current study revealed a significant association between *HHEX* A>G variant and reduced risk of T2DM under allele (A vs G: p=0.004), codominant (AA vs GG: p=0.001), dominant (AA vs AG + GG: p=0.02) and recessive (AA + AG vs GG: p=0.002) inheritance models and lack of significant association between *HHEX* C>T variant and T2DM in all tested models. However, *SLC30A8* C>T variant was associated with increased risk of T2DM under allele (C vs T: p=0.001), dominant (CC vs CT+TT: p=0.001), codominant [(CC vs CT: p=0.007) and (CC vs TT: p<0.001)] and recessive (CC+CT vs TT: p=0.001) inheritance models. The findings of the study suggest that *HHEX* (rs1111875) and *SLC30A8* (rs13266634) gene variants may contribute to the genetic predisposition to T2DM.

Keywords: *HHEX*, *SLC30A8*, Type 2 diabetes mellitus, Meta-analysis

INTRODUCTION

Diabetes mellitus (DM) is a severe metabolic condition defined by fasting and postprandial hyperglycemia. DM is a broad category of long-term metabolic condition which impairs the regulation of blood sugar level due to insulin resistance or inadequate insulin production and the prevalence has been rising fast in low and middle-income countries.[1] According to the World Health Organization (WHO), age-standardized mortality rates due to diabetes increased by 3% between 2000 and 2019. It was estimated that the prevalence rate of diabetes among adults aged 18 years and above increased substantially from 7% in 1990 to 14% in 2022.[2] Type 2 diabetes mellitus (T2DM) is aggravated by inherited factors, peripheral insulin resistance and environmental factors.[3,4] The most frequent diabetes is categorized as T2DM, often known as adult-onset diabetes, which typically develops between the ages of 35 and 40.[5] Genetic background of the individuals play an important role in the etiopathogenesis of T2DM.[6] Genome wide association studies (GWASs) revealed more than 400 genetic loci to be associated with T2DM.[7] Several serious ailments, including cancer, heart diseases, hypertension, and gestational diabetes mellitus, have been associated with T2DM.[8]

The haematopoietically expressed homeobox or *HHEX* gene (MIM: 604420), located on chromosome 10q23.33, activates hepatocyte nuclear factor (HNF)-1a, which regulates the maturation and function of beta-cells. The protein produced by *HHEX* gene works as transcription factor that influences the Wnt signaling pathway, which is essential for cell growth and development.[9] The responsiveness and secretion of insulin are contingent

upon *HHEX* expression.[10] The single nucleotide variant (SNV) rs1111875 located at 3′ untranslated region (3′UTR) of *HHEX* gene is significantly associated with T2DM.[11] The impact of the *HHEX* gene on islet function and insulin signaling determines it as an important biological candidate.[11,12] The function of *HHEX* gene (rs1111875) variant and the insulin secretion response after a glucose load might impact the risk of T2DM mainly via altering pancreatic β-cell activity.[11] *HHEX* gene has been identified as a plausible candidate gene for T2DM risk by GWASs in various populations.[13]

Maintaining zinc homeostasis remains crucial for human health, and its imbalance may culminate in several conditions, such as diabetes, cancer, autoimmunity, Alzheimer's and cardiovascular diseases. The zinc transporter gene, *Solute Carrier Family 30 Member 8* (*SLC30A8*; MIM: 611145), produces a 369-amino acid protein that is primarily expressed in pancreatic β-cells and may play a key role in insulin secretory pathway.[14] Zinc carrier ZnT8, encoded by *SLC30A8* (rs13266634) gene, located on chromosome 8q24.11, promotes maturation, storage and secretion of insulin by transferring zinc from the cytoplasm to insulin secretion granules in the pancreas.[15] The expression level of *SLC30A8* is lower in submaxillary glands, testicles and other organs, but it is robustly expressed in the alpha and beta cells of the pancreatic islet.[16] Previous GWASs have demonstrated an association between *SLC30A8* gene variant and predisposition to T2DM across various populations.[14,17,18]

The present meta-analysis of the association between *HHEX* and *SLC30A8* gene variants and T2DM is carried out to address disagreements and minimize the possibility of inadvertent mistakes leading to false positive or negative comparisons of the individual studies. In this analysis, *HHEX* A>G, *HHEX* C>T and *SLC30A8* C>T gene variants were analyzed using published data of case-control studies.

METHODS

Selection of pertinent studies

The study was conducted between March 2024 and September 2024. A thorough and methodical search of published research articles related to *HHEX* and *SLC30A8* gene variants and T2DM was carried out using PubMed, CNKI, Baidu Scholar, Google Scholar and ScienceDirect databases. The preferred reporting items for systematic reviews and meta-analyses guideline was adopted to conduct this study.[19] Relevant search terms and Boolean combinations were used to identify studies examining *HHEX* and *SLC30A8* genetic variants in relation to T2DM. The search strategy included combinations of terms such as *HHEX*, "*hematopoietically expressed homeobox*," *SLC30A8*, "zinc transporter 8," "type 2 diabetes mellitus," "T2DM," "genetic variant," "polymorphism," "single nucleotide polymorphism," "genotype," "allele," "genetic susceptibility," "genetic risk," and "genetic association." Database-specific search strategies were adapted according to the indexing and search functions of each database. Titles and abstracts of the retrieved records were screened to identify potentially relevant studies. The reference lists of eligible articles and relevant reviews were also examined manually to identify additional studies that might have been missed during the electronic database search. Potentially eligible articles were subsequently assessed in full text according to the predefined inclusion and exclusion criteria.

Inclusion and exclusion parameters

All articles obtained from the databases were examined manually to determine their suitability for inclusion in the analysis. The research articles with incomplete data were excluded from the analysis. The criteria for inclusion of the studies in this meta-analysis were: (i) Published articles related to *HHEX* and *SLC30A8* gene variants and protection and/or risk to T2DM and (ii) Case-control studies having complete genotyping data on *HHEX* and *SLC30A8* gene variants. The exclusion criteria were: (i) Review articles on association of *HHEX* and *SLC30A8* gene variants with risk/protection to T2DM (ii) Studies that were not related to *HHEX* and *SLC30A8* gene variants and (iii) Incomplete genotyping data or studies that did not reveal genotyping frequencies.

Data extraction

The authors reviewed each article and extracted data, addressed disputes, and confirmed all items. Selected data comprised the following information: (i) First author's name, (ii) Publication year, (iii) Country of origin, (iv) Ethnicity, (v) Number of cases, (vi) Number of controls, (vii) genotype frequencies in case and control groups. Furthermore, the Hardy–Weinberg equilibrium (HWE) was estimated using genotyping data. The characteristics of pertinent studies that were taken into consideration for this meta-analysis are presented in Table 1.

Statistical analysis

STATA (Release 17, College Station, USA) was used to analyze the data. The 95% confidence interval (95%CI) and a pooled odds ratio (OR) were used to determine the degree of association of *HHEX* and *SLC30A8* gene variants with T2DM risk/protection. The pooled ORs were determined for the allele (A vs G and C vs T), codominant (AA vs AG, AA vs GG and CC vs CT, CC vs TT), dominant (AA vs AG + GG and CC vs CT+TT) and recessive (AA + AG vs GG and CC+CT vs TT) inheritance models. The level of significance for pooled OR was determined using Z-test and $p<0.05$ was considered statistically significant. The heterogeneity among the studies was determined using Cochran's Q statistics and I^2 test. The existence of heterogeneity was considered when $P_{heterogeneity} <0.01$.[20,21] Random effects model and Mantel-Haenszel fixed effects model were used when the I^2 value was greater than 50% and less than 50%, respectively.[20] The existence of a publication bias was determined using Egger's linear regression test, $p<0.05$ was considered as statistically significant.[22]

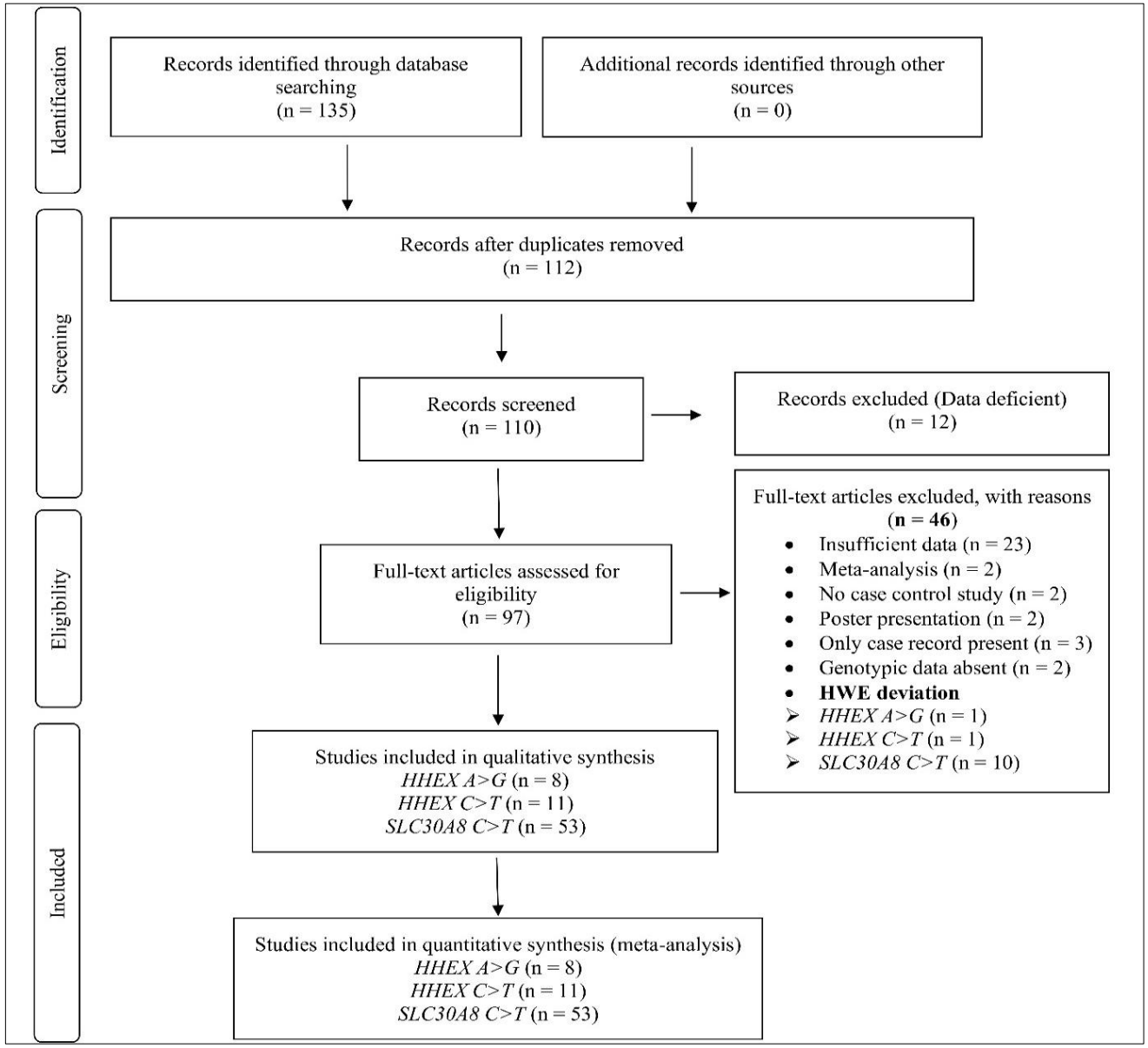

Figure 1: PRISMA flowchart representing the search strategy used to select pertinent studies.

Table 1: Characteristics of the relevant studies included in the analysis.

Authors	Year	Country	Ethnicity	Numbers		Case			Control			HWE	Ref.
				Case	Control	CC	CT	TT	CC	CT	TT		
***HHEX* (rs1111875)**													
Horikoshi et al	2007	Japan	Asian	860	860	394	371	95	461	342	57	0.5447	40
Cauchi et al	2008	France	European	114	4222	10	47	57	681	1968	1573	0.1164	35
Pivovarova et al	2008	Germany	European	221	470	88	97	36	171	215	84	0.2542	36
Rong et al	2009	USA	American	1401	1748	499	661	241	659	841	248	0.4376	38
Tabara et al	2009	Japan	Asian	490	396	44	211	235	35	158	203	0.5942	32
Zhou et al	2010	China	Asian	1852	1993	160	778	914	151	766	1076	0.3674	33
Gutiérrez-Vidal et al	2011	Mexico	Mestizos	234	455	91	111	32	159	220	76	0.9946	39
Sun et al	2016	China	Asian	249	537	26	61	162	44	189	304	0.0657	34
Liju et al	2020	India	Asian	1144	1087	231	505	408	156	493	438	0.3659	101
Li et al	2020	China	Asian	1169	1277	106	486	577	83	525	669	0.1343	28
Aka et al	2021	Bangladesh	Asian	250	246	48	112	90	78	138	30	0.0086	3
Shaker et al	2023	Iraq	Arabian	48	46	21	23	4	21	20	5	0.9419	37
***HHEX* (rs1111875)**				**Case**	**Control**	**AA**	**AG**	**GG**	**AA**	**AG**	**GG**		
Schulze et al	2007	Germany	European	686	2267	97	307	282	394	1101	772	0.966	29
Vliet-Ostaptchouk et al	2008	Netherlands	European	490	908	51	245	194	148	424	336	0.4652	30
Furukawa et al	2008	Japan	Asian	405	340	185	177	43	186	136	18	0.2747	23
Kommoju et al	2016	India	Asian	729	590	248	350	131	189	289	112	0.9349	46
Khodyrev et al	2016	Russia	Asian	440	264	199	168	73	140	101	23	0.4403	25
Plengvidya et al	2018	Thailand	Asian	500	500	234	200	66	254	201	45	0.5656	44
Galavi et al	2019	Iran	Arabian	250	250	155	61	34	215	31	4	0.0605	13
Bhowmick et al	2020	India	Asian	155	100	43	94	18	33	35	32	0.0025	9
Banihashemi et al	2020	Iran	Arabian	108	100	8	11	89	73	0	27	0	78
Verma et al	2021	India	Asian	369	100	189	116	64	44	42	14	0.4437	27
***SLC30A8* (rs13266634)**				**Case**	**Control**	**CC**	**CT**	**TT**	**CC**	**CT**	**TT**		
Horikoshi et al	2007	Japan	Asian	860	859	149	383	328	172	394	293	0.0605	40
Sladek et al	2007	France	European	2562	2878	1440	945	177	1413	1200	265	0.6566	66
Scott et al	2007	Finland	European	2342	2397	1011	1016	315	891	1138	368	0.8826	17
Zeggini et al	2007	United Kingdom	European	1550	2866	794	637	119	1393	1192	281	0.2675	67
Steinthorsdottir et al	2007	Iceland	European	3776	12361	1871	1542	363	5575	5304	1482	0.0001	47

Continued.

Author	Year	Country	Ethnicity	Case	Control	CC	CT	TT	CC	CT	TT	HWE	Ref.
Steinthorsdottir et al	2007	Africa	African	851	1082	804	45	2	1004	74	4	0.0838	47
Steinthorsdottir et al	2007	Hong Kong	Asian	1426	970	464	686	276	259	497	214	0.4012	47
Lee et al	2008	Korea	Asian	908	502	324	459	125	156	248	98	0.9747	43
Sanghera et al	2008	India	Asian	532	349	290	195	47	188	135	26	0.7958	61
Ng et al	2008	China	Asian	433	419	408	24	1	399	20	0	0.6167	45
Cauchi et al	2008	France	European	828	952	360	362	106	367	457	128	0.4461	35
Cauchi et al	2008	Austria	European	437	676	240	167	30	331	283	62	0.8926	35
Cauchi et al	2008	Europe	European	2715	4255	1453	1054	208	2114	1773	368	0.8907	35
Cauchi et al	2008	Morocco	African	517	421	360	145	12	292	118	11	0.8212	35
Cauchi et al	2008	Israel	Arabs	518	492	301	187	30	278	183	31	0.9043	35
Furukawa et al	2008	Japan	Asian	405	340	151	197	57	121	161	58	0.7225	23
Wu et al	2008	China	Asian	518	492	301	187	30	278	183	31	0.9043	48
Omori et al	2008	Japan	Asian	1614	1045	651	740	223	381	491	173	0.4868	49
Horikawa et al	2008	Japan	Asian	1830	1574	690	806	334	522	725	327	0.9003	31
Wang et al	2008	China	Asian	454	311	152	219	83	87	141	83	0.1004	64
Potapov et al	2009	Russia	Russian	588	597	7	231	350	35	244	318	0.1792	75
Tabara et al	2009	Japan	Asian	493	400	162	259	72	133	188	79	0.3949	32
Rong et al	2009	India	Asian	1381	1766	1156	209	16	1455	296	15	0.9899	38
Lin et al	2010	China	Asian	1529	1439	1348	178	3	1328	107	4	0.2859	62
Han et al	2010	China	Asian	992	993	386	457	149	327	487	179	0.9209	90
Huang et al	2010	China	Asian	443	229	134	211	98	64	93	72	0.0046	80
Gutiérrez-Vidal et al	2011	Mexico	Mestizos	455	234	252	176	27	17	89	128	0.7785	39
Wang et al	2011	China	Asian	236	218	82	117	37	48	95	75	0.0899	52
Li et al	2011	China	Asian	125	97	36	81	8	24	55	18	0.1721	65
Zheng et al	2012	China	Asian	227	152	65	114	48	48	76	28	0.828	42
Mohaddese et al	2012	East Azerbaijan	Iranian	125	125	62	63	0	53	71	1	0	81
Kommoju et al	2013	India	Asian	758	621	440	288	30	379	211	31	0.8162	24
Yu et al	2013	China	Asian	97	301	33	46	18	70	133	98	0.0595	53
Zhong and Chang	2013	China	Asian	100	100	23	46	31	27	50	23	0.9872	56
Almawi et al	2013	Lebanon	Arabs	995	1076	585	337	73	612	390	74	0.0106	86
Bazzi et al	2014		Arabs	89	96	62	21	6	69	26	1	0.3572	70
Salem et al	2014	Malaysia	Asian	423	253	158	192	73	84	127	42	0.606	50
Salem et al	2014	China	Asian	291	202	85	115	91	56	90	56	0.1213	50
Salem et al	2014	India	Asian	388	157	263	108	17	83	67	7	0.1389	50
Zhang et al	2014	China	Asian	123	125	48	56	19	30	65	30	0.6547	63

Continued.

Author	Year	Country	Ethnicity	Case	Control	CC	CT	TT	CC	CT	TT	HWE	Ref.
Faghih et al	2014	Iran	Iranian	151	155	90	51	10	89	49	17	0.0186	82
Abu-Seman et al	2015	Malaysia	Asian	506	438	208	215	83	153	202	83	0.2636	41
AliKhan et al	2015	India	Asian	250	250	148	87	15	152	79	19	0.0677	51
Liu et al	2015	China	Asian	136	145	52	64	20	32	84	29	0.0548	54
Zhang et al	2015	China	Asian	263	262	107	116	40	66	141	55	0.2051	57
Su et al	2016	China	Asian	932	932	466	402	64	432	403	97	0.8337	55
Phani et al	2016	India	Asian	578	579	293	236	49	339	209	31	0.869	59
Nikitin et al	2017	Russia	Russian	862	443	449	340	73	268	154	21	0.851	76
Plengvidya et al	2018	Thailand	Asian	500	500	172	242	86	137	268	95	0.0748	44
Sharif et al	2018	Palestine	Arabs	100	100	55	38	7	53	42	5	0.3499	71
Sarkar et al	2019	India	Asian	155	100	74	75	6	44	40	16	0.1893	58
Yazdi et al	2020	Iran	Iranian	106	162	5	23	78	16	64	82	0.5056	74
Soltanian et al	2020	Iran	Iranian	125	125	62	63	0	63	52	10	0.8722	73
Sargazi et al	2020	Iran	Iranian	450	453	205	164	81	161	187	105	0.0006	83
Alharbi et al	2021	Saudi Arab	Arabs	120	120	55	44	21	79	28	13	0.0006	84
Mashal et al	2021	Jordan	Arabs	358	326	228	116	14	172	132	22	0.6201	72
Aka et al	2021	Bangladesh	Asian	250	246	70	162	18	134	92	20	0.4601	3
Goyal et al	2022	India	Asian	400	200	44	158	198	6	42	152	0.1798	10
Jan et al	2022	Pakistan	Asian	100	100	50	38	12	66	23	11	0.0013	79
Muneam et al	2023	Iraq	Iranian	100	100	50	42	8	67	22	11	0.0007	87
Aişeoğlu et al	2023	Turkey	Turkish	43	52	34	3	6	38	12	2	0.4381	77
Ali et al	2024	Pakistan	Asian	100	97	61	30	9	57	35	5	0.2758	60
Mitu et al	2024	Bangladesh	Asian	163	75	111	45	7	26	44	5	0.0149	85

RESULTS

Study characteristics

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart describes the selection process of relevant studies for this meta-analysis and is presented in Figure 1. After completing the initial screening of *HHEX* A>G variant, a total of 8 studies were included with 3869 cases and 5219 controls. For *HHEX* C>T variant and T2DM risk/protection, a total of 11 studies comprising of 7782 cases and 13091 controls were included, while for *SLC30A8* C>T variant, 53 studies comprising of 35259 cases and 35588 controls were included in the analysis.

Among 8 studies with *HHEX* A>G variant, 5 were from Asian, 1 was from Arabian and 2 were from European populations.[13,23-30] Out of 11 studies with *HHEX* C>T variant, 6 were from Asian, 2 were from European and 1 each from Arabian, American and Mestizos populations.[3,28,31–39] Furthermore, out of 53 studies with *SLC30A8* variant, 35 were from Asian, 6 were from European, 4 were from Arabian, 2 each from Iranian, Russian and African and 1 each from Turkish and Mestizos populations.[3,10,17,23,31,32,35,38,39–77] The characteristics of the studies included in the analysis are presented in Table 1. The Hardy Weinberg equilibrium (HWE) test revealed that most of the studies were in HWE except one study related to *HHEX* A>G, two studies related to *HHEX* C>T and ten studies related to *SLC30A8* C>T gene variant.[3,9,47,78–87]

Quantitative synthesis

The findings of the tests of association and heterogeneity for *HHEX* and *SLC30A8* gene variants and T2DM are presented in Table 2. Significant heterogeneity was found in Cochran's Q statistics for all models tested in the current study. *HHEX A>G* variant showed an overall association with reduced risk of T2DM under allele (A vs G: p=0.004), codominant (AA vs GG: p=0.001), dominant (AA vs AG+GG: p=0.02) and recessive (AA+AG vs GG: p=0.002) inheritance models. However, a lack of significant association was observed between *HHEX C>T* variant and T2DM in all tested inheritance models. In contrast, *SLC30A8* C>T gene variant was significantly associated with increased risk of T2DM under allele (C vs T: p=0.001), dominant (CC vs CT+TT: p=0.001), recessive (CC + CT vs TT: p=0.001), codominant [(CC vs CT: p=0.007) and (CC vs TT: p<0.001)] inheritance models.

When subgroup analysis by ethnicity was performed, *HHEX* A>G gene variant showed significant association with reduced T2DM risk in Arbian population under all tested models [allele (A vs G): p<0.001, dominant (AA vs AG + GG): p<0.001, recessive (AA + AG vs GG): p<0.001, codominant (AA vs AG): p<0.001, (AA vs GG): p<0.001], in European population under allele (A vs G: p<0.001), dominant (AA vs AG + GG: p=0.001) recessive (AA + AG vs GG: p=0.001) and codominant (AA vs GG: p<0.001) inheritance models. Further, significant association between *HHEX* A>G variant and reduced risk of T2DM was also observed in Asian population under recessive (AA + AG vs GG: p=0.032) inheritance model. In addition, significant association was observed between *HHEX* C>T gene variant and reduced risk of T2DM in American ethnic group under allele (C vs T: p=0.04), codominant (CC vs TT: p=0.021) and recessive (CC + CT vs TT: p=0.02) inheritance models. A notable association was observed between *SLC30A8* C>T gene variant and increased risk of T2DM under all tested model [allele (C vs T): p=0.001, dominant (CC vs CT + TT): p=0.001, recessive (CC + CT vs TT): p=0.001, codominant (CC vs CT): p=0.007, (CC vs TT): p<0.001] inheritance models. Ethnicity wise subgroup analysis revealed an association between *SLC30A8* variant with increased risk of T2DM in Asian ethnicity under allele (C vs T: p=0.002), dominant (CC vs CT+TT: p=0.018), recessive (CC + CT vs TT: p<0.001), codominant (CC vs TT: p<0.001) inheritance models, European ethnic group under allele (C vs T: p<0.001), dominant (CC vs CT+TT: p<0.001), recessive (CC + CT vs TT: p<0.001), codominant (CC vs CT: p<0.001, CC vs TT: p<0.001) inheritance models, Mestizos ethnic group under all tested inheritance models [Allele (C vs T): p<0.001, dominant (CC vs CT + TT): p<0.001, recessive (CC+CT vs TT): p<0.001, codominant (CC vs CT): p<0.001, (CC vs TT): p<0.001], Arabian ethnic group under dominant (CC vs CT + TT: P=0.043), and codominant (CC vs CT: p=0.046) inheritance models. In contrast, this gene variant was associated with reduced risk of T2DM in Russian ethnic group under allele (C vs T: p<0.001, recessive (CC+CT vs TT: p=0.002) and codominant (CC vs TT: p=0.017) inheritance models.

Test of heterogeneity

Cochran's Q statistics revealed the presence of overall heterogeneity for *HHEX* A>G (allele: I^2 – 87.5%, dominant: I^2=82.8%, recessive: I^2=75.3%, codominant: I^2=73.5% and 77.6%), *HHEX* C>T (allele: I^2=82.6%, dominant: I^2=74.2%, recessive: I^2=77.7%, codominant: I^2=61.3% and 80.1%) and *SLC30A8* C>T (allele: I^2=89.3%, dominant $I^{2=}$82.9%, recessive: I^2=82.7%, codominant: I^2=76.4% and 83.2%) gene variants. Subgroup analysis also revealed very high heterogeneity for *HHEX* A>G variant in Asian ethnic group under allele ($P_{heterogeneity}$=0.004, I^2=73.9%) and codominant ($P_{heterogeneity}$=0.005, I^2=73.5%) inheritance models. In addition, a significantly high heterogeneity was observed for *HHEX* C>T variant in Asian ethnic group under allele ($P_{heterogeneity}$<0.001, I^2=86.1%), recessive ($P_{heterogeneity}$ <0.001, I^2=80.4%), codominant ($P_{heterogeneity}$=0.001, I^2=76.7% and $P_{heterogeneity}$<0.001, I^2=82.9%) inheritance models. Furthermore, subgroup analysis of *SLC30A8* C>T variant revealed very high heterogeneity in Iranian ethnic group under allele ($P_{heterogeneity}$=0.001, I^2=91%,), recessive ($P_{heterogeneity}$=0.005, I^2=87.2%) and codominant ($P_{heterogeneity}$ =0.008, I^2=85.9%) inheritance models, in Russian ethnic group under dominant ($P_{heterogeneity}$=0.003, I^2=88.8%) and codominant ($P_{heterogeneity}$=0.004, I^2=88.1%) inheritance models. Cochran's Q statistics and heterogeneity test for all tested models are presented in Figures 2-4 and Table 2.

Table 2: Meta-analysis of association between the *HHEX* (rs1111875) and *SLC30A8* (rs13266634) gene variants in type 2 diabetes mellitus.

	Population	No. of Studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	P value	Model	P value	I² (%)
***HHEX* A>G (rs1111875)**										
A vs G (Allele Model)	Overall	8	3869	5219	0.75	0.615 - 0.914	0.004	R	<0.001	87.5
	Asian	5	2443	1794	0.856	0.708 - 1.035	0.109	R	0.004	73.9
	Arabian	1	250	250	0.243	0.166 - 0.357	<0.001	F	-	-
	European	2	1176	3175	0.816	0.739 - 0.901	<0.001	F	0.733	-
AA vs AG (Codominant Model)	Overall	8	3869	5219	0.828	0.664 - 1.031	0.092	R	<0.001	73.5
	Asian	5	2443	1794	0.96	0.839 - 1.097	0.546	F	0.11	46.9
	Arabian	1	250	250	0.366	0.227 - 0.592	<0.001	F	-	-
	European	2	1176	3175	0.74	0.505 - 1.085	0.124	R	0.079	67.6
AA vs GG (Codominant Model)	Overall	8	3869	5219	0.579	0.415 - 0.807	0.001	R	<0.001	77.6
	Asian	5	2443	1794	0.671	0.443 - 1.016	0.059	R	0.005	73.5
	Arabian	1	250	250	0.085	0.029 - 0.244	<0.001	F	-	-
	European	2	1176	3175	0.647	0.523 - 0.799	<0.001	F	0.595	0
AA vs AG+GG (Dominant Model)	Overall	8	3869	5219	0.739	0.572 - 0.954	0.020	R	<0.001	82.8
	Asian	5	2443	1794	0.895	0.723 - 1.108	0.308	R	0.03	62.7
	Arabian	1	250	250	0.266	0.171 - 0.412	<0.001	F	-	-
	European	2	1176	3175	0.714	0.586 -0.869	0.001	F	0.20	39.0
AA+AG vs GG (Recessive Model)	Overall	8	3869	5219	0.664	0.511 - 0.861	0.002	R	<0.001	75.3
	Asian	5	2443	1794	0.679	0.476 - 0.967	0.032	R	0.015	67.6
	Arabian	1	250	250	0.103	0.036 - 0.296	<0.001	F	-	-
	European	2	1176	3175	0.796	0.693 - 0.914	0.001	F	0.188	42.3
***HHEX* C>T (rs1111875)**										
C vs T (Allele Model)	Overall	11	7782	13091	0.996	0.882 - 1.124	0.944	R	<0.001	82.6
	Asian	6	5764	6150	1.03	0.88 - 1.206	0.711	R	<0.001	86.1
	Arabian	1	48	46	1.015	0.551 - 1.869	0.963	F	-	-
	European	2	335	4692	0.848	0.494 - 1.458	0.552	R	0.003	88.3
	American	1	1401	1748	0.899	0.812 - 0.995	0.040	F	-	-
	Mestizos	1	234	455	1.158	0.921 - 1.456	0.211	F	-	-
CC vs CT (Codominant Model)	Overall	11	7782	13091	1.077	0.923 - 1.258	0.345	R	0.004	61.3
	Asian	6	5764	6150	1.156	0.896 - 1.491	0.264	R	0.001	76.7
	Arabian	1	48	46	0.87	0.371 - 2.037	0.748	F	-	-
	European	2	335	4692	0.902	0.501 - 1.623	0.73	R	0.117	59.3
	American	1	1401	1748	0.963	0.825 - 1.125	0.637	F	-	-
	Mestizos	1	234	455	1.134	0.804 - 1.6	0.473	F	-	-

Continued.

	Population	No. of Studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	P value	Model	P value	I² (%)
CC vs TT (Codominant Model)	Overall	11	7782	13091	1.028	0.797 - 1.324	0.834	R	<0.001	80.1
	Asian	6	5764	6150	1.118	0.807 - 1.55	0.503	R	<0.001	82.9
	Arabian	1	48	46	1.25	0.294 - 5.314	0.763	F	-	-
	European	2	335	4692	0.718	0.248 - 2.079	0.541	R	0.010	85.0
	American	1	1401	1748	0.779	0.63 - 0.963	0.021	F	-	-
	Mestizos	1	234	455	1.359	0.835 - 2.212	0.217	F	-	-
CC vs CT+TT (Dominant Model)	Overall	11	7782	13091	1.066	0.892 - 1.273	0.483	R	<0.001	74.2
	Asian	6	5764	6150	1.151	0.871 - 1.522	0.322	R	<0.001	82.9
	Arabian	1	48	46	0.926	0.41 - 2.089	0.853	F	-	-
	European	2	335	4692	0.799	0.353 - 1.808	0.591	R	0.025	80.2
	American	1	1401	1748	0.914	0.79 - 1.058	0.228	F	-	-
	Mestizos	1	234	455	1.185	0.855 - 1.641	0.308	F	-	-
CC+CT vs TT (Recessive Model)	Overall	11	7782	13091	0.955	0.81 – 1.126	0.582	R	<0.001	77.7
	Asian	6	5764	6150	0.997	0.826 – 1.204	0.977	R	<0.001	80.4
	Arabian	1	48	46	1.341	0.337 – 5.342	0.677	F	-	-
	European	2	335	4692	0.807	0.434 – 1.501	0.499	R	0.029	79.1
	American	1	1401	1748	0.796	0.656 – 0.965	0.02	F	-	-
	Mestizos	1	234	455	1.266	0.81 – 1.979	0.301	F	-	-
***SLC30A8* C>T (rs13266634)**										
C vs T (Allele Model)	Overall	53	35259	35588	1.144	1.057 - 1.238	0.001	R	<0.001	89.3
	Arabian	4	1065	1014	1.107	0.864 - 1.418	0.422	R	0.074	56.8
	Iranian	2	231	287	0.729	0.271 - 1.958	0.53	R	0.001	91.0
	Asian	35	20213	17434	1.133	1.047 - 1.225	0.002	R	<0.001	80.4
	European	6	10434	14024	1.172	1.126 - 1.219	<0.001	F	0.346	10.8
	Russian	2	1450	1040	0.73	0.638 - 0.836	<0.001	F	0.89	-
	African	2	1368	1503	1.111	0.908 - 1.36	0.305	F	0.235	29.0
	Turkish	1	43	52	0.861	0.398 - 1.86	0.703	F	-	-
	Mestizos	1	455	234	8.293	6.43 - 10.695	<0.001	F	-	-
CC vs CT (Codominant Model)	Overall	53	35259	35588	1.116	1.03 - 1.21	0.007	R	<0.001	76.4
	Arabian	4	1065	1014	1.205	1.003 - 1.447	0.046	F	0.403	0
	Iranian	2	231	287	0.822	0.518 - 1.305	0.406	F	0.913	0
	Asian	35	20213	17434	1.085	0.981 - 1.2	0.113	R	<0.001	73.0
	European	6	10434	14024	1.201	1.138 - 1.268	<0.001	F	0.272	21.5
	Russian	2	1450	1040	0.427	0.123 - 1.486	0.181	R	0.004	88.1

Continued.

	Population	No. of Studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	P value	Model	P value	I² (%)
	African	2	1368	1503	1.109	0.882 - 1.394	0.377	F	0.265	19.5
	Turkish	1	43	52	3.579	0.931 - 13.766	0.064	F	-	-
	Mestizos	1	455	234	7.496	4.310 - 13.036	<0.001	F	-	-
CC vs TT (Codominant Model)	Overall	53	35259	35588	1.332	1.145 - 1.55	<0.001	R	<0.001	83.2
	Arabian	4	1065	1014	1.066	0.534 - 2.126	0.857	R	0.083	55.1
	Iranian	2	231	287	2.087	0.037 - 118.057	0.721	R	0.008	85.9
	Asian	35	20213	17434	1.337	1.164 - 1.537	<0.001	R	<0.001	66.8
	European	6	10434	14024	1.33	1.214 - 1.456	<0.001	F	0.621	-
	Russian	2	1450	1040	0.313	0.121 - 0.809	0.017	R	0.049	74.3
	African	2	1368	1503	1.213	0.577 - 2.552	0.611	F	0.718	-
	Turkish	1	43	52	0.298	0.056 - 1.578	0.155	F	-	-
	Mestizos	1	455	234	70.275	36.943 - 133.68	<0.001	F	-	-
CC vs CT+TT (Dominant Model)	Overall	53	35259	35588	1.158	1.06 - 1.264	0.001	R	<0.001	82.9
	Arabian	4	1065	1014	1.198	1.006 - 1.427	0.043	F	0.192	36.6
	Iranian	2	231	287	0.826	0.532 - 1.284	0.396	F	0.192	41.2
	Asian	35	20213	17434	1.134	1.022 - 1.259	0.018	R	<0.001	77.4
	European	6	10434	14024	1.224	1.163 - 1.288	<0.001	F	0.267	22.2
	Russian	2	1450	1040	0.394	0.111 - 1.401	0.15	R	0.003	88.8
	African	2	1368	1503	1.118	0.895 - 1.397	0.326	F	0.254	23.1
	Turkish	1	43	52	1.392	0.535 - 3.623	0.498	F	-	-
	Mestizos	1	455	234	15.846	9.354 - 26.843	<0.001	F	-	-
CC+CT vs TT (Recessive Model)	Overall	53	35259	35588	1.249	1.095 - 1.425	0.001	R	<0.001	82.7
	Arabian	4	1065	1014	1.095	0.754 - 1.59	0.635	F	0.117	49.0
	Iranian	2	231	287	2.263	0.041 - 125.535	0.69	R	0.005	87.2
	Asian	35	20213	17434	1.266	1.118 - 1.432	<0.001	R	<0.001	67.7
	European	6	10434	14024	1.213	1.113 - 1.323	<0.001	F	0.592	-
	Russian	2	1450	1040	0.722	0.587 - 0.889	0.002	F	0.192	41.1
	African	2	1368	1503	1.207	0.575 - 2.533	0.618	F	0.73	-
	Turkish	1	43	52	0.247	0.047 - 1.292	0.098	F	-	-
	Mestizos	1	455	234	19.142	12.007 - 30.516	<0.001	F	-	-

F – Fixed effect model; R – random effect model. OR – odds ratio, 95% CI – 95% confidence interval.

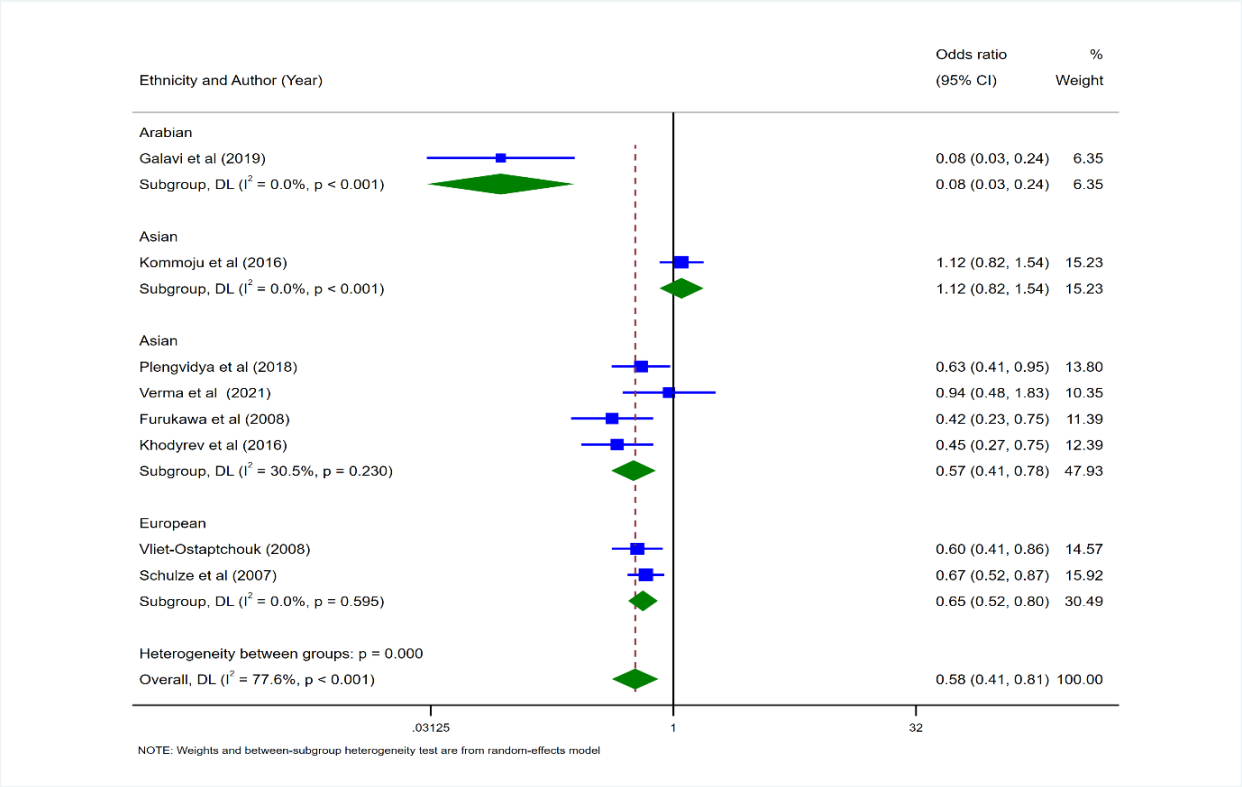

Figure 2: Forest plot of HHEX (rs111187) A>G gene variant and T2DM in subgroup analysis by ethnicity using a random effect model (AA versus GG).

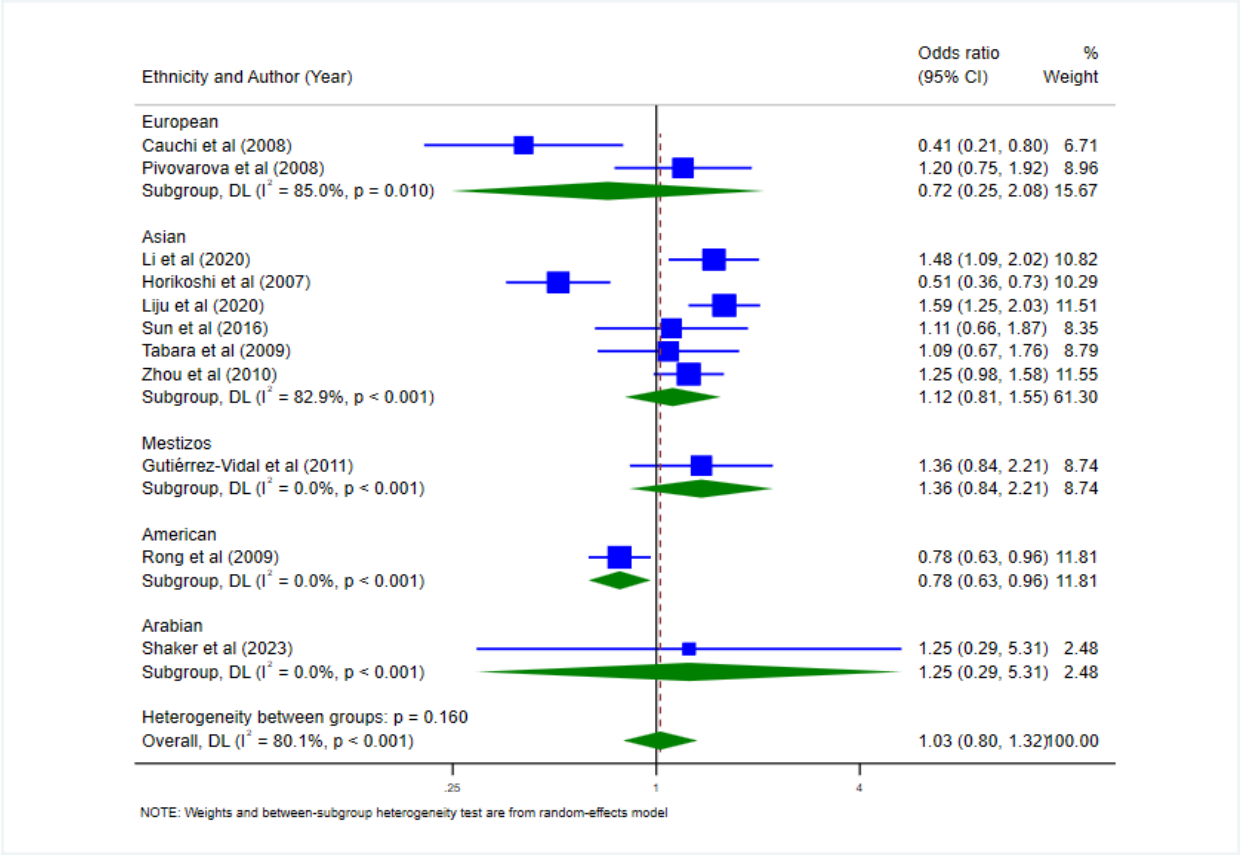

Figure 3: Forest plot of *HHEX* (rs111187) C>T gene variant and T2DM in subgroup analysis by ethnicity using a random effect model (CC versus TT).

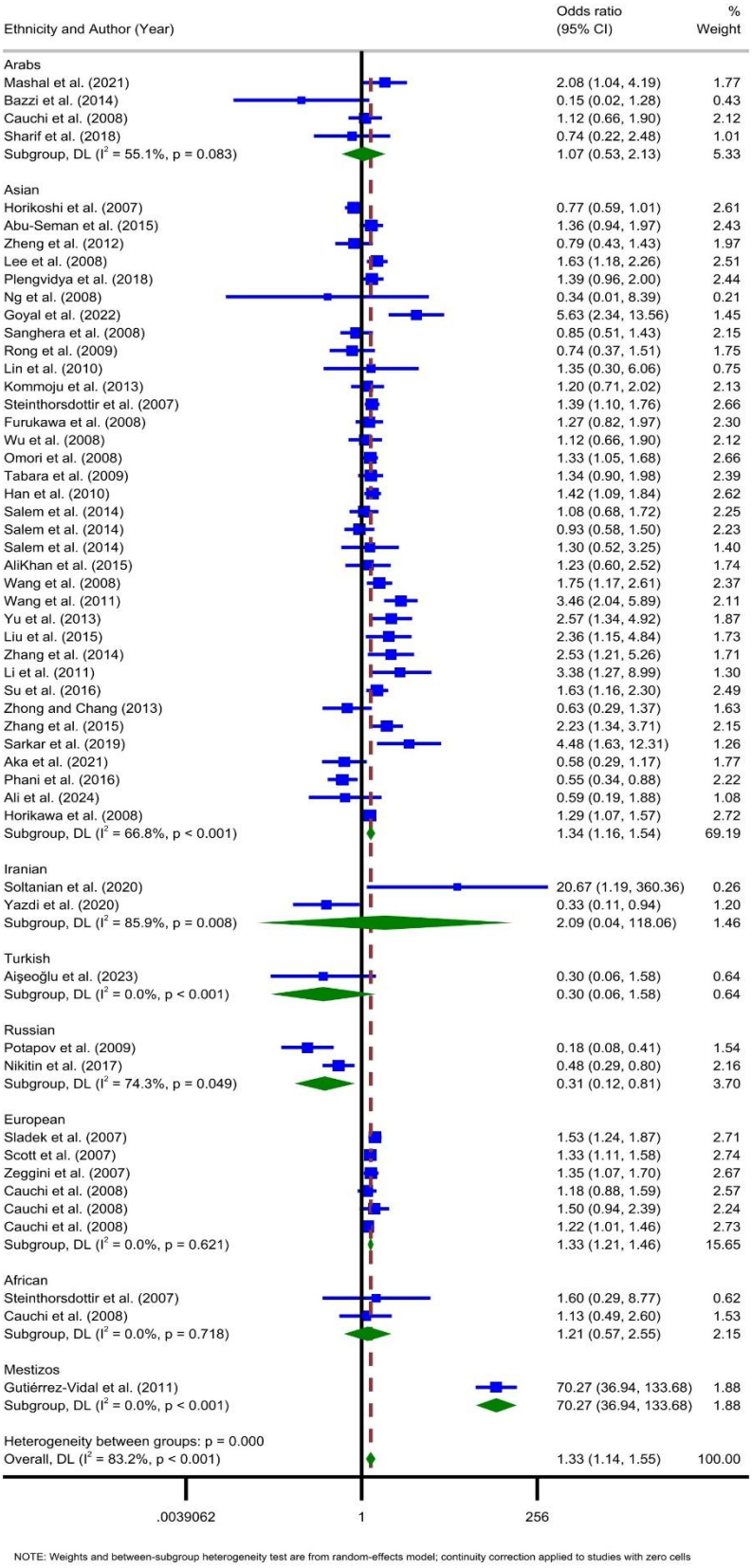

Figure 4: Forest plot of *SLC30A8* C>T (rs13266634) gene variant and T2DM in subgroup analysis by ethnicity using a random effect model (CC versus TT).

Test for publication bias

Publication bias of the studies included in this meta-analysis was determined by Egger's regression test. Egger's linear regression test did not reveal any publication bias for the studies analyzing *HHEX* A>G (AA vs GG: p=0.0873), *HHEX* C>T (CC vs TT: p=0.72) and *SLC30A8* C>T (CC vs TT: p=0.961) variants. Sensitivity analysis did not deviate from pooled odds ratio (OR) quantitively.

DISCUSSION

Genetic and environmental factors are thought to be associated with T2DM, a chronic metabolic disorder in which genetically determined pancreatic beta (β) cells fail over time and cannot withstand the increase insulin resistance.[88] Hepatic insulin resistance results in inadequate suppression of glucose production by the liver, leading to elevated blood glucose level which supports the diminished antilipolytic action of insulin.[88,89] Genetic background is a common concern for researchers to determine the effect of altered allele distribution or expression of certain genes with T2DM susceptibility in various populations across the world. To date, several candidate genes have already been evaluated by various researchers to determine the relationship between genetic variants and T2DM risk. These include *Transcription Factor 7 Like 2 (TCF7L2), Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A/2B), CDK5 Regulatory Subunit Associated Protein 1-Like 1 (CDKAL1), Melatonin Receptor 1b (MTNR1B), Peroxisome proliferator-activated receptor (PPARG), Solute Carrier Family 30 Member 8 (SLC30A8), Potassium Voltage - Gated Channel, Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11), KQT-Like Subfamily Member 1 (KCNQ1), Wolframin ER Transmembrane Glycoprotein (WFS1), Hepatocyte Nuclear Factor 1 Homeobox B (HNF1B), Insulin-Like Growth Factor 2 mRNA Binding Protein 2 (IGF2BP2), and Juxtaposed with Another Zinc Finger Protein 1* (*JAZF1*).[3,9,26,27,61,70,74,76,88–99] *Haematopoietically Expressed Homeobox* or *HHEX* gene plays significant role in the development of ventral pancreas whereas *SLC30A8* is involved in the maturation and storage of insulin in pancreatic beta-cells (β-cells). These are therefore considered as relevant candidate genes for investigation in T2DM risk or protection.[100] Previous studies carried out in the populations of Bangladesh, Japan, South India, Germany, North-East India, Iran, Hong Kong, Korea and China (Han population) have reported significant association between *HHEX* gene variant and T2DM.[3,9,13,23,32,36,40,45,48,98,101] Similarly, significant association between *SLC30A8* gene variant and T2DM has been reported previously in the populations of Bangladesh, North-East India, Thailand, Jordan, Hong Kong, Korea, China and Iran. [3,9,26,45,48,72,74,85,98]

In this meta-analysis, deviation of Hardy-Weinberg equilibrium (HWE) was detected in several studies for *HHEX* and *SLC30A8* gene variants.[3,9,47,77-79,81–84,86,87] The deviation from the HWE might be attributed to various factors such as assortative mating, natural selection, genetic drift, distribution of allele frequencies among populations and sample size. This current study revealed a significant association between *HHEX* A>G variant and reduced risk of T2DM under allele (A vs G: p=0.004), codominant (AA vs GG: p=0.001), dominant (AA vs AG+GG: p=0.02) and recessive (AA+AG vs GG: p=0.002) except under codominant (AA vs AG: p=0.092) inheritance model. Further, positive association was observed between *SLC30A8* C>T variant and T2DM risk under allele (C vs T: p=0.001), dominant (CC vs CT+TT: p=0.001), recessive (CC + CT vs TT: p=0.001) and codominant (CC vs CT: p=0.007 and (CC vs TT: p<0.001) inheritance models. This is the first study, in which both the *HHEX* A>G and *HHEX* C>T variants for SNV rs1111875 were analyzed. *HHEX* A>G variant was associated with reduced T2DM risk in Arabian ethnic group under all tested models and in European ethnic group under allele, dominant, recessive and codominant inheritance models. *HHEX* C>T gene variant was significantly associated with reduced T2DM risk in American ethnic group under allele, codominant and recessive inheritance models. In contrast, *SLC30A8* C>T variant was associated with increased T2DM risk in Asian, Arabian, Russian, European and Mestizos populations. Prior meta-analysis of *SLC30A8* C>T variant and T2DM lacks data for Russian, Arabian and Mestizos populations.[102]

The present meta-analysis demonstrated a substantial degree of heterogeneity across the pooled analyses, as reflected by the I^2 statistics. The highest overall heterogeneity was observed for *SLC30A8* C>T variant under the allelic model (I^2=89.3%), followed by *HHEX* A>G (I^2=87.5%) and *HHEX* C>T (I^2=82.6%) variants. Ethnicity-specific analyses also demonstrated considerable heterogeneity, particularly among Asian populations for *HHEX* variants and Iranian and Russian populations for *SLC30A8* C>T variant. This considerable heterogeneity indicates that the degree of the association between these genetic variants and T2DM was not consistent across the included studies. The variability in I^2 values across populations may reflect differences in genetic background, allele frequencies, demographic characteristics or sample size. Publication bias for the pertinent studies was assessed by Egger's linear regression test.[22] Overall, there was absence of publication bias for all selected studies.

The pathogenesis of T2DM is regulated by multiple genes such as *CDKL1, LOC387761, CDKN2A/2B*, *TCF7L2, IGF2BP2*, *KCNJ11, MTNR1B.*[26,39,49,89,92] However, in this meta-analysis, only *HHEX* and *SLC30A8* gene variants were evaluated for their possible association with T2DM risk or protection. Furthermore, the demographic variables were not considered as the confounding factors in evaluation of association between genetic variants and T2DM.

CONCLUSION

The results of this meta-analysis demonstrated significant association of *HHEX* A>G and *SLC30A8* C>T variants with reduced risk and increased risk of T2DM, respectively. The findings indicate that these gene variants may contribute to the genetic predisposition to T2DM.

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