[Frontiers in Bioscience, Elite, 12, 199-222, March 1, 2020]

Influence of *KCNJ11* gene polymorphism in T2DM of south Indian population

Rajagopalan Aswathi[1], Dhasaiya Viji[1], Prathap Seelan Pricilla Charmine[1], Rehman Syed Rasheed Akram Husain[1], Sahul Hameed Noorul Ameen[2], Shiek SSJ Ahmed[3], Veerabathiran Ramakrishnan[1]

[1]Genetics Lab, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Kelambakkam 603103, Tamil Nadu, India, [2]Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Health City, Kelambakkam 603103, Tamil Nadu, India, [3]Drug Discovery Lab, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Kelambakkam 603103, Tamil Nadu, India

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Materials and methods
3.1. Association based on case-control study
3.1.1. Study sampling
3.1.2. Genotyping and statistical analysis of rs5219
3.2. Meta-analysis of rs5219
3.2.1. Analysis of rs5219 polymorphism
4. Results
4.1. Case-control study
4.2. Meta-analysis
4.2.1. General characteristics
4.2.2. Meta-analysis of rs5219 polymorphism
4.2.3. Sub-group meta-analysis of rs5219
5. Discussion
6. Conclusion
7. Acknowledgments
8. References

1. ABSTRACT

Type-2 Diabetes mellitus (T2DM) is a complex metabolic disease. A case-control study was conducted with 218 T2DM and 214 controls to evaluate the T2DM risk of rs5219 polymorphism in the south Indian population. The analysis of allelic and genotype data showed a significant association of rs5219 polymorphism towards an increased risk of T2DM compared to controls with an odds ratio (OR) of 2.52, confidence interval (CI) (0.96-6.64) and p-value 0.046. The functional influence of rs5219 was tested which showed a significant correlation with HbA1c and serum uric acid levels. Although our results confirm rs5219 is a potential contributor to T2DM, several inconclusive results were noticed across the literature. Hence, the meta-analysis was performed by combining the results of case-control study with previous literature to confirm the rs5219 association with T2DM across various populations. Our meta-analysis revealed a significant risk association of rs5219 in T2DM under five genetic models. In summary, our analysis suggests, rs5219 polymorphism plays a significant role in T2DM susceptibility. Further, studies need to be conducted to determine the influence of rs5219 on the other characteristics of T2DM.

2. INTRODUCTION

Type-2 Diabetes mellitus is a complex metabolic disorder caused due to the development of insulin resistance that leads to hyperglycemia (1). Globally, 347 million people are affected with diabetes, of which most from middle and low-income countries (2). In India, the prevalence of diabetes is expected to increase up to 10.1% by the year 2035 (3). The etiology of T2DM is well reported suggesting interplay of genes, environment, sedentary behavior, and obesity (4). Several genome-wide association studies (GWASs) have documented over 129 loci in genes such as *TCF7L2, PPARG, FTO, PRC1, DUSP9, CDKAL1, NOTCH2, ABCC8, HNF1A, IGF2BP2, KCNQ1,* and *KCNJ11* were found to be related with T2DM (5, 6).

Of several genes, *Potassium Voltage-Gated Channel Subfamily J Member-11 (KCNJ11)* localized at chromosome 11 encode KATP channel protein, containing 390 amino acids considered as a susceptible gene for T2DM (7). In particular, a study from France analyzed variations in *KCNJ11* and *ABCC8* genes among 109 diazoxide-unresponsive patients having congenital hyperinsulinism, which revealed mutations in 82% of the probands (8). Also, several mutations in the *KCNJ11* gene were noticed and considered as one of the causative factors for diseases like congenital hyperinsulinemia and neonatal diabetes (9). Functionally, mutations in the *KCNJ11* gene causes diabetes by reducing the sensitivity of KATP to ATP (potassium channel-adenosine triphosphate), thus preventing the secretion of insulin (10). The earlier study suggests that polymorphic variants identified in KCNJ11-ABCC8 locus were found to be linked with T2DM due to high linkage disequilibrium (LD) (11).

Globally, several polymorphic variants were observed in the *KCNJ11* gene which was positively associated with T2DM across various ethnic populations (12, 13). Among several polymorphisms, the *rs5219* variant (Glu23Lys, results in a modification of glutamic acid to lysine) in the *KCNJ11* gene was selected for the DNA genotyping. The prime interest for selection *rs5219* is based on two fundamental backgrounds, (1) So far no study was conducted reporting the association of *rs5219* polymorphism in T2DM in the South-Indian population. (2) The *rs5219* polymorphism suggests altering the protein function that may cause T2DM (14). Hence this study is conducted to determine the genetic predisposition of *rs5219* polymorphism with T2DM susceptibility in the south Indian population. Despite previous studies of *the KCNJ11* gene (p.E23K) polymorphism, several inclusive results were obtained across ethnic origin on the association of T2DM. To bring the conclusive results, we also examined the relationship between *rs5219* and T2DM risk by an extensive meta-analysis following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria (15).

3. MATERIALS AND METHODS

3.1. Association based on case-control study

3.1.1. Study sampling

The T2DM patients were recruited from the Department of General Medicine, Chettinad Health City, Kanchipuram district, Tamil Nadu, India, between January to June 2017. All recruited participants are belonging to South India, Asian ethnic backgrounds. The fasting blood glucose and Haemoglobin-A1c levels were determined based on WHO regulations (16) for the confirmation of T2DM. Similarly, the control group was screened for T2DM to confirm the participants are healthy control. The present study protocol was following the Helsinki Declaration and was approved by the Human Ethics Committee (205/IHEC/12-16) of the Chettinad Academy of Research and Education. The signed informed consent written in the local language was obtained from the study participant before sample collection. The general characteristics from each participant were obtained through a structured questionnaire. Besides the HbA1c levels, serum uric acid was measured in the participants were recorded and used while analysis.

3.1.2. Genotyping and statistical analysis of *rs5219*

Approximately 3 ml of venous blood was collected from T2DM subjects and controls; Genomic DNA was extracted from the collected samples using a standard protocol followed by ethanol precipitation (17). Genotyping of *rs5219* polymorphism was executed by newly designed allele-specific primers using Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) (Table 1) (18). The PCR mixture contained, a 20 µl reaction mix

Table 1. Primers for *KCNJ11 (rs5219)* genotyping

Primer-ID	Primer Sequence (5'-3')	Allele	No of base pairs	Tm (ºC)	Total Length (Bp)
SNP-1 OF -	CCACCAGCGTGGTGAACACGTCCTGCAG		28	68	300
SNP-1 OR -	CCCAGGGTGAGAAGGTGCCCACCGAGAG		28	68	
SNP-1 IF -	CGCTGGCGGGCACGGTACCTGGGATT	**T**	26	68	200
SNP-1 IR -	CTGACACGCCTGGCAGAGGACCCTGACG	**C**	28	68	154
IF-inner forward, IR- inner reverse, OF-outer forward, OR- outer reverse					

was used with 25 ng DNA, 10 mM dNTPs, 12 pmol/µl of forward primer and reverse primer and 1 Unit Taq polymerase. The ARMS-PCR reaction was performed in the Eppendorf Master Cycler Gradient (Hamburg, Germany). The cycling conditions for ARMS-PCR reaction were: initial denaturation at 92°C for 5 mins, 36 cycles of 92°C for 45 secs, 62°C for 45 secs, 72°C for 45 secs and 72°C for 7 mins. The PCR products were electrophoresed in agarose gel (1.6%) along with 100 bp DNA Ladder Dye Plus (Cat no: 3422A, Takara Bio). Further, the polymorphism was confirmed from the randomly selected samples (Controls = 10; T2DM =12) using DNA sequencing (ABI 3100, USA). To identify the chromosomal interactions between the SNPs, a 3DSNP software package was used for visualizing the genomic data by generating the Circos plots based on r^2 values (19). The genotype distribution in controls was examined for Hardy-Weinberg equilibrium (HWE value >0.05) by Fisher's exact test. The distribution of allelic and genotypic frequencies among T2DM subjects and the control group were determined by Pearson's chi-square test. Further, the effects were examined by calculating the odds ratio (OR), and confidence intervals (95% CIs) in dominant (F-major, f-minor allele: Ff + ff vs. FF) and recessive (ff vs. FF + Ff) genetic models. Both the allelic and genotype data were analyzed by SPSS software V-21 (IBM Analytics, USA). Further, the associations of rs5219 polymorphism with HbA1c and serum uric acid levels in T2DM were tested using the chi-square test.

3.2. Meta-analysis of *rs5219*

3.2.1. Analysis of *rs5219* polymorphism

To determine the association between *rs5219* polymorphism and T2DM susceptibility, a meta-analysis was performed by including the results of case-control study. The eligible studies for this meta-analysis were identified through a systematic electronic search from databases such as NCBI-PubMed, Google Scholar, Cochrane Library, EMBASE and MEDLINE up to December 2017, respectively. The Key Words used for literature mining were "Type-2 Diabetes mellitus", "T2DM", "*Potassium Voltage-Gated Channel Subfamily J Member-11*", "*KCNJ11* gene", "*rs5219*", and "Polymorphism". The language selection for the article included in this meta-analysis was limited to the English language. A study was included in the meta-analysis based on the following criteria: first, it should be a case-control study, second, the association of *rs5219* gene polymorphism with T2DM was determined and third it should provide sufficient genotype data to calculate OR and 95% confidence intervals. We excluded the few articles based on: first, if the studies containing overlapping data, second if the studies were from *in vitro,* cell lines, case reports, animal models and studies that lack genotype frequencies, respectively. The data for this meta-analysis were extracted by two independent researchers (PA and DV) and any disagreement was solved by a team (AH, SSJ and RK). The following study characteristics, including author name, publication year, country, ethnic background, sample size (T2DM cases and controls), the source of DNA isolation, Diagnostic criteria of T2DM, genotype frequency and genotyping method were extracted.

The quality assessment of all the included studies was verified using Hardy-Weinberg equilibrium (HWE) with P-value > 0.05 in controls (20) and by the Newcastle Ottawa Scale (NOS) (21). In this scale maximum, 9 points represent the high quality of studies, 6 points or above were considered in this analysis. All the statistics for meta-analyses were executed using

Table 2. Demographic characteristics of T2DM patients and control subjects

Characteristics	T2DM Cases (N = 218)	Controls (N = 214)
Men : women	144:74	128:86
Mean Age	54.45±07.48	53.15±06.57
Body mass index (kg/m2)	28.65±4.88	23.87±3.71
Age of disease onset	46.54±07.63	Nil
Duration of diabetes (years)	5.16±4.18	Nil
Family history of diabetes	102	35
HbA1c	7.34±0.58	5.39±0.27
Uric Acid	5.35±0.63	3.21±0.64
T2DM-Type 2 Diabetes Mellitus, Data are presented as mean ±standard deviation (SD) for continuous variables		

RevMan V-5.0 (Cochrane Community, UK) and STATA V-12.0 (Stata Corp., USA). The significance of meta-analysis of pooled and subgroup (Caucasian, Asian and others) were confirmed using the odds ratios (OR) and 95% confidence interval (CI) with (P-value < 0.05) under allelic (j vs. J) (J-major, j-minor allele), homozygote (jj vs. JJ), heterozygote (Jj vs. JJ), dominant (Jj + jj vs. JJ) and recessive (jj vs. JJ +Jj) genetic models, respectively. The Q-test and I^2 statistics (22) was used to assess the study heterogeneity in this meta-analysis. Based on the heterogeneity values (I^2<50), a Mantel-Haenszel's (fixed effect) model was used else DerSimonian and Laird's (23) (random-effect) model was used. Further, the funnel plot and Egger's regression analysis were used to evaluate the publication bias in this meta-analysis. The findings of our meta-analysis were validated using a sensitivity test (Leave one out method) (24).

4. RESULTS

4.1. Case-control study

The demographic characteristics of T2DM subjects (N=218) and healthy controls (N=214) were represented in Table 2. The mean ± standard deviation (SD) for age in T2DM and control were 54.45±07.48 and 53.15±06.57 years. Further, the HbA1c levels and serum uric acid were determined in all the participants showed HbA1c: control (5.39±0.27) and T2M (7.34±0.63). Similarly, the average serum uric acid in control was 3.21±0.64 and in T2DM was 5.35±0.63 mg/dL.

The allelic and genotypic distributions of *rs5219* polymorphism were illustrated in Table 3. An Agarose gel electrophoresis result of ARMS-PCR was represented in the fig1. The genotype distribution in control was not deviated from HWE (P = 0.183). The genotype frequencies of *rs5219* polymorphism were 77.06% (CC), 16.51% (CT) and 06.41% (TT) in the T2DM. Whereas, in control, 70.64% (CC), 24.29% (CT) and 03.73% (TT), respectively. The distribution of *rs5219* (TT genotype) was significantly increased in T2DM patients compared with control, OR=2.52 (95% CI (0.96-6.64)) P-value = 0.046. The results of dominant and recessive genetic models revealed no significant difference between T2DM and controls. The sequence electropherograms of *KCNJ11 rs5219* polymorphism were presented in fig2. Alternatively, the results of the ARMS PCR were further confirmed with the DNA sequencing method which showed similar results. The *KCNJ11* nucleotide sequences were deposited *(MF109894, MF110273,* and *MF110298)* in NCBI-Genbank. The Circos plot (outer to the inner circle) shows *rs5219* variant associated other polymorphisms with r^2 along with the annotated genes, chromatin states and 3D chromatin interactions (fig3). Further, the influence of polymorphism on clinical parameters showed a significant association of *rs5219* with high HbA1c (Table 4) and serum uric acid (Table 5) concentration in T2DM patients.

4.2. Meta-analysis

4.2.1. General characteristics

Our initial literature search in the selected databases identified 946 papers published up to

Table 3. Allele frequency and genotype distribution of rs5219 polymorphism in T2DM and controls

Polymorphism	Frequencies	Type 2 Diabetes Mellitus n =218 (%)	Controls n =214 (%)	HWE	OR	95% CI	χ2	P-value
rs5219	Allele							
	C	372 (85.32)	360 (84.11)	-		Reference	0.24	0.344
	T	64 (14.67)	68 (15.88)	-	0.91	(0.62-1.31)		
	Genotype							
	CC	168 (77.06)	154 (70.64)	0.183		Reference	3.51	0.070
	CT	36 (16.51)	52 (24.29)		0.63	(0.39-1.02)		
	TT	14 (06.41)	08 (03.73)		2.52	(0.96-6.64)	3.67	0.046*
Genetic models								
Dominant	CT +TT vs CC	-	-	-	1.30	(0.84-2.02)	1.48	0.134
Recessive	TT vs CC+ CT	-	-	-	1.76	(0.72-4.30)	1.61	0.146

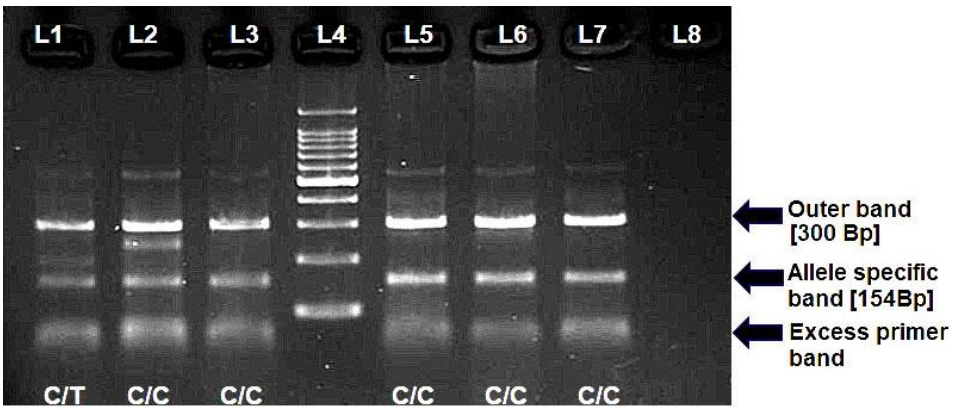

Figure 1. Agarose (1.6) gel electrophoresis results of ARMS-PCR. Lanes: L1-CT genotype, L2 & L3-CC genotype, L4-100 Bp DNA Ladder, L5, L6 & L7 CC genotype, L8-Negative control.

December 2017. The articles were screened for relevance which met the inclusion and exclusion criteria. Finally, 34 studies (12,13, 25-56) were finally selected for meta-analysis which include 26,991 T2DM cases and 35,899 controls. The characteristics of the included studies in the meta-analysis were illustrated in Table 6. Further, the genotype and allele frequencies were extracted from each study involved in the meta-analysis is represented in Table 7.

4.2.2. Meta-analysis of *rs5219* polymorphism

The analysis of *rs5219* SNP, revealed mild heterogeneity was observed in the heterozygote (I2=31%) and in allelic (I2=60%), homozygote (I2=53%) dominant (I2=54%) and recessive (I2=44%) genetic models moderate heterogeneity was observed. The fixed effects (Mantel-Haenszel's) model was used which showed significant (P< 0.05) association with T2DM risk in heterozygote (Jj vs. JJ), with OR = 0.86, (95% CI (0.82-0.91)), and recessive (jj vs. JJ +Jj) with OR = 1.19, (95% CI (1.14-1.25)), Random-effect (DerSimonian and Laird's) model was implemented which revealed a positive association with T2DM susceptibility in for allelic (j vs J) with OR = 1.13, (95% CI (1.08-1.18)), homozygote (jj vs. JJ), with OR = 1.30, (95% CI (1.19-1.41)), and dominant (Jj + jj vs. JJ) with OR = 1.14,(95% CI (1.08-1.21)) genetic models. The meta-analysis results were represented as allelic

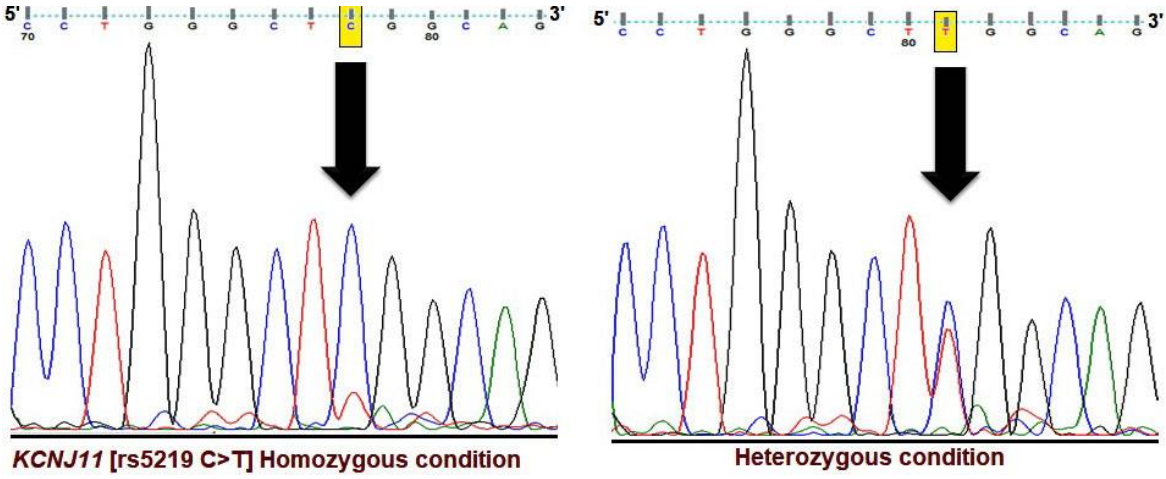

Figure 2. DNA sequence electropherograms of *rs5219* polymorphism in the KCNJ11 gene.Examples of homozygous dominant (CC genotype) and heterozygote (CT genotype) condition of the current SNP

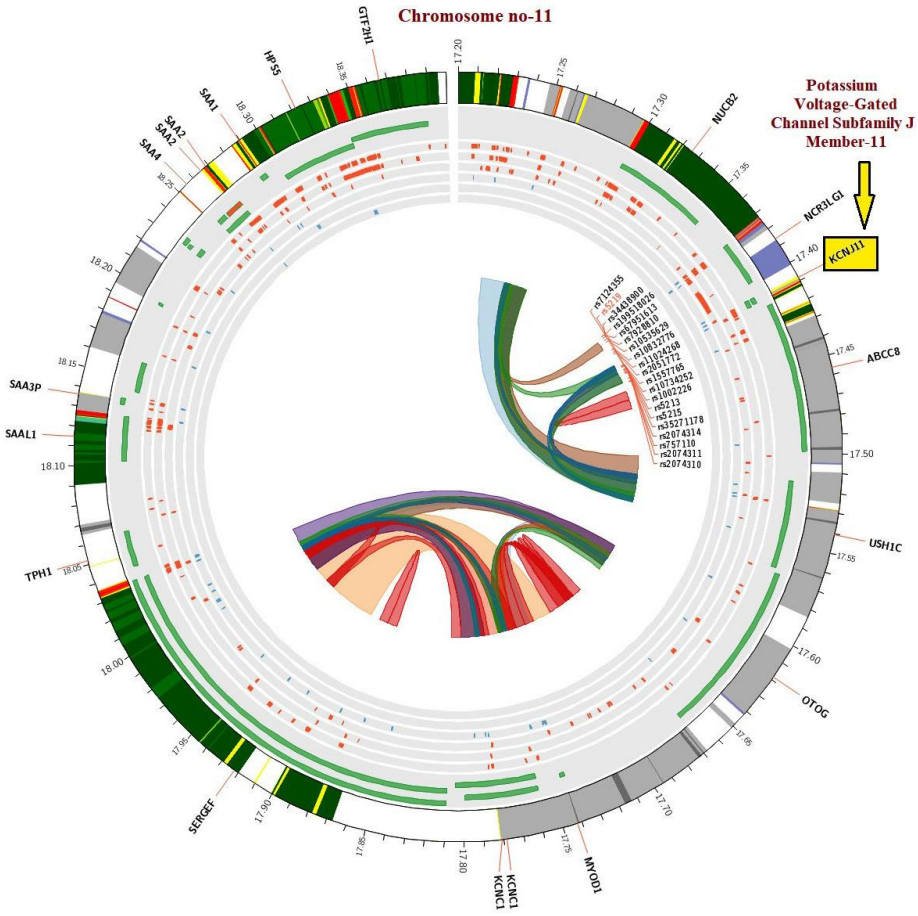

Figure 3. Circos plot showing the chromosomal interactions among the studied variant *(rs5219)* and its associated SNPs.

Table 4. Association of HbA1c levels (Low ≤ 7.3 and High > 7.4) with genotypes in T2DM

Genotype	Levels			P-value
	Low	High	Total	0.003
CC	89	79	168	
TT	15	21	14	
CT	1	13	36	
Total	105	113	218	

Table 5. Association of uric acid levels (Low ≤ 5.3 mg/dL and High > 5.4 mg/dL) with genotypes in T2DM

Genotype	Levels			P-value
	Low	High	Total	
CC	88	80	168	0.016
TT	2	12	14	
CT	15	21	36	
Total	105	113	218	

(Table 8), homozygote (Table 9), heterozygote (Table 10), dominant (Table 11) and recessive (Table 12) model. Further, the funnel plot for pooled (fig.4) and sub-group of Caucasian (fig.5) and Asian (fig.6) were performed. Similarly, Egger's linear regression analysis were performed which revealed no publication bias in the investigated five genetic models.

4.2.3. Sub-group meta-analysis of *rs5219*

In a meta-analysis of sub-groups, the selected articles were stratified based on the ethnic background such as Caucasian (21 studies), others (04 studies) and Asian (12 studies), respectively. The results of sub-grouping Caucasian ethnicity revealed moderate heterogeneity in all the analyzed genetic models. Hence, the random-effects model was adopted to test the influence of polymorphism in the five genetic models. Similarly, the sub-group stratification results of the *rs5219* variant in Asian ethnicity exhibited moderate heterogeneity in all the analyzed genetic models. Based on heterogeneity results, the fixed effects model was used which showed positive (p = 0.05) association with T2DM susceptibility in jj vs. JJ with OR = 1.21, (95% CI (1.05-1.40)), and Jj + jj vs. JJ with OR = 1.12, (95% CI (1.06-1.18)) respectively. Random-effect model was adopted which showed positive (p = 0.05) association with a risk of T2DM in j vs. J with OR = 1.10, (95% CI (1.02-1.20)) and jj vs. JJ +Jj with OR = 1.16, (95% CI (1.01-1.33)) genetic models respectively. Further, the Asian sub-group analysis was divided into (South-Asian=03, East-Asian=08, West-Asian =01) ethnic background. The results of subgroup analyses were illustrated in (Table 13).

5. DISCUSSION

The current global prevalence of T2DM has been increased exponentially in recent years, which represents a major challenge to health care professionals and considered a global health concern with an impact on premature mortality, morbidity, and its related (Microvascular and Macrovascular) complications, especially in the elderly people (57). Previous studies suggest that T2DM is a multifactorial disorder caused because of complex genetic interactions and environmental factors (58, 59). The *KCNJ11* gene based on its position in the chromosome, considered as a promising candidate gene for T2DM which functions in regulating glucose-induced insulin secretion (60). It has been documented that the *rs5219* variant observed in the 11p15.1 region might play a significant role in T2DM development, hence making it a biomarker for assessing the *KCNJ11* gene (25). In the association study, the relationship between *KCNJ11* p.E23K polymorphism with T2DM susceptibility was identified, to the best of our understanding; this is the first study in South Indian population to determine the relationship between *KCNJ11* gene *rs5219* polymorphism and T2DM risk. The results of the case-control study showed a significant (P-value < 0.05) relationship with the genotype frequencies among T2DM subjects and controls revealing that the *rs5219* variant may be a potential risk factor in the South Indians population. A study from UK diabetic

Table 6. The characteristics of included studies in this meta-analysis

Reference	Year	Country	Ethnicity	Source	Diagnostic criteria	Cases	Controls	NOS Score	Method
29	2008	Saudi Arabia	West-Asian	Blood	WHO	550	335	07	Real-time PCR
34	2003	USA	Caucasian	Blood	NA	499	494	08	FP-TDI
35	2008	UK	Caucasian	NA	ADA	2734	4234	08	Real-time PCR
36	2007	Czech	Caucasian	Blood	WHO	172	113	08	PCR-RFLP
30	2009	UK	Caucasian	Blood	WHO	588	597	08	PCR-RFLP
37	2009	USA	Caucasian	blood	ADA	2709	3344	08	OpenArray
38	2005	Netherland	Caucasian	Blood	WHO	192	296	07	PCR-RFLP
33	2007	Japan	East-Asian	NA	WHO	550	1433	07	Real-time PCR
39	2009	Tunisia	Others	Blood	ADA	805	503	08	Real-time PCR
27	2004	Scandinavia	Caucasian	Blood	WHO	477	473	08	MALDI
27	2004	Canada	Caucasian			104	98		
27	2004	Sweden	Caucasian			496	506		
40	2016	Egypt	Others	Blood	ADA	53	30	07	AD-PCR
12	2001	UK	Caucasian	Blood	WHO	319	324	07	PCR-SSCP.
41	2003	UK	Caucasian	Blood	WHO	854	1182	07	PCR-SSCP.
42	2010	India	South-Asian	NA	WHO	190	158	08	DNA Sequencing
26	1998	France	Caucasian	Blood	NA	191	114	07	PCR-SSCP
43	1997	Denmark	Caucasian	Blood	WHO	58	75	08	PCR-SSCP
44	2005	Denmark	Caucasian	Blood	WHO	1187	4791	08	PCR-RFLP
45	2007	Japan	East-Asian	NA	NA	858	862	08	DNA Sequencing
32	2010	China	East-Asian	Blood	WHO	397	392	07	DNA Sequencing
13	2010	Israel	Others	Blood	NA	573	843	07	Pyrosequencing
46	2003	Denmark	Caucasian	Blood	WHO	803	862	08	PCR-RFLP
31	2007	USA	Caucasian	Blood	NA	682	1078	07	Real-time PCR
28	2007	Japan	East-Asian	Blood	WHO	906	889	07	Real-time PCR
47	1996	UK	Caucasian	Blood	NA	100	82	07	PCR-SSCP
48	2007	USA	Others	Blood	NA	572	587	07	Mass array
49	2008	India	South-Asian	Blood	ADA	532	374	08	Real-time PCR
25	2015	Russia	Caucasian	Blood	WHO	1384	414	08	Real-time PCR
50	2009	Japan	East-Asian	Blood	ADA	484	397	07	Real-time PCR
This study	2017	India	South-Asian	Blood	WHO	218	214	07	ARMS-PCR
51	2009	Norway	Caucasian	Blood	NA	750	1879	07	PCR-RFLP
52	2008	UK	Caucasian	NA	ADA	287	2684	07	Real-time PCR
53	2010	China	East-Asian	Blood	WHO	1165	1135	07	Real-time PCR
54	2007	USA	Caucasian	NA	WHO	1114	953	08	Mass array
55	2006	Japan	East-Asian	Blood	WHO	1590	1244	07	Mass array
56	2009	China	East-Asian	Blood	WHO	1848	1910	07	PCR

FP-TDI: Fluorescence polarization template-directed incorporation, SSCP: Single Stranded Conformational Polymorphism, AD PCR: Allelic Discrimination PCR, NA-Not available, ADA: American Diabetes Association, WHO: World Health Organization

subject's revealed a significant association of *rs5219* (TT genotype) compared with age-matched controls, OR=2.54 (95% CI (1.23-5.25)) P-value = 0.016, respectively (30). The results of the association study

Table 7. Genotype and allele frequencies of KCNJ11 gene rs5219 polymorphism of meta-analysis

Cases (CC/CT/TT)	Controls (CC/CT/TT)	Cases (C/T-Allele)	Controls (C/T-Allele)	HWE/ Chi-square
341/187/22	252/75/8	869/231	579/91	0.396/0.717
198/220/81	212/225/57	616/382	649/339	0.817/0.053
1112/1220/402	1625/2006/603	3444/2024	5256/3212	0.687/0.162
66/85/21	48/47/18	217/127	143/83	0.396/0.717
134/339/115	183/352/62	607/569	718/476	0.000/31.511
1055/1275/379	1382/1536426/	3385/2033	4300/2388	0.980/0.0006
66/92/34	119/141/36	224/160	379/213	0.558/0.342
202/263/85	617/655/161	667/433	1889/977	0.515/0.422
371/352/82	250/213/40	1094/516	713/293	0.564/0.332
113/244/120	129/250/94	470/484	508/438	0.171/1.871
27/54/23	27/50/21	108/100	104/92	0.810/0.057
174/237/85	209/229/68	585/407	647/365	0.674/0.176
36/14/3	23/6/1	86/20	52/8	0.460/0.543
267/47/5	288/33/3	581/57	609/39	0.072/3.217
308/412/134	491/534/157	1028/680	1516/848	0.535/0.384
68/88/34	48/71/39	224/156	167/149	0.216/1.527
53/87/51	45/53/16	193/189	143/85	0.950/0.003
21/26/11	33/34/8	68/48	100/50	0.862/0.03
423/568/196	1955/2195/641	1414/960	6105/3477	0.525/0.402
334/393/131	332/417/113	1061/655	1081/643	0.314/1.012
131/180/86	147/187/58	442/352	481/303	0.906/0.013
228/266/79	339/404/100	722/424	1082/604	0.219/1.505
287/382/134	330/408/124	956/650	1068/656	0.013/0.907
245/322/115	446/505/127	812/552	1397/759	0.378/0.776
333/446/127	386/396/107	1112/700	1168/610	0.725/0.123
38/45/17	44/27/11	121/79	115/49	0.052/3.762
514/52/6	505/81/1	1080/64	1091/83	0.224/1.476
226/ 247 /59	148/169/57	699/365	465/283	0.446/0.580
535/ 656/ 193	158/204/52	1726/1042	520/308	0.266/1.236
169/ 232 /83	152/195/50	570/398	499/295	0.390/0.736
168/36/14*	154/52/8*	372/64*	360/68*	0.183/1.766*
26/360/125	661/883/335	890/610	2205/1553	0.08/2.98
101/137/49	994/1287/403	339/235	3275/2093	0.682/0.166
395/587/183	425/517/193	1377/953	1367/903	0.096/2.754
284/560/270	286/486/181	1128/1100	1058/848	0.316/1.004
610/734/246	503/570/171	1954/1226	1576/912	0.638/0.220
656/863/329	692/930/288	2175/1521	2314/1506	0.395/0.721
HWE, Hardy Weinberg equilibrium, OR-Odd's ratio, $\chi 2$- Chi-square; P value-one tailed test; * - Results of current case-control study				

Table 8. T2DM risk associated with *KCNJ11 rs5219* polymorphism in allelic model with OR and 95% CI

Homozygote model						
Study or Subgroup	**Cases Events**	**Total**	**Controls Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
29	22	363	8	260	0.1%	2.03[0.89, 4.64]
34	81	279	57	269	0.4%	1.52[1.03, 2.25]
35	402	1514	603	2228	0.9%	0.97[0.84, 1.13]
36	21	87	18	66	0.2%	0.85[0.41, 1.76]
30	115	249	62	245	0.4%	2.53[1.73, 3.71]
37	379	1434	426	1808	0.9%	1.17 [0.99,1.37]
38	34	100	36	155	0.2%	1.7[0.98, 2.97]
33	85	287	161	778	0.5%	1.61 [1.19, 2.19]
39	82	453	40	290	0.4%	1.38[0.92, 2.08]
27	120	233	94	223	0.4%	1.46[1.01, 2.11]
27	23	50	21	48	0.1%	1.10 [0.49,2.43]
27	85	259	68	277	0.4%	1.5[1.03, 2.19]
40	3	39	1	24	0.0%	1.92[0.19, 19.56]
12	5	272	3	291	0.0%	1.8[0.43, 7.60]
41	134	442	157	648	0.6%	1.36[1.04, 1.78]
42	34	102	39	87	0.2%	0.62[0.34, 1.11]
26	51	104	16	61	0.2%	2.71[1.36, 5.38]
43	11	32	8	41	0.1%	2.16[0.75, 6.25]
44	196	619	641	2596	0.8%	1.41 [1.17, 1.71]
45	131	465	113	445	0.6%	1.15 [0.86,1.55]
32	86	217	58	205	0.4%	1.66[1.11, 2.50]
13	79	307	100	439	0.5%	1.17 [0.84,1.65]
46	134	421	124	454	0.6%	1.24[0.93, 1.66]
31	115	360	127	573	0.6%	1.65[1.23, 2.22]
28	127	460	107	493	0.6%	1.38[1.02, 1.85]
47	17	55	11	55	0.1%	1.79[0.75, 4.29]
48	6	520	1	506	0.0%	5.89 [0.71, 49.14]
49	59	285	57	205	0.4%	0.68[0.45, 1.03]
25	193	728	52	210	0.5%	1.10 [0.77,1.56]
50	83	252	50	202	0.4%	1.49[0.99, 2.26]
This study	14	182	8	162	0.1%	1.6[0.65, 3.93]
51	125	390	335	996	0.7%	0.93[0.72, 1.20]
52	49	150	403	1397	0.4%	1.2[0.83, 1.72]
53	183	578	193	618	0.7%	1.02[0.80, 1.30]
54	270	554	181	467	0.7%	1.5[1.17, 1.93]
55	246	856	171	674	0.7%	1.19 [0.94,1.49]
56	329	985	288	980	0.8%	1.21 [1.00, 1.46]
Subtotal (95% CI)		14683		19476	15.5%	1.30 [1.19,1.41]
Total events	4129		4838			
Heterogeneity: Chi-Square = 76.71, df= 36 (P < 0.00001);1^2= 53%						Odds Ratio > 1; Increased Risk
Test for overall effect: Z= 5.93 (P < 0.00001)						Odds Ratio < 1; Decreased Risk

Table 9. T2DM risk associated with *KCNJ11 rs5219* polymorphism in homozygote model with OR and 95% CI model

Allelic model						
Study or Subgroup	**Cases Events**	**Total**	**Controls Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
29	231	1100	91	670	0.6%	1.69[1.30,2.20]
34	382	998	339	988	0.8%	1.19 [0.99,1.43]
35	2024	5468	3212	8468	1.1%	0.96[0.90,1.03]
36	127	344	83	226	0.5%	1.01[0.71,1.43]
30	569	1176	476	1194	0.9%	1.41[1.20,1.66]
37	2033	5418	2388	6688	1.1%	1.08[1.00,1.16]
38	160	384	213	592	0.6%	1.27[0.98,1.65]
33	433	1100	977	2866	0.9%	1.26[1.09,1.45]
39	516	1610	293	1006	0.9%	1.15 [0.97,11.36]
27	484	954	438	946	0.8%	1.19 [1.00,1.43]
27	100	208	92	196	0.4%	1.05[0.71,1.55]
27	407	992	365	1012	0.8%	1.23[1.03,1.48]
40	20	106	8	60	0.1%	1.51[0.62,3.68]
12	57	638	39	648	0.4%	1.53[1.00,2.34]
41	680	1708	848	2364	1.0%	1.18 [1.04,1.34]
42	156	380	149	316	0.6%	0.78[0.58,1.05]
26	189	382	85	228	0.5%	1.65[1.18, 2.30]
43	48	116	50	150	0.3%	1.41[0.85,2.33]
44	960	2374	3477	9582	1.1%	1.19 [1.09,1.31]
45	655	1716	643	1724	0.9%	1.04[0.90,1.19]
32	352	794	303	784	0.8%	1.26[1.03,1.55]
13	424	1146	604	1686	0.9%	1.05[0.90,1.23]
46	650	1606	656	1724	0.9%	1.11[0.96,1.27]
31	552	1364	759	2156	0.9%	1.25[1.09,1.44]
28	700	1812	610	1778	0.9%	1.21[1.05,1.38]
47	79	200	49	164	0.3%	1.53[0.99,2.38]
48	64	1144	83	1174	0.5%	0.78[0.56,1.09]
49	365	1064	283	748	0.8%	0.86[0.71,1.04]
25	1042	2768	308	828	0.9%	1.02[0.87,1.20]
50	398	968	295	794	0.8%	1.18 [0.97,1.43]
This study	64	436	68	428	0.4%	0.91[0.63,1.32]
51	610	1500	1553	3758	1.0%	0.97[0.86,1.10]
52	235	574	2093	5368	0.8%	1.08[0.91,1.29]
53	953	2330	903	2270	1.0%	1.05[0.93,1.18]
54	1100	2228	848	1906	1.0%	1.22[1.08,1.38]
55	1226	3180	912	2488	1.0%	1.08[0.97,1.21]
56	1521	3696	1506	3820	1.1%	1.07[0.98,1.18]
Subtotal (95% CI)		53982		71798	28.4%	1.13 [1.08,1.18]
Total events	20566		26099			
Heterogeneity: Chi ^{2}= 90.03, df= 36 (P < 0.00001);1^2= 60%						Odds Ratio > 1; Increased Risk
Test for overall effect: Z=5.53 (P < 0.00001)						Odds Ratio < 1; Decreased Risk

Table 10. T2DM risk associated with *KCNJ11 rs5219* polymorphism in heterozygote model with OR and 95% CI

Heterozygote model						
Study or Subgroup	**Cases Events**	**Total**	**Controls Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
29	187	209	75	83	0.0%	0.91[0.39,2.13]
34	220	301	225	282	0.2%	0.69[0.47,1.01]
35	1220	1622	2006	2609	1.4%	0.91 [0.79,1.05]
36	85	106	47	65	0.0%	1.55[0.75,3.20]
30	339	454	352	414	0.3%	0.52[0.37,0.73]
37	1275	1654	1536	1962	1.2%	0.93[0.80,1.09]
38	92	126	141	177	0.1%	0.69[0.40,1.18]
33	263	348	655	816	0.3%	0.76[0.56,1.03]
39	352	434	213	253	0.2%	0.81[0.53,1.22]
27	244	364	250	344	0.3%	0.76[0.55,1.06]
27	54	77	50	71	0.1%	0.99[0.49,2.00]
27	237	322	229	297	0.2%	0.83[0.57,1.20]
40	14	17	6	7	0.0%	0.78[0.07,9.08]
12	47	52	33	36	0.0%	0.85[0.19,3.83]
41	412	546	534	691	0.4%	0.9[0.69,1.18]
42	88	122	71	110	0.1%	1.42[0.82,2.48]
26	87	138	53	69	0.1%	0.51[0.27,0.99]
43	26	37	34	42	0.0%	0.56[0.20,1.58]
44	568	764	2195	2836	0.9%	0.85[0.70,1.02]
45	393	524	417	530	0.4%	0.81 [0.61,1.08]
32	180	266	187	245	0.2%	0.65[0.44,0.96]
13	266	345	404	504	0.3%	0.83[0.60,1.16]
46	382	516	408	532	0.4%	0.87[0.65,1.15]
31	322	437	505	632	0.4%	0.7[0.53,0.94]
28	446	573	396	503	0.3%	0.95[0.71,1.27]
47	45	62	27	38	0.0%	1.08[0.44,2.64]
48	52	58	81	82	0.0%	0.11[0.01,0.91]
49	247	306	169	226	0.1%	1.41 [0.93,2.1 3]
25	656	849	204	256	0.3%	0.87[0.61,1.22]
50	232	315	195	245	0.2%	0.72[0.48,1.07]
This study	36	50	52	60	0.0%	0.4[0.15,1.04]
51	360	485	883	1218	0.5%	1.09[0.86,1.39]
52	137	186	1287	1690	0.2%	0.88[0.62,1.24]
53	587	770	517	710	0.5%	1.2[0.95,1.51]
54	560	830	486	667	0.6%	0.77[0.62,0.97]
55	734	980	570	741	0.6%	0.9[0.72,1.12]
56	863	1192	930	1218	0.9%	0.81 [0.68,0.98]
Subtotal (95% CI)		16437		21261	12.0%	0.86[0.82. 0.91]
Total events	12308		16423			
Heterogeneity: Chi-Square = 52.22, df=36 (P =0.04); 12= 31%						Odds Ratio > 1; Increased Risk
Test for overall effect: Z=5.73 (P < 0.00001)						Odds Ratio < 1; Decreased Risk

Table 11. T2DM risk associated with *KCNJ11 rs5219* polymorphism in dominant model with OR and 95% CI

Dominant model						
Study or Subgroup	**Cases Events**	**Total**	**Controls Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
29	209	550	83	335	0.5%	1.86[1.38,2.52]
34	301	499	282	494	0.7%	1.14[0.89,1.47]
35	1622	2734	2609	4234	1.0%	0.91[0.82,1.00]
36	106	172	65	113	0.3%	1.19[0.73,1.92]
30	454	588	414	597	0.6%	1.5[1.16,1.94]
37	1654	2709	1962	3344	1.0%	1.1[1.00,1.22]
38	126	192	177	296	0.4%	1.28[0.88,1.87]
33	348	550	816	1433	0.8%	1.3[1.06,1.59]
39	434	805	253	503	0.7%	1.16[0.92,1.44]
27	364	477	344	473	0.6%	1.21[0.90,1.62]
27	77	104	71	98	0.2%	1.08[0.58,2.02]
27	322	496	297	506	0.6%	1.3[1.01,1.68]
40	17	53	7	30	0.1%	1.55[0.56,4.32]
12	52	319	36	324	0.3%	1.56[0.99,2.46]
41	546	854	691	1182	0.8%	1.26[1.05,1.51]
42	122	190	110	158	0.3%	0.78[0.50,1.23]
26	138	191	69	114	0.3%	1.7[1.04,2.78]
43	37	58	42	75	0.2%	1.38[0.69,2.80]
44	764	1187	2836	4791	1.0%	1.25[1.09,1.42]
45	524	858	530	862	0.8%	0.98[0.81,1.19]
32	266	397	245	392	0.6%	1.22[0.91,1.63]
13	345	573	504	843	0.7%	1.02[0.82,1.26]
46	516	803	532	862	0.8%	1.12[0.91,1.36]
31	437	682	632	1078	0.8%	1.26[1.03,1.53]
28	573	906	503	889	0.8%	1.32[1.09,1.60]
47	62	100	38	82	0.2%	1.89[1.04,3.42]
48	58	572	82	587	0.5%	0.69[0.49,0.99]
49	306	532	226	374	0.6%	0.89[0.68,1.16]
25	849	1384	256	414	0.7%	0.98[0.78,1.23]
50	315	484	245	397	0.6%	1.16[0.88,1.52]
This study	50	218	60	214	0.4%	0.76[0.49,1.18]
51	485	750	1218	1879	0.8%	0.99[0.83,1.19]
52	186	287	1690	2684	0.6%	1.08[0.84,1.40]
53	770	1165	710	1135	0.9%	1.17[0.98,1.38]
54	830	1114	667	953	0.8%	1.25[1.03,1.52]
55	980	1590	741	1244	0.9%	1.09[0.94,1.27]
56	1192	1848	1218	1910	1.0%	1.03[0.90,1.18]
Subtotal (95% CI)		26991		35899	23%	1.14 [1.08,1.21]
Total events	6437		21261			
Heterogeneity: Tau-= 0.01; Chi^2= 78.53 ,df= 36 (P =0.0001); 1^2= 54%						Odds Ratio > 1; Increased Risk
Test for overall effect: Z=4.56 (P < 0.00001)						Odds Ratio < 1; Decreased Risk

Table 12. T2DM risk associated with *KCNJ11 rs5219* polymorphism in recessive model with OR and 95% CI

Recessive model						
Study or Subgroup	**Cases Events**	**Total**	**Controls Events**	**Total**	**Weight**	**Odds Ratio M-H, Fixed, 95% CI**
29	22	550	8	335	0.0%	1.70 [0.75,3.87]
34	81	499	57	494	0.2%	1.49 [1.03,2.14]
35	402	2734	603	4234	1.5%	1.04 [0.91,1.19]
36	21	172	18	113	0.1%	0.73 [0.37,1.45]
30	115	588	62	597	0.2%	2.10 [1.50,2.93]
37	379	2709	426	3344	1.2%	1.11 [0.96,1.29]
38	34	192	36	296	0.1%	1.55 [0.93,2.58]
33	85	550	161	1433	0.3%	1.44 [1.09,1.92]
39	82	805	40	503	0.2%	1.31 [0.88,1.95]
27	120	477	94	473	0.3%	1.36 [1.00,1.84]
27	23	104	21	98	0.1%	1.04 [0.53,2.03]
27	85	496	68	506	0.2%	1.33 [0.94,1.88]
40	3	53	1	30	0.0%	1.74 [0.17, 17.51]
12	5	319	3	324	0.0%	1.70 [0.40,7.19]
41	134	854	157	1182	0.4%	1.22 [0.95,1.56]
42	34	190	39	158	0.1%	0.67 [0.40,1.12]
26	51	191	16	114	0.1%	2.23 [1.20,4.14]
43	11	58	8	75	0.0%	1.96 [0.73,5.24]
44	196	1187	641	4791	0.8%	1.28 [1.08,1.52]
45	131	858	113	862	0.3%	1.19 [0.91,1.57]
32	86	397	58	392	0.2%	1.59 [1.10,2.30]
13	79	573	100	843	0.3%	1.19 [0.87,1.63]
46	134	803	124	862	0.4%	1.19 [0.91,1.55]
31	115	682	127	1078	0.3%	1.52 [1.16,2.00]
28	127	906	107	889	0.3%	1.19 [0.90,1.57]
47	17	100	11	82	0.0%	1.32 [0.58,3.01]
48	6	572	1	587	0.0%	6.21 [0.75, 51.76]
49	59	532	57	374	0.2%	0.69 [0.47, 1.03]
25	193	1384	52	414	0.3%	1.13 [0.81, 1.57]
50	83	484	50	397	0.2%	1.44 [0.98, 2.10]
This study	14	218	8	214	0.0%	1.77 [0.73, 4.30]
51	125	750	335	1879	0.6%	0.92 [0.74, 1.15]
52	49	287	403	2684	0.2%	1.17 [0.84, 1.61]
53	183	1165	193	1135	0.6%	0.91 [0.73, 1.13]
54	270	1114	181	953	0.5%	1.36 [1.10, 1.69]
55	246	1590	171	1244	0.6%	1.15 [0.93, 1.42]
56	329	1848	288	1910	0.8%	1.22 [1.03, 1.45]
Subtotal (95% CI)		26991		36899	11.4%	1.19 [1.14, 1.26]
Total events	4129		4838			
Heterogeneity: Chi-Square = 64.47, df=36 (P = 0.002); 1^2= 44%						Odds Ratio > 1; Increased Risk
Test for overall effect: Z=7.38 (P < 0.00001)						Odds Ratio < 1; Decreased Risk

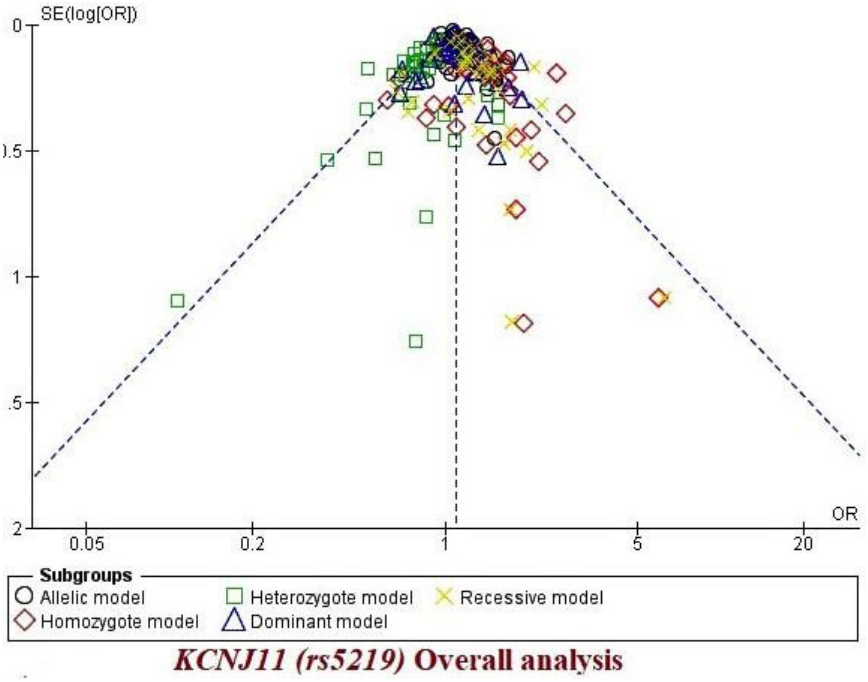

Figure 4. Funnel plot for association between *KCNJ11 rs5219* polymorphism and T2DM susceptibility. Funnel plot for publication bias on five genetic models in pooled analysis.

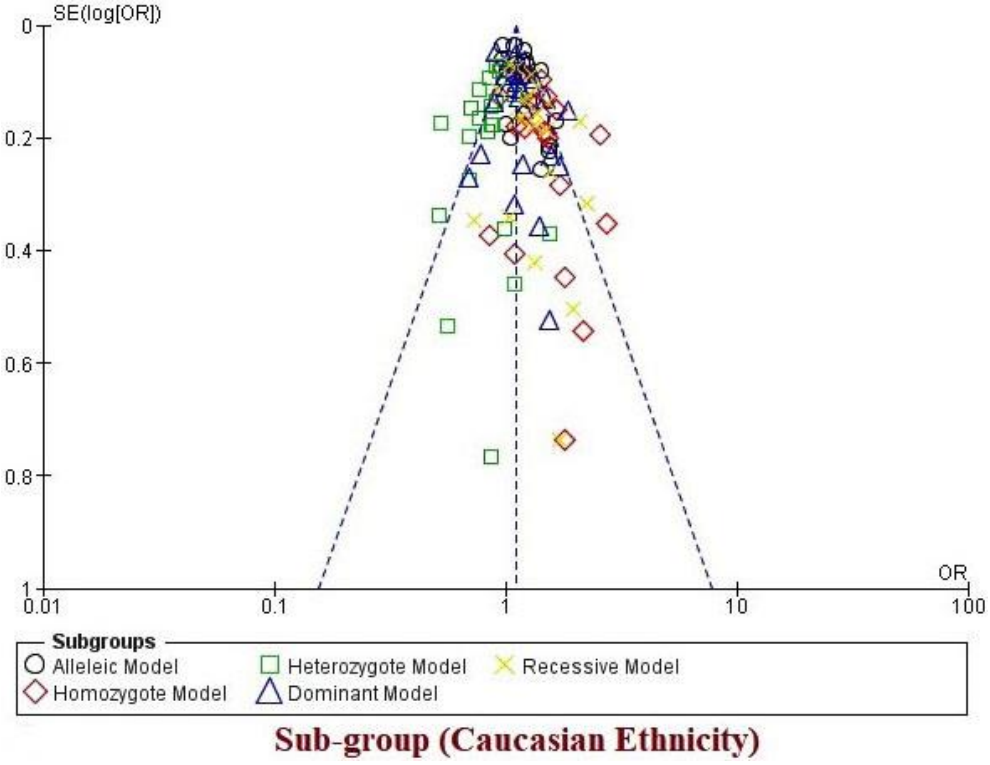

Figure 5. Funnel plot for association between *KCNJ11 rs5219* polymorphism and T2DM susceptibility. Funnel plot for publication bias on five genetic models in sub-group analysis of Caucasian population.

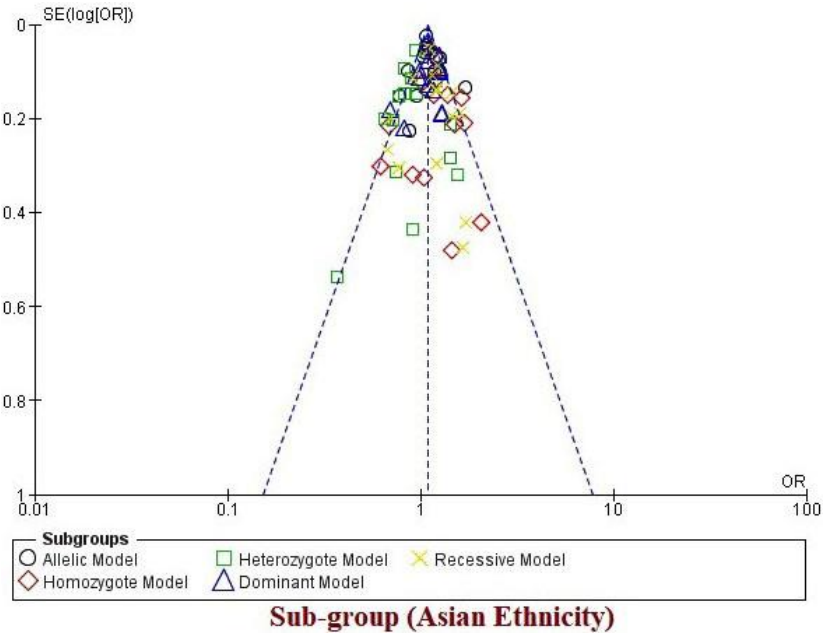

Figure 6. Funnel plot for association between *KCNJ11 rs5219* polymorphism and T2DM susceptibility. Funnel plot for publication bias on five genetic models sub-group analysis of Asian population.

were in similarity with previously published studies from France (26), Sweden (27), Japanese (28) and Saudi-Arabian (29) T2DM subjects belonging to Caucasian and Asian ethnic populations. Our results from the case-control study confirm the involvement of the *KCNJ11* gene *rs5219* SNP in the T2DM etiology, despite the populations and also with the geographical locations, respectively. Besides, the *rs5219* polymorphism showed an insight towards high HbA1c and serum uric acid, which confirms its functional importance in T2DM patients.

An extensive meta-analysis was executed to determine the relationship between *KCNJ11 rs5219* SNP with T2DM among Asian and Caucasian ethnic populations. The research articles related to the *KCNJ11* gene were identified through a systematic search followed by the quality assessment using HWE and NOS scores. The meta-analysis results for *rs5219* SNP showed a significant association (P-value < 0.05) among the allelic (T vs C) homozygote (TT vs CC), heterozygote (CT vs CC), dominant (CT+TT vs CC) and recessive (TT vs CC+CT) genetic models. These results were in agreement with previously published studies from UK (30), USA (31), Chinese (32), Japanese (33) and T2DM cases belonging to Caucasian and Asian ethnic backgrounds. However, the insignificant association was observed in Finland (61), and Czech (36) T2DM subjects. The discrepancies in the outcomes might be because of the fewer sample size, bias and study heterogeneity. The stratification analysis based on Asian and Caucasian sub-groups revealed a significant association of *rs5219* polymorphism with T2DM susceptibility among the studied genetic models. The cell line (*in vitro*) based studies on the p.E23K variant have suggested that it leads to a decrease in the sensitivity of Kir6.2 (subunit) towards the ATP, thus inhibiting the insulin secretion (62).

The potential strength of our *KCNJ11 rs5219* meta-analysis includes a large sample size of 26,991 T2DM subjects and 35,899 controls there are few considerable limitations. First, we determined the association between *rs5219* variant with T2DM risk, and the relationships with other confounding factors such as fasting insulin, fasting glucose concentrations, and lifestyle were not included in our case-control

Table 13. Meta-analyses of *rs5219* polymorphism and T2DM risk in each sub-group

Genetic models							
SNP-ID: *rs5219*	**No of studies**	**Ethnicity**	**I^2 (%)**	**Model**	**OR (95%CI)**	**Z-Test**	**P-value**
C vs T Allelic Model	21	Caucasian	62	random	1.06 (1.09-1.23)	4.97	<0.00001
	12	Asian	65	random	1.10 (1.02-1.20)	2.49	0.01
	03	South-Asian	00	fixed	0.85 (0.73-0.98)	2.19	0.03
	08	East-Asian	20	fixed	1.11 (1.06-1.17)	4.64	<0.00001
	04	Others	36	fixed	1.06 (0.95-1.18)	1.08	0.28
CC vs TT Homozygote Model	21	Caucasian	60	random	1.35 (1.20-1.52)	5.01	<0.00001
	12	Asian	44	fixed	1.21 (1.05-1.40)	2.55	0.01
	03	South-Asian	41	fixed	0.74 (0.54-1.02)	1.87	0.06
	08	East-Asian	22	fixed	1.25 (1.14-1.38)	4.58	<0.00001
	04	Others	00	fixed	1.31 (1.01-1.69)	2.06	0.04
CT vs TT Heterozygote Model	21	Caucasian	20	fixed	0.84 (0.78-0.97)	4.39	<0.0001
	12	Asian	51	random	0.89 (0.78-1.03)	1.56	0.12
	03	South-Asian	67	random	1.07 (0.58-1.95)	0.21	0.84
	08	East-Asian	42	fixed	0.87 (0.79-0.95)	2.95	0.003
	04	Others	13	fixed	0.78 (0.61-1.01)	1.87	0.06
CC + CT vs TT Dominant Model	21	Caucasian	61	random	1.14 (1.04-1.25)	2.91	0.004
	12	Asian	49	fixed	1.12 (1.06-1.18)	3.9	<0.0001
	03	South-Asian	82	random	0.90 (0.58-1.38)	0.49	0.63
	08	East-Asian	33	fixed	1.16 (1.08-1.25)	3.89	0.0001
	04	Others	00	fixed	1.31 (1.14-1.50)	3.89	0.0001
CC vs CT + TT Recessive Model	21	Caucasian	66	random	1.21 (1.14-1.28)	6.32	<0.00001
	12	Asian	55	random	1.16 (1.01-1.33)	2.10	0.04
	03	South-Asian	49	fixed	0.76 (0.57-1.02)	1.81	0.07
	08	East-Asian	36	fixed	1.19 (1.09-1.30)	3.96	<0.0001
	04	Others	00	fixed	1.28 (1.01-1.68)	2.02	0.04

study. Second, stratification analysis based on gender, age, lifestyle factors were not performed, because of the lack of uniform background data. Third, articles published in the English language were only considered. Fourth, we could not explain the underlying mechanisms of gene-environmental interactions.

6. CONCLUSION

In conclusion, the *rs5219* polymorphism in *the KCNJ11* gene was found to be associated with T2DM susceptibility in south Indians. Our findings, together with previous reports from Asians and Caucasians, show that the *KCNJ11* gene possesses a significant association with T2DM across multiple ethnicities. The results of meta-analysis, further add growing evidence of the positive effect of *rs5219* SNP on T2DM susceptibility. However, T2DM confounding factors such as hyperlipidemia, obesity, environmental, gene-gene interactions are necessary for verifying this association.

7. ACKNOWLEDGMENTS

Rajagopalan Aswathi, Dhasaiya Viji, Prathap seelan and Pricilla Charmine equally contributed this work. These three authors thank Chettinad Academy of Research and Education for funding this research. All the authors were thankful to the patients and controls for participating in the study. The author (Akram Husain) wishes to acknowledge Chettinad Academy of Research and Education (CARE) for providing chettinad research fellowship. All the

authors declare that they have no conflict of interest.

8. REFERENCES

1. D. Fang, B.-h. Zhang, S.-l. Zheng, X.-x. Huang, X.-b. Du, K.-h. Zhu, X.-j. Chen, J. Wu, D.-d. Liu and Z.-h. Wen: Association between SLC30A8 rs13266634 polymorphism and risk of T2DM and IGR in Chinese population: a systematic review and meta-analysis. Front. Endocrinol 9, 564 (2018)
DOI: 10.3389/fendo.2018.00564
PMid:30319545 PMCid:PMC6167413

2. L. Guariguata, D. R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp and J. E. Shaw: Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 103(2), 137-149 (2014)
DOI: 10.1016/j.diabres.2013.11.002
PMid:24630390

3. S. R. Joshi: Diabetes care in India. Ann. Glob. Health 81(6), 830-838 (2015)
DOI: 10.1016/j.aogh.2016.01.002
PMid:27108150

4. M. Murea, L. Ma and B. I. Freedman: Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. Rev Diabet Stud 9(1), 6-22 (2012)
DOI: 10.1900/RDS.2012.9.6
PMid:22972441 PMCid:PMC3448170

5. W. Zhao, A. Rasheed, E. Tikkanen, J.-J. Lee, A. S. Butterworth, J. M. Howson, T. L. Assimes, R. Chowdhury, M. Orho-Melander and S. Damrauer: Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease. Nat Genet 49(10), 1450 (2017)
DOI: 10.1038/ng.3943
PMid:28869590 PMCid:PMC5844224

6. M. Imamura, A. Takahashi, T. Yamauchi, K. Hara, K. Yasuda, N. Grarup, W. Zhao, X. Wang, A. Huerta-Chagoya and C. Hu: Genome-wide association studies in the Japanese population identify seven novel loci for type 2 diabetes. Nat. Commun 7, 10531 (2016)

7. S. Rizvi, S. T. Raza, Q. Rahman and F. Mahdi: Role of GNB3, NET, KCNJ11, TCF7L2 and GRL genes single nucleotide polymorphism in the risk prediction of type 2 diabetes mellitus. 3 Biotech 6(2), 255-255 (2016)
DOI: 10.1007/s13205-016-0572-x
PMid:28330327 PMCid:PMC5135703

8. C. Bellanné-Chantelot, C. Saint-Martin, M.-J. Ribeiro, C. Vaury, V. Verkarre, J.-B. Arnoux, V. Valayannopoulos, S. Gobrecht, C. Sempoux and J. Rahier: ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. J Med Genet 47(11), 752-759 (2010)
DOI: 10.1136/jmg.2009.075416
PMid:20685672

9. A. J. Smith, T. K. Taneja, J. Mankouri and A. Sivaprasadarao: Molecular cell biology of K ATP channels: implications for neonatal diabetes. Expert Rev Mol Med 9(21), 1-17 (2007)
DOI: 10.1017/S1462399407000403
PMid:17666135

10. M. S. Remedi and J. C. Koster: KATP channelopathies in the pancreas. Pflugers Arch, 460(2), 307-320 (2010)
DOI: 10.1007/s00424-009-0756-x

PMid:19921246

11. D. Viji, P. Aswathi, P. Pricilla Charmine, R. S. Akram Husain, S. Noorul Ameen, Sheik. S. S. J. Ahmed and V. Ramakrishnan: Genetic association of ABCC8 rs757110 polymorphism with Type 2 Diabetes Mellitus risk: A case-control study in South India and a meta-analysis. Gene Rep. 13, 220-228 (2018) DOI: 10.1016/j.genrep.2018.10.015

12. A. L. Gloyn, Y. Hashim, S. J. Ashcroft, R. Ashfield, S. Wiltshire and R. C. Turner: Association studies of variants in promoter and coding regions of beta-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with Type 2 diabetes mellitus (UKPDS 53) Diabet Med 18(3), 206-12 (2001) DOI: 10.1046/j.1464-5491.2001.00449.x PMid:11318841

13. R. J. Neuman, J. Wasson, G. Atzmon, J. Wainstein, Y. Yerushalmi, J. Cohen, N. Barzilai, I. Blech, B. Glaser and M. A. Permutt: Gene-gene interactions lead to higher risk for development of type 2 diabetes in an Ashkenazi Jewish population. PLoS One 5(3), e9903 (2010) DOI: 10.1371/journal.pone.0009903 PMid:20361036 PMCid:PMC2845632

14. C. Schwanstecher, U. Meyer and M. Schwanstecher: KIR6. 2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic β-cell ATP-sensitive K+ channels. Diabetes 51(3), 875-879 (2002) DOI: 10.2337/diabetes.51.3.875 PMid:11872696

15. V. Ramakrishnan, R. A. Husain and S. S. Ahmed: Genetic predisposition of IL-10 promoter polymorphisms with risk of multiple sclerosis: A meta-analysis. J Neuroimmunol 306, 11-18 (2017) DOI: 10.1016/j.jneuroim.2017.02.015 PMid:28385181

16. R. Kumar, L. P. Nandhini, S. Kamalanathan, J. Sahoo and M. Vivekanadan: Evidence for current diagnostic criteria of diabetes mellitus. World J Diabetes 7(17), 396 (2016) DOI: 10.4239/wjd.v7.i17.396 PMid:27660696 PMCid:PMC5027003

17. C. G. P. Mathew. The isolation of high molecular weight eukaryotic DNA. In: Nucleic Acids. Eds: J. M. Walker, Humana press, US (1984)

18. S. Ye, S. Dhillon, X. Ke, A. R. Collins and I. N. Day: An efficient procedure for genotyping single nucleotide polymorphisms. Nucleic Acids Res 29(17), e88-e88 (2001) DOI: 10.1093/nar/29.17.e88 PMid:11522844 PMCid:PMC55900

19. Y. Lu, C. Quan, H. Chen, X. Bo and C. Zhang: 3DSNP: a database for linking human noncoding SNPs to their three-dimensional interacting genes. Nucleic Acids Res D643-D649, 15 (2016) DOI: 10.1093/nar/gkw1022 PMid:27789693 PMCid:PMC5210526

20. S. S. Ahmed, R. A. Husain, S. Kumar and V. Ramakrishnan: Association between NOS1 Gene Polymorphisms and Schizophrenia in Asian and Caucasian Populations: A Meta-Analysis. Neuro-molecular Med 19(2-3), 452-461 (2017) DOI: 10.1007/s12017-017-8460-z PMid:28795310

21. A. Stang: Critical evaluation of the Newcastle-Ottawa scale for the

assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9), 603-605 (2010)
DOI: 10.1007/s10654-010-9491-z
PMid:20652370

22. V. Ramakrishnan, R. A. Husain and S. S. Ahmed: PSEN1 gene polymorphisms in Caucasian Alzheimer's disease: A meta-analysis. Clin Chim Acta 473, 65-70 (2017)
DOI: 10.1016/j.cca.2017.08.016
PMid:28821390

23. R. DerSimonian and N. Laird: Meta-analysis in clinical trials revisited. Contemp Clin Trials 45, 139-145 (2015)
DOI: 10.1016/j.cct.2015.09.002
PMid:26343745 PMCid:PMC4639420

24. R. S. A. Husain, K. Subramaniyan, S. S. S. J. Ahmed and V. Ramakrishnan: Association of PSEN1 rs165932 polymorphism with Alzheimer's disease susceptibility: An extensive meta-analysis. Meta Gene 19, 123-133 (2018).
DOI: 10.1016/j.mgene.2018.11.007

25. E. A. Sokolova, I. A. Bondar, O. Y. Shabelnikova, O. V. Pyankova and M. L. Filipenko: Replication of KCNJ11 (p. E23K) and ABCC8 (p. S1369A) association in Russian diabetes mellitus 2 type cohort and meta-analysis. PLoS One 10(5), e0124662 (2015)
DOI: 10.1371/journal.pone.0124662
PMid:25955821 PMCid:PMC4425644

26. E. Hani, P. Boutin, E. Durand, H. Inoue, M. Permutt, G. Velho and P. Froguel: Missense mutations in the pancreatic islet beta cell inwardly rectifying K+ channel gene (KIR6. 2/BIR): a meta-analysis suggests a role in the polygenic basis of Type II diabetes mellitus in Caucasians. Diabetologia 41(12), 1511-1515 (1998)
DOI: 10.1007/s001250051098
PMid:9867219

27. J. C. Florez, N. Burtt, P. I. De Bakker, P. Almgren, T. Tuomi, J. Holmkvist, D. Gaudet, T. J. Hudson, S. F. Schaffner and M. J. Daly: Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes 53(5), 1360-1368 (2004)
DOI: 10.2337/diabetes.53.5.1360
PMid:15111507

28. Y. Sakamoto, H. Inoue, P. Keshavarz, K. Miyawaki, Y. Yamaguchi, M. Moritani, K. Kunika, N. Nakamura, T. Yoshikawa and N. Yasui: SNPs in the KCNJ11-ABCC8 gene locus are associated with type 2 diabetes and blood pressure levels in the Japanese population. J Hum Genet 52(10), 781 (2007)
DOI: 10.1007/s10038-007-0190-x
PMid:17823772

29. O. Alsmadi, K. Al-Rubeaan, S. M. Wakil, F. Imtiaz, G. Mohamed, H. Al-Saud, N. A. Al-Saud, N. Aldaghri, S. Mohammad and B. F. Meyer: Genetic study of Saudi diabetes (GSSD): significant association of the KCNJ11 E23K polymorphism with type 2 diabetes. Diabetes Metab Res Rev 24(2), 137-140 (2008)
DOI: 10.1002/dmrr.777
PMid:17922473

30. D. Chistiakov, V. Potapov, D. Khodirev, M. Shamkhalova, M. Shestakova and V. Nosikov: Genetic variations in the pancreatic ATP-sensitive potassium channel, β-cell dysfunction, and susceptibility to type 2 diabetes. Acta

Diabetol 46(1), 43-49 (2009)
DOI: 10.1007/s00592-008-0056-5
PMid:18758683

31. L. Qi, R. Van Dam, F. Asselbergs and F. Hu: Gene-gene interactions between HNF4A and KCNJ11 in predicting Type 2 diabetes in women. Diabet Med 24(11), 1187-1191 (2007)
DOI: 10.1111/j.1464-5491.2007.02255.x
PMid:17894829

32. L. Liu, J. Lei, H. Liu, Q. Zou, Y. Sun, Y. Xu, H. Bi, F. Deng, X. Shao and S. Liu: Identification of susceptibility genes loci associated with type 2 diabetes. Wuhan Univ J Nat Sci 15(2), 171-175 (2010)
DOI: 10.1007/s11859-010-0216-7

33. Y. Doi, M. Kubo, T. Ninomiya, K. Yonemoto, M. Iwase, H. Arima, J. Hata, Y. Tanizaki, M. Iida and Y. Kiyohara: Impact of Kir6. 2 E23K polymorphism on the development of type 2 diabetes in a general Japanese population: The Hisayama Study. Diabetes (2007)
DOI: 10.2337/db06-1709
PMid:17965318

34. I. Barroso, J. a. Luan, R. P. Middelberg, A.-H. Harding, P. W. Franks, R. W. Jakes, D. Clayton, A. J. Schafer, S. O'Rahilly and N. J. Wareham: Candidate gene association study in type 2 diabetes indicates a role for genes involved in β-cell function as well as insulin action. PLoS biology, 1(1), e20 (2003)
DOI: 10.1371/journal.pbio.0000020
PMid:14551916 PMCid:PMC212698

35. S. Cauchi, K. T. Nead, H. Choquet, F. Horber, N. Potoczna, B. Balkau, M. Marre, G. Charpentier, P. Froguel and D. Meyre: The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications for association studies. BMC Med Genet, 9(1), 45 (2008)
DOI: 10.1186/1471-2350-9-45
PMid:18498634 PMCid:PMC2412856

36. P. Čejková, P. Novota, M. Černá, K. Kološtová, D. Nováková, P. Kučera, J. Novak, M. Anděl, P. Weber and E. ŽDÁRSKÝ: KCNJ11 E23K polymorphism and diabetes mellitus with adult onset in Czech patients. Folia Biol (Praha), 53, 173-175 (2007)

37. M. C. Cornelis, L. Qi, C. Zhang, P. Kraft, J. Manson, T. Cai, D. J. Hunter and F. B. Hu: Joint effects of common genetic variants on the risk for type 2 diabetes in US men and women of European ancestry. Ann Intern Med 150(8), 541-550 (2009)
DOI: 10.7326/0003-4819-150-8-20090-4210-00008
PMid:19380854 PMCid:PMC3825275

38. R. Van Dam, B. Hoebee, J. Seidell, M. Schaap, T. De Bruin and E. Feskens: Common variants in the ATP-sensitive K+ channel genes KCNJ11 (Kir6. 2) and ABCC8 (SUR1) in relation to glucose intolerance: population-based studies and meta-analyses. Diabetic Med 22(5), 590-598 (2005).
DOI: 10.1111/j.1464-5491.2005.01465.x
PMid:15842514

39. I. Ezzidi, N. Mtiraoui, S. Cauchi, E. Vaillant, A. Dechaume, M. Chaieb, M. Kacem, W. Y. Almawi, P. Froguel and T. Mahjoub: Contribution of type 2 diabetes associated loci in the Arabic population from Tunisia: a case-control study. BMC Med Genet 10(1), 33 (2009)
DOI: 10.1186/1471-2350-10-33

PMid:19368707 PMCid:PMC2678106

40. A. I. Ghanem, S. Rushdy and M. Mokhtar: Association between KCNJ11 & ABCC8 Genetic Polymorphism and Type 2 Diabetes in Egyptian Patients. Med. J. Cario Univ 84, 1501-1510 (2016)

41. A. L. Gloyn, M. N. Weedon, K. R. Owen, M. J. Turner, B. A. Knight, G. Hitman, M. Walker, J. C. Levy, M. Sampson and S. Halford: Large-scale association studies of variants in genes encoding the pancreatic β-cell KATP channel subunits Kir6. 2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52(2), 568-572 (2003)
DOI: 10.2337/diabetes.52.2.568
PMid:12540637

42. V. Gupta, R. Khadgawat, H. K. T. Ng, S. Kumar, A. Aggarwal, V. R. Rao and M. Sachdeva: A validation study of type 2 diabetes-related variants of the TCF7L2, HHEX, KCNJ11, and ADIPOQ genes in one endogamous ethnic group of North India. Ann Hum Genet 74(4), 361-368 (2010)
DOI: 10.1111/j.1469-1809.2010.00580.x
PMid:20597906

43. L. Hansen, S. M. Echwald, T. Hansen, S. A. Urhammer, J. O. Clausen and O. Pedersen: Amino acid polymorphisms in the ATP-regulatable inward rectifier Kir6. 2 and their relationships to glucose-and tolbutamide-induced insulin secretion, the insulin sensitivity index, and NIDDM. Diabetes 46(3), 508-512 (1997)
DOI: 10.2337/diab.46.3.508
DOI: 10.2337/diabetes.46.3.508
PMid:9032110

44. S. K. Hansen, E.-M. D. Nielsen, J. Ek, G. Andersen, C. Glümer, B. Carstensen, P. Mouritzen, T. Drivsholm, K. Borch-Johnsen and T. Jørgensen: Analysis of separate and combined effects of common variation in KCNJ11 and PPARG on risk of type 2 diabetes. J Clin Endocrinol Metab, 90(6), 3629-3637 (2005)
DOI: 10.1210/jc.2004-1942
PMid:15797964

45. M. Horikoshi, K. Hara, C. Ito, N. Shojima, R. Nagai, K. Ueki, P. Froguel and T. Kadowaki: Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 50(12), 2461-2466 (2007)
DOI: 10.1007/s00125-007-0827-5
PMid:17928989

46. E.-M. D. Nielsen, L. Hansen, B. Carstensen, S. M. Echwald, T. Drivsholm, C. Glümer, B. Thorsteinsson, K. Borch-Johnsen, T. Hansen and O. Pedersen: The E23K variant of Kir6. 2 associates with impaired post-OGTT serum insulin response and increased risk of type 2 diabetes. Diabetes 52(2), 573-577 (2003)
DOI: 10.2337/diabetes.52.2.573
PMid:12540638

47. H. Sakura, N. Wat, V. Horton, H. Millns, R. Turner and F. Ashcroft: Sequence variations in the human Kir6. 2 gene, a subunit of the beta-cell ATP-sensitive K-channel: no association with NIDDM in white Caucasian subjects or evidence of abnormal function when expressed *in vitro*. Diabetologia 39(10), 1233-1236 (1996)
DOI: 10.1007/BF02658512
PMid:8897013

48. M. M. Sale, S. G. Smith, J. C. Mychaleckyj, K. L. Keene, C. D. Langefeld, T. S. Leak, P. J. Hicks, D. W. Bowden, S. S. Rich and B. I. Freedman: Variants of the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in an African-American population enriched for nephropathy. Diabetes 56(10), 2638-2642 (2007)
DOI: 10.2337/db07-0012
PMid:17601994

49. D. K. Sanghera, L. Ortega, S. Han, J. Singh, S. K. Ralhan, G. S. Wander, N. K. Mehra, J. J. Mulvihill, R. E. Ferrell and S. K. Nath: Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTO variants confer a significant risk. BMC Med Genet 9(1), 59 (2008)
DOI: 10.1186/1471-2350-9-59
PMid:18598350 PMCid:PMC2481250

50. Y. Tabara, H. Osawa, R. Kawamoto, H. Onuma, I. Shimizu, T. Miki, K. Kohara and H. Makino: Replication study of candidate genes associated with type 2 diabetes based on genome-wide screening. Diabetes 58(2), 493-498 (2009)
DOI: 10.2337/db07-1785
PMid:19033397 PMCid:PMC2628625

51. P. Thorsby, K. Midthjell, N. Gjerlaugsen, J. Holmen, K. Hanssen, K. Birkeland and J. Berg: Comparison of genetic risk in three candidate genes (TCF7L2, PPARG, KCNJ11) with traditional risk factors for type 2 diabetes in a population-based study-the HUNT study. Scand J Clin Lab Invest 69(2), 282-287 (2009)
DOI: 10.1080/00365510802538188
PMid:18972257

52. M. Vaxillaire, J. Veslot, C. Dina, C. Proença, S. Cauchi, G. Charpentier, J. Tichet, F. Fumeron, M. Marre and D. Meyre: Impact of common type 2 diabetes risk polymorphisms in the DESIR prospective study. Diabetes 57(1), 244-254 (2008)
DOI: 10.2337/db07-0615
PMid:17977958

53. J. Wen, T. Rönn, A. Olsson, Z. Yang, B. Lu, Y. Du, L. Groop, C. Ling and R. Hu: Investigation of type 2 diabetes risk alleles support CDKN2A/B, CDKAL1, and TCF7L2 as susceptibility genes in a Han Chinese cohort. PloS One 5(2), e9153 (2010)
DOI: 10.1371/journal.pone.0009153
PMid:20161779 PMCid:PMC2818850

54. C. J. Willer, L. L. Bonnycastle, K. N. Conneely, W. L. Duren, A. U. Jackson, L. J. Scott, N. Narisu, P. S. Chines, A. Skol and H. M. Stringham: Screening of 134 single nucleotide polymorphisms (SNPs) previously associated with type 2 diabetes replicates association with 12 SNPs in nine genes. Diabetes 56(1), 256-264 (2007)
DOI: 10.2337/db06-0461
PMid:17192490

55. N. Yokoi, M. Kanamori, Y. Horikawa, J. Takeda, T. Sanke, H. Furuta, K. Nanjo, H. Mori, M. Kasuga and K. Hara: Association studies of variants in the genes involved in pancreatic β-cell function in type 2 diabetes in Japanese subjects. Diabetes 55(8), 2379-2386 (2006)
DOI: 10.2337/db05-1203
PMid:16873704

56. D. Zhou, D. Zhang, Y. Liu, T. Zhao, Z. Chen, Z. Liu, L. Yu, Z. Zhang, H. Xu and

L. He: The E23K variation in the KCNJ11 gene is associated with type 2 diabetes in Chinese and East Asian population. J Hum Genet 54(7), 433 (2009)
DOI: 10.1038/jhg.2009.54
PMid:19498446

57. X. Ding, Q. Hao, M. Yang, T. Chen, S. Chen, J. Yue, S. X. Leng and B. Dong: Polymorphism rs189037C> T in the promoter region of the ATM gene may associate with reduced risk of T2DM in older adults in China: a case control study. BMC Med Genet 18(1), 84 (2017)
DOI: 10.1186/s12881-017-0446-z
PMid:28806901 PMCid:PMC5557265

58. M. Guewo-Fokeng, E. Sobngwi, B. Atogho-Tiedeu, O. S. Donfack, J. J. N. Noubiap, E. N. Ngwa, E. P. Mato-Mofo, P. P. Fosso, E. Djahmeni and R. Djokam-Dadjeu: Contribution of the TCF7L2 rs7903146 (C/T) gene polymorphism to the susceptibility to type 2 diabetes mellitus in Cameroon. J Diabetes Metab Disord 14(1), 26 (2015)
DOI: 10.1186/s40200-015-0148-z
PMid:25897419 PMCid:PMC4403887

59. M. Song, F. Zhao, L. Ran, M. Dolikun, L. Wu, S. Ge, H. Dong, Q. Gao, Y. Zhai, L. Zhang, Y. Yan, F. Liu, X. Yang, X. Guo, Y. Wang and W. Wang: The Uyghur population and genetic susceptibility to type 2 diabetes: potential role for variants in CDKAL1, JAZF1, and IGF1 genes. OMICS, 19(4), 230-7 (2015)
DOI: 10.1089/omi.2014.0162
PMid:25785549 PMCid:PMC4390191

60. P. Haghvirdizadeh, Z. Mohamed, N. A. Abdullah, P. Haghvirdizadeh, M. S. Haerian and B. S. Haerian: KCNJ11: Genetic Polymorphisms and Risk of Diabetes Mellitus. J Diabetes Res 2015, 908152 (2015)
DOI: 10.1155/2015/908152
PMid:26448950 PMCid:PMC4584059

61. V. Lyssenko, A. Jonsson, P. Almgren, N. Pulizzi, B. Isomaa, T. Tuomi, G. Berglund, D. Altshuler, P. Nilsson and L. Groop: Clinical risk factors, DNA variants, and the development of type 2 diabetes. N. Engl. J. Med 359(21), 2220-2232 (2008)
DOI: 10.1056/NEJMoa0801869
PMid:19020324

62. C. Y. Cheung, A. W. Tso, B. M. Cheung, A. Xu, C. H. Fong, K. Ong, L. S. Law, N. M. Wat, E. D. Janus and P. C. Sham: The KCNJ11 E23K polymorphism and progression of glycaemia in Southern Chinese: a long-term prospective study. PLoS One, 6(12), e28598 (2011)
DOI: 10.1371/journal.pone.0028598
PMid:22163043 PMCid:PMC3230634

Abbreviations: T2DM, Type-2 Diabetes Mellitus; GWAS, Genome-Wide Association Studies; *KCNJ11, Potassium Voltage-Gated Channel Subfamily J Member-11*; LD, Linkage Disequilibrium; PRISMA, Preferred Reporting Items For Systematic Reviews And Meta-Analysis; ARMS-PCR, Amplification Refractory Mutation System-Polymerase Chain Reaction; HWE, Hardy-Weinberg Equilibrium; NOS, Newcastle Ottawa Scale; OR, Odds Ratios; CI, Confidence Interval.

Key Words: Diabetic Mellitus, *KCNJ11*, Polymorphism, Association, E23

Send correspondence to: Veerabathiran Ramakrishnan, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Chettinad Health City, Kelambakkam, 603 103, Tel: 044-4741109041, Fax: 044-47411011, E-mail: rkgenes@gmail.com