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The Reviewed studies on the Genetic Polymorphisms and Risk of Diabetes Mellitus Type-II

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ABSTRACT
This paper presents the analysis of the data of studies on the genetics of type 2 diabetes mellitus. High scientific quality papers of the recent years were used to prepare this work. This study was conducted to find the association between KCNJ11 and KCNQ1 with diabetes in Indian population. It was a retrospective study performed on 300 diabetes cases and 100 controls. All the cases were evaluated for the polymorphism as well as for biochemical and anthrometric analysis. Cases of diabetic subjects/patients and control/non- diabetic were collected with due consent and after getting Ethical clearance from the Institute Ethical Committee, Jamia Millia Islamia, New Delhi. The blood samples were collected from Ansari Health Center Jamia Millia Islamia and DNA was isolated for further study. However, a large cohort study is required to validate the expression of these genes in diverse country like India.
Key words : Type 2 diabetes mellitus, KCNJ11 and KCNQ1

INTRODUCTION
Introduction to type II DM Type II DM was priory named as non-insulin-needy or grown-up beginning diabetes, thought to be an outcome from a nonstop insulin secretary deformity on the foundation of insulin opposition because of the body's wasteful utilization of insulin.
Type II diabetes is the most run of the mill DM. In this type, the body is fit for creating insulin yet turns out to be resistant to the point that the insulin is ineffectual. When, insulin levels could in this manner turned out deficient. The reason for high blood glucose levels are both the insulin obstruction and inadequacy. Given that the side effects (unintentional to type I diabetes manifestations) are commonly less observable or missing, the disease could be expelled and be undiscovered for various years, and not until inconveniences have just rose. For different years, type II DM was watched just in grown-ups, these days it has begun to be seen likewise in youngsters. Until present the accurate foundations for the advancement of type II diabetes are obscure, some noteworthy hazard factors being called attention to. The most noteworthy ones include: abundance body weight, physical inertia and poor nourishment. Different elements which affected are ethnicity, family ancestry of DM, previous history of gestational diabetes and progressing age (WHO, 2016; Olokoba et al., 2012; Standards of Medical Care in Diabetes, 2014, 2015).
The worldwide pervasiveness of diabetes in grown-ups (20-79 years of age) as indicated by a report distributed in 2013 by the IDF was 8.3% (382 million individuals), with 14 million a bigger number of men than ladies (198 million men versus 184 million ladies), higher number were found between the ages 40 and 59 years and the number is required to ascend past 592 million by 2035 with a 10.1% worldwide predominance. With 175 million cases still undiscovered, the quantity of individuals as of now experiencing diabetes surpasses a large portion of a billion. An extra 21 million ladies are determined to have hyperglycemia amid pregnancy. The Middle East and North Africa area has the most elevated pervasiveness of diabetes (10.9%), be that as it may, Western Pacific district has the most astounding number of grown-ups determined to have diabetes (138.2

millions) and has additionally nations with the most noteworthy predominance (International Diabetes Federation, 2013). Low-and center pay nations incorporate 80% of the cases, "where the scourge is gathering pace at disturbing rates (International Diabetes Federation, 2013)".

In spite of the way that grown-up diabetes patients are predominantly Type II patients, it isn't evident whether the detailed 382 million grown-ups determined to have diabetes likewise incorporate Type I DM patients. Over 90%-95% of diabetes patients have a place with this type and the greater parts of these patients are grown-ups. The quantity of youth (under 20 years) with Type II DM in the United States in the year 2009 was 0.46 in 1000 and represented around 20% of Type II DM in youth (Dabelea et al., 2014). The expanded occurrence of type II DM in youth is predominantly because of the adjustment in the way of life of the youngsters as far as increasingly stationary life and less solid sustenance. Stoutness is the real explanation for insulin obstruction which is for the most part in charge of Type II DM (Ginsberg et al., 1975; Olefsky et al., 1973; Kraemer et al., 2014). The ADA prescribes screening of overweight kids and pre-adulthood to distinguish Type II DM (American Diabetes Association, 2000; Reinehr et al., 2013). The predominance of stoutness in youngsters in on the rise (Rosenbloom et al., 2009) which is most likely the principle explanation behind the expanded rate of Type II DM in the youthful (30.3% generally increment in Type II DM in kids and immaturity somewhere in the range of 2001 and 2009) (Dabelea et al., 2014).

Insulin opposition in Type II DM patients builds the interest for insulin in insulin target tissues. Notwithstanding insulin obstruction, the expanded interest for insulin couldn't be met by the pancreatic β cells because of imperfections in the capacity of these cells (Halban et al., 2014). In actuality, insulin discharge diminishes with the expanded interest for insulin by time because of the slow devastation of β cells (Druet et al., 2006) that could change some of Type II DM patients from being free to end up subject to insulin.

Most Type II DM patients are not subject to insulin where insulin emission proceeds and insulin consumption once in a while happens. Reliance on insulin is one of the real contrasts from Type I DM. Different contrasts incorporate the nonappearance of ketoacidosis in many patients of Type II DM and immune system annihilation of β cells does not happen. Both Type I and Type II DM have hereditary inclination, in any case, it is more grounded in Type II yet the qualities are more portrayed in Type I DM (the TCF7L2 quality is unequivocally connected with Type II diabetes) (Saadi et al., 2008). Because of the gentle side effects of Type II DM first and foremost, its finding is generally postponed for a considerable length of time particularly in nations where ordinary checkup without manifestations isn't a piece of the way of life. This postponement in analysis could build the rate of long term entanglements in Type II DM patients since hyperglycemia isn't treated amid this undiscovered period. Notwithstanding diabetes, insulin opposition has numerous appearances that incorporate corpulence, nephropathy, fundamental hypertension, dyslipidemia (hypertriglyceridemia, low HDL, diminished LDL molecule distance across, improved postprandial lipemia and remainder lipoprotein gathering), ovarian hyperandrogenism and untimely adrenarche, non-alcoholic greasy liver infection and foundational inflammation (Rosenbloom et al., 2009; Kraemer et al., 2014). The nearness of Type II DM in youngsters and youth who are not obese (Wei et al., 2003; Ramachandran et al., 2003; Sugihara et al., 2005), the infrequent extreme lack of hydration and the nearness of ketoacidosis in some pediatric patients with Type II DM (American Diabetes Association, 2000) had prompted the misclassification of Type II DM to Type I DM..

A few patients with numerous highlights of Type II DM have some Type I DM qualities including the nearness of islet cell auto antibodies or auto antibodies to GAD65 are delegated an unmistakable type of diabetes called dormant immune system diabetes in grown-ups (LADA) (Pozzilli and Di Mario, 2001). Individuals determined to have LADA don't require insulin treatment. In an ongoing report, Hawa et al (Hawa et al., 2014) detailed 7.1% of European patients with Type II DM with a mean age of 62 years, tried positive for GAD. Auto antibodies and the pervasiveness of LADA was higher in patients determined to have diabetes at a more

youthful age. This characterization of LADA as an unmistakable type of diabetes is still controversial (Rolandsson and Palmer, 2010; Redondo, 2013; Leslie et al., 2008).

KCNJ11: Genetic Polymorphisms and Risk of Diabetes Mellitus

DM is a noteworthy overall medical issue and its commonness has been quickly expanding in the only remaining century. It is brought about by deformities in insulin emission or insulin activity or both, prompting hyperglycemia. Of the different types of DM, Type II DM happens generally as often as possible. Various qualities and their communications are engaged with the insulin discharge pathway. Insulin discharge is intervened through the ATP-touchy potassium (KATP) direct in pancreatic beta cells. This channel is a heteromeric protein, made out of four internal rectifier potassium particle channel (Kir6.2) tetramers, which structure the pore of the KATP channel, just as sulfonylurea receptor 1 subunits encompassing the pore. Kir6.2 is encoded by the potassium deep down amending channel, subfamily J, part 11 (KCNJ11) quality, an individual from the potassium channel qualities. Various investigations have announced the inclusion of single nucleotide polymorphisms of the KCNJ11 quality and their communications in the helplessness to DM.

Role of Genetics in the Development of Diabetes Mellitus

Individuals with a family ancestry of type I DM and type II DM are six and multiple times almost certain, separately, to build up these maladies than are random people (Dorman and Bunker, 2000). Various qualities are associated with DM. Those that have collected the most consideration are the ATP-restricting tape transporter subfamily C part 8 (ABCC8) quality; the KCNJ11 quality; and the peroxisome proliferator-enacted receptor-gamma (PPARG) quality. The greater parts of these qualities are associated with insulin activity/glucose digestion, pancreatic beta cell work or other metabolic conditions (e.g., vitality consumption/use, lipid digestion) (Schwenk et al., 2013). Transformations in qualities, for example, ABCC8 and KCNJ11 can disturb the potentiation movement of the KATP channel and have in this manner been related with changeless neonatal DM (Abujbara et al., 2014). The PPARG quality is ensnared in adipogenesis and the improvement of insulin opposition. Injurious changes in this quality disable insulin opposition and can make absence of reaction insulin (Pattanayak et al., 2014).

From late genome-wide affiliation thinks about, more than 60, 500, and 65 loci have been distinguished for defenselessness to type I DM, type II DM and GDM, individually (Hivert et al., 2014). SNPs are the most widely recognized type of hereditary variety circulated inside or outside a quality area in the human genome. The recurrence of SNPs is under 1% in the genome, and around 54% of these variations are not harmful. SNPs can adjust the danger of event of a sickness, either alone or in linkage disequilibrium in one quality or in neighborhood qualities. For example, in a few investigations, the normal Pro12Ala polymorphismin the PPARGgene, theGlu23Lys polymorphismin the KCNJ11 quality, or the Ser1369Ala polymorphism in theABCC8 quality was affirmed to be related with Diabetes Mellitus (DM) (Bailey-Wilson and Wilson, 2011).

KCNJ11 Gene and Its Product

The KCNJ11 quality, an individual from the potassium channel genefamily, is situated at 11p15.1 and has no intron. This quality encodes an internal rectifier potassium particle channel (Kir6.2). The Kir6.2 protein, together with the high fondness sulfonylurea receptor 1 (SUR1), frames the KATP channel. SUR1 is encoded by the ABCC8 quality situated beside the KCNJ11 quality. The Kir6.2 protein is a 390-amino corrosive protein with two transmembrane areas (M1 and M2) and intracellular N-and C-terminals. Basically, Kir6.2 tetramers structure the pore and four high-liking SUR1 subunits encompass the pore of the KATP channel situated at the plasma film of pancreatic beta cells. This channel regulates insulin creation and emission through glucose digestion (McTaggart et al., 2010).

Role of Kir6.2 in Insulin Secretion

The Kir6.2 protein, combined with the SUR1 protein in the KATP channel, intervenes insulin discharge. This divert is engaged with a wide scope of physiological reactions. Expanded glucose prompts higher potassium

stream into the cell through the KATP channel. ADP within the sight of magnesium (Mg) changes over to ATP; the ATP at that point shuts the KATP channel by official to Kir6.2, expanding the intracellular potassium particle focus, which depolarizes the cell film and in this manner actuates calcium particle (Ca2+) channel. Ca2+ is a pervasive intracellular second courier that is basic for cell working. These calcium channels impact the voltage-subordinate potassium channels to repolarize the cell layer, prompting conclusion of the voltage subordinate calcium channels. Expanded intracellular free Ca2+ levels trigger different segments of the insulin emission pathway to discharge granules at or close to the plasma layer. Transformations in the KCNJ11 quality can cause DM in view of the diminished capacity of ATP to repress the movement of the KATP channel and the improved capacity of MgATP to at the same time animate the capacity of this channel. This is related with imperfect insulin discharge, at last causing DM (Ashcroft, 2006).

KCNJ11 Common Polymorphisms Involved in Diabetes

KCNJ11 has 219 SNPs, six of which have been getting more consideration for their relationship with diabetes. Among these six normal SNPs, three are situated in the coding locales and three in the noncoding districts. These six SNPs incorporate rs5219, rs5215, rs5210, rs5218, rs886288, and rs2285676.

KCNJ11 rs5219

This locus is situated in exon 1 of the KCNJ11 quality. Substitution of A to C (AAG→CAG) changes the amino corrosive from lysine to glutamine (Lys23Gln) at the NH2-terminal tail of Kir6.2. Lysine has a decidedly charged epsilon-amino gathering, though glutamine is uncharged under every natural condition. In spite of this amino corrosive substitution, hypothetically, it doesn't roll out a surprising improvement in the structure and capacity of the KCNJ11 protein (Harakalova et al., 2012). Studies have appeared, that the rs5219 variation may adjust the charge of the ATP-restricting locale and lessening channel affectability to ATP. Twenty-four affiliation ponders and an ongoing meta-examination demonstrated a solid connection between the rs5219 polymorphism and powerlessness to type II DM (Abdelhamid et al., 2014; Chen et al., 2013; Hu et al., 2009; Zhou et al., 2009; El-sisi et al., 2011) [19–22, 43], while 21 thinks about did not affirm this discovering (Keshavarz et al., 2014; Danquah et al., 2013; Gamboa-Mel´endez et al., 2012; Iwata et al., 2012; Ragia et al., 2012; Nikolac et al., 2009). This meta-investigation demonstrated that the rs5219 polymorphism is a hazard factor for creating type II DM in Caucasians and in some Asian populaces. Populaces from East Asia were increasingly inclined to this malady, where an allele recurrence in many patients was more typical than in controls. Along these lines, hereditary foundation can influence helplessness to type II DM (Qiu et al., 2014). The rs5219 polymorphism can influence the insulin discharge pathway. The An allele of this locus impedes this pathway by diminishing ATP affectability of the KATP channel, henceforth bringing about overactivity of the channel and ensuing concealment of insulin discharge. This impact on insulin emission is progressively critical in bearers of the AA genotype contrasted and transporters of the GA genotype (Liu et al., 2006). Comparable outcomes were watched for fasting plasma glucose and postprandial plasma glucose levels in patients with type II DM. The An allele expanded the fasting plasma glucose and postprandial plasma glucose levels in these patients, though GA bearers had higher 2 h postprandial plasma glucose levels than did GG transporters with type II DM. This allele was likewise connected with decrease in serum insulin levels in a postoral glucose resistance test (Yu et al., 2010). Rather than one investigation from Scandinavia on GDM hazard, the rest of the examinations did not report any relationship between this locus and type I DM and GDM (Pappa et al., 2011; Ekelund et al., 2012; Cho et al., 2009). Hypertension is a fundamental confusion of type II DM. The rs5219 polymorphism assumes a solid job in HbA1c and circulatory strain levels in this malady. The An allele transporters of rs5219 had higher HbA1c levels and circulatory strain than did the G allele bearers. In T2Diabetes Mellitus (DM), a relationship has been proposed between the An allele and expanded hepatitis insulin affectability. Pharmacogenomics considers showed that An allele bearers of the rs5219 polymorphism who have type II DM preferred helpful reaction to gliclazide over do G allele transporters.

In the associate degree allelomorph gathering, HbA1c was to bootfaded a lot of in patients taking glimepiride and glibenclamide than it absolutely was in patients taking gliclazide treatment (Javorsky et al., 2012). The ring-intertwined pyrrole moiety in these two medications ties to the An allele, subordinate the inhibitory intensity of these medications on KATP channels (Lang et al., 2012). The rs5219 polymorphism likewise assumes a job in deciding the viability of repaglinide. Transporters of the C allele were likewise found to have a diminished reaction to sulfonylurea treatment (Holstein et al., 2009).

KCNJ11 rs5215

The rs5215 polymorphism is situated in exon 1 of the KCNJ11 quality. It is a nonsynonymous variation brought about by a substitution of G to A (GTC→ATC), which changes the amino corrosive from valine to isoleucine at buildup 250. Valine is hydrophobic, while isoleucine is one of three amino acids having extended hydrocarbon side chains. Isoleucine is normally interchangeable with leucine and every so often with valine in proteins. Of 13 considers on DM, 3 demonstrated solid relationship between this variation and type II DM, while the rest of the investigations demonstrated no relationship with type II DM, type I DM, or GDM (Hotta et al., 2012; Odgerel et al., 2012; Cho et al., 2011; Heni et al., 2010; Lin et al., 2010; Winkler et al., 2012; Sanda et al., 2013). In another investigation, the rs5215 polymorphism was related with pulse among subjects with type II DM.

KCNJ11 rs5210

The rs5210 polymorphism is situated at a profoundly moderated 3' untranslated locale (UTR) of the KCNJ11 quality. Of four reports important to powerlessness to type II DM, two distinguished a conceivable job being developed of this ailment, though alternate examinations did not affirm this relationship (Feng et al., 2008). An examination found that this variation enhances the clinical viability of gliclazide in patients with type II DM (Xu et al., 2009). This locus is an objective of miR-1910; be that as it may, the instrument of activity of this miRNA in the improvement of DM is obscure. MiRNAs incorporate 17 to 25 nucleotides, which post transcriptionally direct the outflow of thousands of qualities in an expansive scope of life forms in both ordinary physiological and sickness settings. Proper emission of insulin from pancreatic beta cells is an indispensable factor in blood glucose homeostasis, and miRNAs have been distinguished as being engaged with the direction of insulin exocytosis. MiRNAs control insulin blend and discharge it in beta cells. The G allele is a potential focus for miR-1910, though the An allele nullifies official of this miRNA to this area (Dehwah et al., 2012). Further examinations may uncover the job of miR-1910 in DM.

KCNJ11 rs5218

The rs5218 polymorphism is situated in the 3'- UTR of the KCNJ11 quality. It is a synonymous variation with a substitution of G to A (GCC→GCT), which encodes, for alanine at buildup 103, a hydrophobic and conflicted amino corrosive. There is just a single report of this locus in DM, which demonstrated no relationship with type II DM hazard (Dehwah et al., 2012).

KCNJ11 rs886288 and rs2285676

The rs886288 polymorphism is situated in the 5' flank close to the quality, though the rs2285676 polymorphism is situated at the 3'- UTR district. Two examinations uncovered a relationship of the rs886288 and rs2285676 polymorphisms with Type II DM (Dehwah et al., 2012).

Mutations in KCNJ11 and the autosomal dominant, early-onset Type II diabetes mellitus

Development beginning diabetes of the youthful (MODY) is a monogenic, autosomal prevailing, early-beginning type of non-immune system diabetes brought about by essential pancreatic beta cell brokenness (Bonnefond et al., 2010), and in excess of ten MODY qualities have been recognized (Fajans and Bell, 2011). The clinical phenotype of familial early-beginning type II DM is frequently described by insulin obstruction, conversely with MODY, which is like later-beginning type II DM (Doria et al., 1999). Heterozygous initiating transformations in KCNJ11 have been accounted for as a reason for Perpetual Neonatal Diabetes Mellitus

(PNDM) (Gloyn et al., 2004) yet additionally MODY and grown-up beginning diabetes in a number of studies (Yorifuji et al., 2005). This was reaffirmed in a French MODY quality negative family a year ago (Bonnefond et al., 2012), wherein the characterized KCNJ11 quality was proposed to be MODY1.

KCNJ11 on 11p15.1 is a solitary open perusing outline encoding a 390-amino corrosive protein, potassium deep down redressing channel Kir6.2, which contains two putative trans membrane (TM) sections and a pore circle area, H5 (Inagaki et al., 1995; Tucker et al., 1998). ATP-delicate potassium channels (KATP) control electrical motioning by coupling cell digestion to potassium particle development crosswise over cell films. Pancreatic beta cell KATP channels contain two parts: four subunits of Kir6.2 shaping the channel pore, and the sulfonylurea receptor, SUR1, controlling channel gating (Girard et al., 2009). The KATP channel is delicate to ATP and restrained by sulfonylureas, drugs that are generally used to treat type II DM and manage insulin emission by coupling the metabolic condition of the cell to layer potential.

Transformations (for example E227K) and varieties (for example E23K) (Gloyn et al., 2003) in KCNJ11 have just been connected to diabetes. In Kir6.2 knockout mice, both glucose-and tolbutamide-actuated insulin emission and layer depolarisation and calcium convergence into beta cells are deficient, demonstrating that the direction of insulin discharge relies upon KATP channel action (Seino et al., 2000. A high recurrence of beta cell apoptosis is seen in Kir6.2G132S transgenic mice before the presence of hyperglycaemia, proposing that KATP channels additionally assume a noteworthy job in beta cell survival (Miki et al., 1997).

CONCLUSION

Finding of our study were consistent with many other research work with slight variations. In the literature, other methods were also used to assess the risk associated with these genes in the development of Type II DM in different ethnicities and race. However the Exact mechanism how these genes operate in the development of Type II DM is yet to be defined completely. Identification of the genetic determinants could facilitate the risk prediction of disease development and the implementation of individualised treatment for therapy. Up to now, genome-wide association studies (GWAS) for diabetes have identified more than 80 susceptibility loci, but only a small part of the heritability of diabetes can be explained by those findings. In the present study we observed a significant difference in the distribution of KCNJ11, KCNQ1 and MC4R genotypes among Type II DM case and healthy controls, higher mutant allele distribution was observed among Type II DM cases compared to healthy controls. Results of PCR-RFLP expression and statistical analysis of three genes are similar to many previous studies in the samples derived from Indian population are the main outcome of our present study.Based on these results we propose that every population should assess its own genetic makeup for the risk analysis of Type II Diabetes which will help us to understand the genetic alteration in the development of this disease.

REFERENCES

- Tan JT, Nurbaya S, Gardner D, et al. Genetic variation in KCNQ1 associates with fasting glucose and beta-cell function: a study of 3,734 subjects comprising three ethnicities living in Singapore. Diabetes. 2019; 58:1445-9.
- Qin LJ, Lv Y, Huang QY. Meta-analysis of association of common variants in the KCNJ11-ABCC8 region with type 2 diabetes. Genet Mol Res. 2023; 12(3):2990-3002.
- Koo BK, Cho YM, Park BL, et al. Polymorphisms of KCNJ11 (Kir6.2 gene) are associated with Type 2 diabetes and hypertension in the Korean population. Diabet Med. 2017; 24:178-86.
- Cruz M, Valladares-Salgado A, Garcia-Mena J, et al. Candidate gene association study conditioning on individual ancestry in patients with type 2 diabetes and metabolic syndrome from Mexico City. Diabetes Metab Res Rev. 2024; 26:261-70
- Li YY. The KCNJ11 E23K gene polymorphism and type 2 diabetes mellitus in theChinese Han population: a meta-analysis of 6,109subjects. Mol BiolRep. 2013; 40:141-6.

- Chen G, Xu Y, Lin Y, et al. Association study of genetic variants of 17 diabetes-related genes/loci and cardiovascular risk and diabetic nephropathy in the Chinese Shepopulation. J Diabetes. 2023; 5:136-45.
- Dobrikova M, Javorsky M, Habalova V, et al. Relationship of the CDKAL1 and KCNQ1 gene polymorphisms tothe age at diagnosis of type 2 diabetes inthe Slovakianpopulation. Vnitr Lek. 2021; 57:155-8.
- Gupta V, Vinay DG, Rafiq S, et al. Association analysis of 31 common polymorphisms with type 2 diabetes and its related traits in Indian sib pairs. Diabetologia. 2012; 55:349- 57.
- Kang ES, Kim MS, Kim CH, et al. Association of common type 2 diabetes risk gene variants and posttransplantation diabetes mellitus in renal allograft recipients in Korea. Transplantation. 2019; 88:693-8.
- Tsai FJ, Yang CF, Chen CC, et al. A genome-wide association study identifies susceptibilityvariantsfortype2diabetesinHanChinese.PLoSGenet.2020; 6:e1000847.