Journal of Diabetes and Clinical Practise

Extended Abstract Open Access

Diabetes Global 2016: Association of KCNJ11 E23K (rs5219) polymorphism to Type 2 diabetes mellitus: A case-control study in Indian population of Eastern Uttar Pradesh- Sunita Singh- Banaras Hindu University

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Abstract:

Aim: Potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11) genes has a key role in insulin secretion and is of substantial interest as a candidate gene for Type 2 Diabetes (T2D). The current work was performed to delineate the genetic influence of the most associated SNP of KCNJ11 gene E23K (rs5219) polymorphism on risk of T2D in Indian population of eastern Uttar Pradesh through case-control association study.

Method: A case-control study of 240 T2D cases and 229 controls was performed using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) approach to analyze the association of KCNJ11 E23K (rs5219) polymorphism on the risk of T2D. Odds ratio with 95% Confidence Interval (CI) was used to assess the association strength.

Result: Type 2 diabetes patients studied for the gene had significantly higher levels of Fasting Plasma Glucose (FPG) and 2 hours PPPG (P than healthy controls. The genetic variants of loci show Hardy-Weinberg distributions in our study. The genotype and allele distributions of polymorphism are significantly different between the T2D patients and healthy control groups. Our data show weak association to T2D with odds ratio 1.086 (95% CI 0.832-1.416; P=0.544).

Conclusion: Our data provides valuable information for comparison with other ethnic groups as well as in determining disease susceptibility in Indian population of eastern Uttar Pradesh. However, in view of the genetic diversity of Indians, the result needs to be replicated in other groups. Interestingly, our data for the SNP show small effect size than those reported in European and East Asian populations; and North-Western Indian populations.

Keywords: Association, Body Mass Index, KCNJ11, Ethnicity, SNP, Type 2 Diabetes, KATP Channel, E23K Polymorphism, Caucasian Population.

Introduction: Type 2 Diabetes mellitus (T2D) is a public health problem, which affects a millions worldwide. T2D is considered a multifactorial disorder, with both environmental and genetic factors contributing to its development. Impaired insulin secretion and insulin resistance both contribute to the pathogenesis of type 2 diabetes. The recently discovered genes by Genome-wide Association Studies (GWAS) suggest a shift from genes involved in insulin action to those involved in insulin secretion, indicating pivotal role of beta-cell dysfunction in the pathogenesis of T2D (reviewed in Singh, 2015). An important issue linked with diabetes development is the failure of the insulin releasing mechanism in pancreatic beta cells. Therefore, genes encoding proteins critical in pancreatic beta-cell functions including those associated with insulin secretion are particularly good candidates for susceptibility to T2D.

Material and Methods:

A. Sample Collection: Samples were collected from Eastern Uttar Pradesh in this case-control study. Blood from diabetic patients and normal healthy controls (>35 years) was collected after informed consent according to the approved protocol by the Institutional Ethical Committee of Banaras Hindu University from the patients attending out-patient departments of Institute of Medical Sciences, Banaras Hindu University, Heritage Hospital and Prakash Pathology, Varanasi.

B. Screening of the Study Subjects: We have genotyped single nucleotide polymorphism of KCNJ11gene E23K (rs5219) in 469 unrelated individuals from eastern Uttar Pradesh, India, including 240 type 2 diabetic patients and 229 ethnically matched control subjects. Subjects were diagnosed diabetic according to WHO criteria. Subjects were included in the diabetes group if they had fasting glucose concentrations ≥126 mg/dl or 2-hour glucose concentrations ≥200 mg/dl after a 75g Oral Glucose Tolerance Test (OGTT). Clinical history of diabetes and associated complications as well as the family history were recorded.

C. Anthropometric and Biochemical Evaluation: Anthropometric measurements including weight, height, and waist were obtained using standard protocol. The BMI was calculated as the weight in kilograms divided by the square of height in meters. Clinical and biochemical data (Fasting Plasma Glucose (FPG) and 2 hours Postprandial Plasma Glucose (PPPG) were obtained as part of our study protocol.

D. DNA Analysis and Genotyping: Blood sample (4-5ml) was taken in 0.5 M EDTA (Sigma, USA) vials. Genomic DNA was extracted from peripheral blood leukocytes using the standard salting-out method,

Statistical Analysis: Clinical characteristics of the studied patients and controls were recorded. Data on quantitative characteristics are expressed as mean ± SD. Comparison of allele and genotype frequencies.

Discussion: The KCNJ11 gene on chromosome 11p15.1 has attracted considerable attention as a promising candidate for T2D because of its function as a key factor in the regulation of glucose-induced insulin secretion. Although inconsistent results have been obtained in some earlier studies by Hani et al. and Yamada et al., but Gloyn et al and Love-Gregory et al confirmed the association of KCNJ11 rs5219 polymorphism and the susceptibility to T2D in Caucasian subjects. Later studies in Caucasians have shown that normoglycemic lysine carriers show consistently a defect in insulin secretion. Functional studies suggested that the KK genotype might induce a critical inhibition of glucose-induced insulin release from pancreatic bcells.

Results: Clinical characteristics of the studied patients & controls are shown in. Type 2 diabetes patients studied for the gene had significantly higher levels of Fasting Plasma Glucose (FPG) and 2hr PPPG (P<0.003). The Waist Circumference (WC) and BMI were also significantly different between diabetic patients and normal healthy controls (P<0.001; P<0.015, respectively). The genetic variants of loci show Hardy-Weinberg distributions in our study.

This work is partly presented at 13th Global Diabetes Conference & Medicare Expo on August 08-10, 2016 in Birmingham, UK .