

Genotype of Potassium Inwardly Rectifying Channel, Subfamily J, Member 11 (KCNJ 11) Gene and Glycaemia Control in Diabetic Patients: A Narrative Review

Dyah Aryani Perwitasari^{a*}, Imaniar Noor Faridah^a, Haafizah Dania^a, Lalu Muhammad Irham^a, Fathia Vikri Salsabila^a, Rita Maliza^b

^aFaculty of Pharmacy, Universitas Ahmad Dahlan, Jl Prof Dr Soepomo, Janturan, Yogyakarta, 55164, Indonesia

^bFaculty of Science and Applied Technology, Universitas Ahmad Dahlan, Kampus Utama, Jl Jend A Yani, Yogyakarta, Indonesia

*Corresponding author: Dyah Aryani Perwitasari

Email: dyah.perwitasari@pharm.uad.ac.id

ABSTRACT

There are several factors that may affect the body response to the medicine and the drug response. One of the factors is the genetic variations. Some genes are predicted to have significant roles in oral antidiabetic response. This review is intended to define the role of Potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) genotypes to the glycemia control in Diabetes melitus type 2 (DMT2) patients. We conducted literature review using keywords "genotype description, *kcnj11* gene, blood sugar level, diabetes melitus type 2" in Pubmed, Science Direct, BMC, PMC and Google Scholar database. Among the fourteen articles, we found that the most alleles studied was: rs5219 and rs5215. The homozygous wildtypes of rs5219 have no correlation with the risk of DMT2. However, the correlation between the allele of rs5219 and the medication response are still unclear. Furthermore, the correlation of alleles of rs5215 and the risk of DMT2 and medication response are still contradictory. The future studies are still needed to confirm the correlation between allele of rs5219, rs5215 and the risk of DMT2 and medication response.

Keywords: Provide *KCNJ11*, Diabetic, medication, response

Correspondence:

Dyah Aryani Perwitasari

Faculty of Pharmacy, Universitas Ahmad Dahlan, Jl Prof Dr Soepomo, Janturan, Yogyakarta, 55164, Indonesia

Email: dyah.perwitasari@pharm.uad.ac.id

INTRODUCTION

Diabetes melitus type 2 (DMT2) is the metabolic disturbance indicated with the increase of Blood Sugar Level (BSL) due to the insulin resistance (1). DMT2 caused the sixth of death in the world in 2016 (2). The number of DMT2 in Indonesia is getting increase yearly and will reach 21.3 juta penduduk pada tahun 2030 (3). Genetic studies are needed of define the risk factor of genetic in DMT2. The results of genetic studies can be used to design prevention strategic and treatment (4). The *Genome Wide Association Study* (GWAS) reported some genes as the risk factors of DMT2, such as: *ABCC8*, *KCNJ11*, *PPAR γ* , *U1I*, *TCF7L2*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, *HHEX/IDE*, *FTO*, dan *SLC30A8*(5-9). One of the gene associated with DMT2 is *potassium inwardly rectifying channel (KCNJ11)*. This gen has a role in the expression of Kir6.2, the subdomain of integrated protein *K_{ATP} channel*, β pancreatic cell with the function of K⁺ selective membrane (4). The *KCNJ11* expressed the K⁺ ion channel which sensitive to the ATP and has significant role in controlling the insulin secretion (10). The polymorphism of *KCNJ11* related to rs5219, describes the substitution of glutamate to lysine which can cause the decrease sensitivity of K_{ATP}. This situation can open the channel more frequent and inhibit the insulin secretion (11)(12). Some previous studies found that genes variation can be the risk factor of DMT2 and some are associated with the glycaemic control (9,12). The aim of this narrative review is to describe the role of *KCNJ11* gene as the risk factors of DMT2 and its association with the glycaemia control.

MATERIAL AND METHODS

Materials

We found 5.290 articles from PubMed (446), *Google Scholar* (4.202), *Science Direct* (59), DOAJ, *BioMed Central* (44), dan *Europe PMC* (529) that were accessed during June 2020. After the critical appraisal, we identified 14 articles relevant

to the topic. The study outcomes were Fasting Blood Glucose (FBG), Blood Sugar Level (BSL) and HbA1C (Hemoglobin A1c).

METHOD

This review used a narrative review. The articles were found from *PubMed*, *Science Direct*, and *Google Scholar*. The inclusion criteria for the articles were full text articles and published from 2010 to 2020. Exclusion criteria was no genotype variations discussed in the article. The PICO were "*Genotype Description*" AND "*KCNJ11 gene*" OR "*ABCC8*" AND "*Blood Sugar Level*" OR *Diabetes Mellitus Type 2*. From the 5290 articles, we extracted 3797 articles due to the year limitation (2010-2020). The next procedures were selecting the articles based on the review objective and we got 29 articles. After the critical appraisal, we identified 14 articles met the criteria (Table 1).

RESULTS AND DISCUSSION

We found 15 articles which conducted in Egypt, Syrian, Mexico, Gaza, Russia, Iran, Kirgizstan and Indonesia. Table 2 shows the results of articles review. All of the studies are original articles with 9 studies of case control, 4 studies of RCT and 1 study of cross-sectional design. The total number of subjects participated in all studies were 3918, with 3129 among them are the DMT2 patients and the rests were subjects in control groups. We identified these SNPs; rs5219 (E23K dan Glu23Lysy), rs5218 (A190A), rs5216 (L267L), rs1800467 (L270V) and rs5215 (I337V).

The study of Gonen et al, 2012 in Turkish population, shows that the CC genotype of L5216, GA genotype of E23K, CC genotype of L267L and AA genotype of I337V are dominantly found in the case group. In the case group, the frequency of heterozygous and homozygous mutant is high (13). The study of Abed et al, 2013, in Gaza population, presents that KK genotype has high proportion in case

group (83%) and EE genotype has high proportion in control group (61.8%) (14). The study of Klen, et al, 2014, finds that the risk of hypoglycaemia is dominantly found in the heterozygous type of rs5215 and rs5219 (48.7% and 48.7%, respectively). However, the statistical analysis does not show the significant association between the genotypes and hypoglycemia risk (15). According to this result, the *KCNJ11* polymorphism have no association with treatment and hypoglycaemia risk. The study of Li et al, 2014, in 108 DMT2 patients treated with glicazide for 16 weeks, shows that subjects with KK genotype has better response for glicazide, compared to EE and EK genotypes. During the treatment, the carriers of K show the lower BGL and HbA1C compared to the carrier E (16). These results are consistent to study by Rastegari et al, 2015, in 40 DMT2 patients. The study shows that subjects with K allele carriers have higher risk of DMT2 risk and the healthy subjects have E allele carrier (17). In Russian population of DMT2, the prevalence of E and K alleles are 36.6% and 63.4%, respectively. The proportion of EE, EK and KK were 41%, 44.8% and 14.2%, respectively. Ghanem, et al, 2016 (18), also finds that the proportion of KK in the DMT2 group was higher than its proportion in the control group, even though there was no significant association. The study conducted by, Rodriguez-rivera, et al, 2017, in Mexican-Mestizo population. The highest proportion genotype is EK (45.3%) (19).

Isakova, et al, 2018 in Kirgiztan population presents that K allele has high proportion in DMT2 group than in the control group (44% vs 32.6%)(20). Sanchez-Ibara, et al, 2018 presents that the rs5219 has significant effect to the sulfonylurea response and the rs5215 did not have significant effect to sulfonylurea response. The individual with KK genotype of rs5219 has higher HbA1C level than other genotypes (21). Regarding to the drug response, some previous studies present the correlation between gene variants and drug response. The response of repaglinide and rosiglitazone were found influenced by *CYP2C8*, *SLCO1B1*, *PAX4* and *PSMD6* genes (22–25). The *KCNJ11* and *ABCC8* variants are more related to the sulfonylurea response (26). The clearance of sulfonylurea also associated with variants of *CYP2C9*2* and **3* (27,28). However, rs11212617 has association with the metformin response. The *SLC22A1* gene, is a marker for efficacy and excretion of metformine (29,30).

The other study by Muhammad, et al, 2018 also shows that the KK genotype has higher proportion in DMT2 patients than in the control group (15.4%) (31). The study of Makhzoom, et al 2019, in Suriah shows that DMT2 patients had 80% of genotype KK than in the control group (32). This results also supported by the study results of Sunita, et al, 2020 (33). Table 3 summarizes the *KCNJ11* genotype's role in the DMT2 disease and the treatment. Most of the studies in this review confirmed that the genotype KK of *KCNJ11* gene is related to the DMT2 disease risk. It caused by the mechanism of insulin secretion defect and mechanism of potassium channel affected by the lysin (10,34). One of the studies described the proportion of K allele among different population. The higher proportion is shown by China population and the lower proportion is shown by Mauretanian population (40% vs 19%, respectively). Generally, the proportion of K allele in North African is around 20%, in the Asian around 36%-40% and 37-39% in Caucasian (32). This proportion is appropriate to the incidence of DMT2 over the world with China, North African and Europe as the top highest prevalence of DM in the world (35). In various population, the individual with KK genotype has an increased risk of DMT2 as 1.25 to 3.8 times with the

recessive models (9,12,16,17,32,36,37). The DMT2 is a disorder which is not only caused by genetic, but also influenced by some others factors like diet, exercise and other lifestyle. The previous study in China, designed the epidemiology and genetic risk factors as the predictors of DMT2. More than 80 loci of genetic variants, combined with epigenetic, gene-environment interactions, and environment factors are considered as the DMT2 risk factors (38). Thus, in the future, the study of genetic polymorphism in DMT2, based on the ethnicities must be consider the other possible risk factors, like lifestyle and environmental support. The limitation of this review is according to the data we have, it is recommended to learn about other SNPs of *KCNJ11* and its role in the future. We suggest using Scifinder for the literatures search.

CONCLUSION

Our study finds that the genotypes of KK of rs5219 increased the risk of DMT2. However, the association of this SNPs with antidiabetic drug response and hypoglycemia risk must be explored in the future studies.

ACKNOWLEDGEMENT

The authors thank to the students participated in the narrative review of pharmacogenomic project.

CONFLICT OF INTEREST

All authors have no conflict of interests

REFERENCES

1. S Soegondo, P Soewondo, I Subekti S, Penatalaksanaan diabetes melitus terpadu: sebagai panduan penatalaksanaan diabetes melitus bagi dokter maupun edukator. Jakarta: Fakultas Kedokteran Universitas Indonesia; 2011.
2. Anonymous. The Top-10 Cause of Death [Internet]. [cited 2020 Aug 30]. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>
3. American Association of Diabetes. *Diagnosis and Classification of Diabetes Mellitus*. 2010;33:S62-69.
4. Vejrazková D, Bendlová B. [Two promising candidate genes in the ethiopathogenesis of DM2 - *PPARG* and *KCNJ11*]. *Cas Lek Cesk* 11 (2005): 721–726.
5. Jablonski KA, McAteer JB, de Bakker PIW, Franks PW, Pollin TI, Hanson RL, et al. *Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program*. *Diabetes*. 59 (2010):2672–2681.
6. Chen J, Sun M, Adeyemo A, Pirie F, Carstensen T, Pomilla C, et al. *Genome-wide association study of type 2 diabetes in Africa*. *Diabetologia*. 62 (2019):1204–1211.
7. Feng R-N, Li Y, Sun C-H. *TNF 308 G/A polymorphism and type 1 diabetes: a meta-analysis*. *Diabetes Res Clin Pract*. 85 (2009) : 4-7.
8. Zhao Y, Fang S, Que K, Xu G, Zhang H, Qi C, et al. *Urotensin-II gene rs228648 polymorphism associated with the risk of diabetes mellitus*. *Biosci Rep*. 38 (2018). doi: 10.1042/BSR20181275.
9. Benrahma H, Charoute H, Lasram K, Boulouiz R, Atig RK-B, Fakiri M, et al. *Association analysis of IGF2BP2, KCNJ11, and CDKAL1 polymorphisms with type 2 diabetes mellitus in a Moroccan population: a case-control study and meta-analysis*. *Biochem Genet*. 52 (2014):430–442.
10. Riedel MJ, Boora P, Steckley D, de Vries G, Light PE. *Kir6.2 polymorphisms sensitize beta-cell ATP-sensitive*

- potassium channels to activation by acyl CoAs: a possible cellular mechanism for increased susceptibility to type 2 diabetes? *Diabetes*. 52 (2003) 2630–2635.
11. He Y, Zhang R, Shao X, Hu C, Wang C, Lu J, et al. Association of *KCNJ11* and *ABCC8* genetic polymorphisms with response to repaglinide in Chinese diabetic patients. *Acta Pharmacol Sin*. 29 (2008):983–989.
 12. Chistiakov DA, Potapov VA, Khodirev DC, Shamkhalova MS, Shestakova M V, Nosikov V V. Genetic variations in the pancreatic ATP-sensitive potassium channel, beta-cell dysfunction, and susceptibility to type 2 diabetes. *Acta Diabetol*. 46 (2009) :43–49.
 13. Gonen MS, Arikoglu H, Erkok Kaya D, Ozdemir H, Ipekci SH, Arslan A, et al. Effects of single nucleotide polymorphisms in *K(ATP)* channel genes on type 2 diabetes in a Turkish population. *Arch Med Res*. 43 (2012):317–323.
 14. Asaf Abed, Basim Mohammad Ayesh, Osama Mohammad Hamdona A. Single nucleotide polymorphism *E23K* of *KCNJ11* gene and other risk factors associated with type-2 diabetes mellitus in Gaza. *Int J Chem Life Sci*. 2 (2013):1146–1152.
 15. Klen J, Dolžan V, Janež A. *CYP2C9*, *KCNJ11* and *ABCC8* polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients. *Eur J Clin Pharmacol*. 70 (2014) :421–428.
 16. Li Q, Chen M, Zhang R, Jiang F, Wang J, Zhou J, et al. *KCNJ11 E23K* variant is associated with the therapeutic effect of sulphonylureas in Chinese type 2 diabetic patients. *Clin Exp Pharmacol Physiol*. 41 (2014):748–754.
 17. Rastegari A, Rabbani M, Sadeghi HM, Imani EF, Hasanzadeh A, Moazen F. Association of *KCNJ11 (E23K)* gene polymorphism with susceptibility to type 2 diabetes in Iranian patients. *Adv Biomed Res*. 4 (2015): doi: 10.4103/2277-9175.148256
 18. Ghanem, Suzan Rushdy, Mohamed Mokhtar, Mohamed A.M.Atia, Shaimaa A Shouman AI. Association between *KCNJ11* & *ABCC8* Genetic Polymorphism and Type 2 Diabetes in Egyptian Patients. *Med J Cairo Univ*. 84 (2018):1501–1510.
 19. Rodríguez-Rivera NS, Cuautle-Rodríguez P, Castillo-Nájera F, Molina-Guarneros JA. Identification of genetic variants in pharmacogenetic genes associated with type 2 diabetes in a Mexican-Mestizo population. *Biomed reports*. 7 (2017):21-28
 20. Isakova J, Talaibekova E, Vinnikov D, Saadanov I, Aldasheva N. *ADIPOQ*, *KCNJ11* and *TCF7L2* polymorphisms in type 2 diabetes in Kyrgyz population: A case-control study. *J Cell Mol Med*. 23 (2019):1628–1631.
 21. Sanchez-Ibarra HE, Reyes-Cortes LM, Jiang X-L, Luna-Aguirre CM, Aguirre-Trevino D, Morales-Alvarado IA, et al. Genotypic and Phenotypic Factors Influencing Drug Response in Mexican Patients With Type 2 Diabetes Mellitus. *Front Pharmacol*. 9 (2018):320. doi: 10.3389/fphar.2018.00320
 22. Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, Neuvonen PJ. Polymorphism in *CYP2C8* is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther*. 74 (2003):380–387.
 23. Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M. Different effects of *SLCO1B1* polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J Clin Pharmacol*. 48 (2008):311–321.
 24. Aquilante CL, Bushman LR, Knutsen SD, Burt LE, Rome LC, Kosmiski LA. Influence of *SLCO1B1* and *CYP2C8* gene polymorphisms on rosiglitazone pharmacokinetics in healthy volunteers. *Hum Genomics*. 3 (2008):7–16.
 25. Chen M, Hu C, Zhang R, Jiang F, Wang J, Peng D, et al. A variant of *PSMD6* is associated with the therapeutic efficacy of oral antidiabetic drugs in Chinese type 2 diabetes patients. *Sci Rep*. 5 (2015):10701. doi: 10.1038/srep10701.
 26. Song J, Yang Y, Mauvais-Jarvis F, Wang Y-P, Niu T. *KCNJ11*, *ABCC8* and *TCF7L2* polymorphisms and the response to sulphonylurea treatment in patients with type 2 diabetes: a bioinformatics assessment. *BMC Med Genet*. 18 (2017):64. doi: 10.1186/s12881-017-0422-7
 27. Holstein A, Plaschke A, Ptak M, Egberts E-H, El-Din J, Brockmöller J, et al. Association between *CYP2C9* slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol*. 60 (2005):103–106.
 28. Ragia G, Petridis I, Tavridou A, Christakidis D, Manolopoulos VG. Presence of *CYP2C9*3* allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulphonylureas. *Pharmacogenomics*. 10 (2009):1781–1787.
 29. Nies AT, Koepsell H, Winter S, Burk O, Klein K, Kerb R, et al. Expression of organic cation transporters *OCT1 (SLC22A1)* and *OCT3 (SLC22A3)* is affected by genetic factors and cholestasis in human liver. *Hepatology*. 50 (2009):1227–1240.
 30. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1 (*OCT1*) on metformin action. *J Clin Invest*. 117 (2007):1422–1431.
 31. Muhammad , Agussalim AA A. Polymorphism Genes Sulphonylurea Receptpr-1 and Potassium InwardlyRectifying Channel Subfamily J Member 11 as a Risk Factor for Type 2 Diabetes Mellitus in Ethnic of Ternate. *Anat Physiol Curr Res*. 8 (2018):1–4.
 32. Makhzoom O, Kaban Y, Al-Quobaili F. Association of *KCNJ11 rs5219* gene polymorphism with type 2 diabetes mellitus in a population of Syria: a case-control study. *BMC Med Genet*. 20(2019):107. doi: 10.1186/s12881-019-0846-3.
 33. Sunita, Sahidan S, Hidayat R, Meinisasti R R. Polymorphism *E23K* *KCNJ11* Gen as a Risk Factor of Diabetes Mellitus in Serawai Tribe Of Bengkulu. *J Biomed Transl Res*. 4 (2020):11–18.
 34. Schwanstecher C, Meyer U, Schwanstecher M. *K(IR)6.2* polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic beta-cell ATP-sensitive *K(+)* channels. *Diabetes*. 52 (2002)87:875–879.
 35. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 157 (2019)107843. doi: 10.1016/j.diabres.2019.107843
 36. Abdelhamid I, Lasram K, Meiloud G, Ben Halim N, Kefi R, Samb A, et al. *E23K* variant in *KCNJ11* gene is associated with susceptibility to type 2 diabetes in the Mauritanian population. *Prim Care Diabetes*. 8 (2014):171–175.
 37. Fischer A, Fisher E, Möhlig M, Schulze M, Hoffmann K, Weickert MO, et al. *KCNJ11 E23K* affects diabetes risk and is associated with the disposition index: results of two independent German cohorts. *Diabetes Care*. 31 (2008):87–89.
 38. Hu C, Jia W. Diabetes in China: Epidemiology and Genetic Risk Factors and Their Clinical Utility in Personalized Medication. *Diabetes*. 67 (2018):3–11.

Table 1: The results of articles searching

Database	Key words	Articles found
PubMed	"genotype description" AND "KCNJ11 gene" OR "ABCC8" AND "Blood Sugar Level"	59
PubMed	"genotype description" AND "KCNJ11 gene" OR "ABCC8" AND "diabetes mellitus"	368
PubMed	"diabetes mellitus type 2") AND "KCNJ11 gene" AND "genotype description"	1
PubMed	"genotype description" AND "KCNJ11 gene" AND "diabetes mellitus"	2
PubMed	"genotype KCNJ11" AND "Diabetes mellitus type 2" AND "blood sugar level"	16
Google Scholar	"Genotype Description KCNJ11 gene Diabetes Mellitus type 2"	4.200
Google Scholar	"Deskripsi Genotip Gen KCNJ11 pada Diabetes Mellitus type 2"	2
Science Direct	"Genotype Description KCNJ11 gene Diabetes Mellitus type 2"	59
DOAJ	"type 2 diabetes mellitus and genotype KCNJ11 gene"	10
BioMed Center	"type 2 diabetes mellitus and genotype KCNJ11 gene"	44
Europe PMC	"Diabetes Mellitus type 2 and KCNJ11 polymorphism"	529
Total number of articles		5.290

Table 2: Studies related to the KCNJ11 gene and its glycaemic control

Author, year, country	title	Number of subjects	Method	SNPs related	Results
Gonen, et al (2012) Turki	Effects of Single Nucleotida Polymorphism in K(ATP) channel genes on Diabetes in Turkish Population	Case group: 169 Control group: 119	Case-control	rs2519 (E23K); rs5218 (A190A); rs5216 (L267L); rs1800467 (L270V); rs5215 (I337V)	The subjects with heterozygous are dominant in case group.
Abed, et al (2013) Gaza	Single Nucleotide Polymorphism E23K of KCNJ11 Gene and Other Risk Factors Associated with Type-2 Diabetes Mellitus In Gaza	Case group: 100 Control group: 100	Case-control	E23K	The subjects with K allele have risk factors of DMT2
Klen, (2014) Slovenia	CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients	21 DMT2 patient with sulfonilurea 35 DMT2 patients with sufonilurea + metformin	RCT	rs5219 (Lys23Glu) rs5215 (Val250lle)	rs5219 has no association with hypoglycemia
Li, (2014) China	KCNJ 11; E23K variant is associated with the therapeutic effect of sulphonylureas in Chinese type 2 diabetic patients	108 DMT2 patients treated with glicazid	RCT	rs5219	Subjects with K allele show high response to glicazid
Nikitin, et al (2015) Russia	Association of FTO, KCNJ11, SLC30A8, and CDKN2B polymorphism with type 2 diabetes mellitus	Case group: 440 Control group: 246	Case control	rs2519	Subjects with KK genotype shows higher risk of DMT2
Rastegari, et al (2015) Iran	Association of KCNJ11 (E23K) gene polymorphism with susceptibility to type 2 diabetes in Iranian patients	40 DMT2 patients	case-control	rs5219	Subjects with KK genotype shows higher risk of DMT2
Sorokina, et al (2016) Moskow	Evaluation of An Association Between Rs5219 Polymorphism of KCNJ11 Gene And The Risk Of Type 2 Diabetes Mellitus	1050 DMT2 patients	RCT	rs5219	Subjects with K allele have higher risk of DMT2
Ghanem, et al (2016) Mesir	Association between KCNJ11 & ABCC8 Genetic Polymorphism and Type 2 Diabetes in Egyptian Patients	Case group: 53 Control group: 30	case-control	rs5219 (E23K)	The genotypes show no association with DMT2 risk

Rodríguez-Rivera, et al (2017) Meksiko	Identification of genetic variants in pharmacogenetic genes associated with type 2 diabetes in a Mexican-Mestizo population	247 DMT2 patients	RCT	rs2519 (E23K)	Subjects with heterozygous show higher risk of DMT2
Isakova, et al (2018) Kirgistan	ADIPOQ, KCNJ11 and TCF7L2 polymorphisms in type 2 diabetes in Kyrgyz population: A case-control study	Case group: 114 Control group: 114 Control group: 109	case-control	rs5219	Subjects with K allele have higher risk of DMT2
Sanchez-Ibarra, et al (2018) Meksiko	Genotypic and Phenotypic Factors Influencing Drug Response in Mexican Patients with Type 2 Diabetes Mellitus	495 DMT2 patients	Cross sectional	Glu23Lys	Subjects with wildtype and homozygous mutant have higher level of HbA1C
Muhammad, et al (2018) Indonesia	Polymorphism Genes Sulfonylurea Receptpr-1 and Potassium Inwardly- Rectifying Channel Subfamily J Member 11 as a Risk Factor for Type 2 Diabetes Mellitus in Ethnic of Ternate	Case group: 52 Control group: 52	case-control	E23K	Subjects with EK genotype have protecting effect for DMT2 risk
Makhzoom, (2019) Siria	Association of KCNJ11 rs5219 gene polymorphism with type 2 diabetes mellitus in a population of Syria: a case-control study	Case group: 6 Control group: 63	case-control	rs5219	Subjects with K allele have higher risk of DMT2
Sunita, et al (2020) Indonesia	Polymorphism E23K KCNJ11 Gen as a Risk Factor of Diabetes Mellitus in Serawai Tribe of Bengkulu	Case group: 50 Control group: 50	Case-control	E23K	Subjects with K allele have higher risk of DMT2

Table 3: The KCNJ11 genotypes' role in the DMT2 disease and the treatment

rs id	Genotype' role	Genotype' role	Genotype' role
rs5219 (E23K)	GG has no risk to DMT2	GA has no risk to DMT2	AA has a risk to DMT2
rs5219 (E23K)	EE has low risk to DMT2 and has response to glicazide	EK has risk to DMT2 and has response to glicazide	KK has high risk to DMT2 and has response to glicazide
rs5219 (E23K)	CC has no association with drug response and hypoglycemia risk and low risk to DMT2	CT has no association with drug response and hypoglycemia risk and has risk to DMT2	TT has no association with drug response and hypoglycemia risk and high risk to DMT2 DMT2
rs5219 (Glu23Lys)	CC has low response to sulfonylurea and high risk to DMT2	CT has high response to sulfonylurea and has risk to DMT2	TT has low response to sulfonylurea and high risk to DMT2
rs5219 (Glu23Lys)	GluGlu has low risk to DMT2	GluLys has risk to DMT2	LysLys has high risk to DMT2
rs5218 (A190A)	C/C has no association with DMT2	C/T has no association with DMT2	T/T has no association with DMT2
rs5216 (L267L)	C/C has no association with DMT2	C/G has no association with DMT2	-
rs1800467 (L270V)	C/C has no association with DMT2	C/G has no association with DMT2	G/G has no association with DMT2
rs5215 (I337V)	A/A has low risk to DMT2	A/G has low risk to DMT2	G/G has low risk to DMT2
rs5215 (I337V)	TT has no association with drug response and hypoglycaemia risk	TC has no association with drug response and hypoglycaemia risk	CC has no association with drug response and hypoglycaemia risk