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Genetic polymorphisms in *KCNJ11 (E23K, rs5219)* and *SDF-1β (G801A, rs1801157)* genes are associated with the risk of type 2 diabetes mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a global major health problem resulting from interaction of environmental and genetic factors, examples of the latter being *KCNJ11* (coding for part of the ATP-sensitive potassium channel) and *SDF-1β* (coding for chemokine CXCL12). Our case-control study was conducted to assess whether recessive, dominant or additive genotype model associations of *KCNJ11 (E23K, rs5219) and SDF-1β (G801A, rs1801157)* were more strongly linked to type 2 diabetes.

Subjects & Methods: Genetic polymorphism analysis was performed by polymerase chain reaction-restriction fragment length polymorphism. Alleles and genotype frequencies between 200 cases and 200 controls were determined and compared.

Results: The dominant (EE v EK + KK, $p = 0.022$) and additive (EK v EE + KK, $p = 0.021$) models, but not the recessive model (KK v EE + EK, $p = 0.727$) of *KCNJ11* were linked to diabetes. Similarly, the dominant (GG v GA + AA, $p < 0.001$) and additive (AG v GG + AA, p=<0.001) models, but not the recessive model (AA v AG + GG, $p = 0.430$) of *SDF-1β* were linked to diabetes. The A allele ($p = 0.006$) of SDF-*1β* was protective against the risk of T2DM.

Conclusion: Both dominant and additive models in both *KCNJ11 (E23K, rs5219)* and *SDF-1β (G801A, rs1801157)* genetic polymorphisms are significantly associated with type 2 diabetes.

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Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder where high levels of glucose have adverse effects on various major organs of the body leading to diseases such as kidney failure, cardio-vascular diseases, neuropathy and impotence. China, India and U.S.A. are among the top three countries with a high number of diabetics, and diabetes rates have increased significantly in various low- and middle-income countries (India, China, Indonesia, Pakistan, Egypt and Mexico) [1]. The number of diabetics was 20.4 million in China (1980) rising to 102.9 million (2014), a rise equally dramatic in India of 11.9 million in 1980 to 64.5 million in 2014 [1]. This form of diabetes has a multifactorial aetiology, where genetic factors in combination with environmental factors confer the risk of the development and progression of this disease [2]. The incidence, prevalence and mortality due to diabetes in North India is distinct from other ethnic populations. The causes of these disparities are manifold, including intrinsic differences (such as genetic variation), and extrinsic differences (dissimilarities in social, economic and geographical environments). Among the various risk factors, obesity and lack of exercise due to changes in lifestyle (which increases the obesity rate from 8 to 38% in rural and 13 to 50% in urban areas) are leading causes and which also poses challenges in treatment [3].

However, not all type 2 diabetes can be attributed to these two features. More than 120 distinct genetic loci, with more than 150 variants, (such as *TCF7L2, GNB3, SDF-1β, KCNJ11* and *PPARG*) have been identified that may be involved in the pathogenesis of diabetes [4]. ATP-sensitive potassium channels (KATP) are transmembrane proteins present on beta cells encoded by *KCNJ11* and *ABCC8* genes. This channel protein regulates insulin secretion by the beta cells where an increase in the blood sugar levels reduce the permeability of KATP channels and an increase in Ca^2 + influx into the cell which causes insulin secretion [5]. Genetic alterations in *KCNJ11* are associated with diabetes due to the effect of KATP channels on insulin secretion. Various genetic polymorphisms in *KCNJ11* gene had been identified, of which *E23K (rs5219)* was found to be strongly associated with diabetes risk [2]. This polymorphism results in substitution of A to C (AAG → CAG) in codon 23 of the amino terminal tail of Kir6.2, changing the amino acid from lysine to glutamine (Lys23Gln) [6]. Studies have shown that the

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rs5219 variant may alter the charge of the ATP-binding region and decrease channel sensitivity to ATP. Several studies have linked *KCNJ11* with the disease, including a meta-analysis on 4000 individuals [7–9].

Stromal cell derived factor-1 (SDF-1), also known as CXCL12, is a peptide chemokine (coded for by a gene on chromosome 10q11.1) having two isoforms: SDF-1α and SDF-1β [10]. These have been found to play a role in type 2 diabetes and its associated secondary complications where peripheral blood monocytes were seen to express more inflammatory cytokines in patients than in their healthy counterparts [11]. *G801A,* a single nucleotide polymorphism (rs1801157), is the most studied polymorphism in *SDF-1β*. It occurs at position 801 in the 3′ untranslated region of *SDF-1β* gene resulting in a G > A transition where the mutant A allele results in upregulation of *SDF-1β* gene expression [12]. This polymorphism has been studied in various diseases, including diabetes, HIV infection and cancer [13–15].

Many of the published links between polymorphisms in *KCNJ11* and *SDF-1β* and diabetes consider only a single genotype model, and some are contradictory. We hypothesised that recessive, dominant or additive genotypes would describe stronger links with type 2 diabetes.

Materials and methods

We tested our hypothesis in 200 type 2 diabetes patients and 200 age, sex and ethnicity matched healthy controls, all enrolled from the Diabetic clinic of the Department of Medicine at Era's Lucknow Medical College & Hospital, Lucknow, India. The study was conducted after approval of Institutional Ethics Committee of Era's Lucknow Medical College & Hospital and a written informed consent was taken from all subjects before commencement of the study. Subjects with fasting plasma glucose (FBS) ≥7.0 mmol/l or 2–h post prandial blood sugar (PPBS) concentrations ≥11.1 mmol/l were categorised as cases. Control samples were defined as those with fasting blood sugar level ≤6.1 mmol/L without family history of diabetes. No subject was receiving any medications at the time of participation. Exclusion criteria were type 1 diabetes, gestational diabetes, maturity-onset diabetes of the young or having secondary diabetic complications, those suffering from acute or chronic diseases of the heart liver or kidney, and having a malignancy. Standard routine clinical and laboratory data (age, sex, blood pressure, body mass index, height, weight, HbA1c (%), lipid profile, etc.) was collected.

Fasting blood sugar was measured by glucose oxidase–peroxidase method; serum cholesterol by cholesterol oxidase–peroxidase method; serum triglyceride by glycerol phosphate oxidase–peroxidase amidopyrine method; Serum creatinine levels were measured by kinetic Jaffe method whereas high-density lipoprotein (HDL), HbA1C and cholesterol (immunoinhibition) were assessed by XL-300 Transasia Fully Auto Analyzer Transasia, Mannheim, Germany. For HbA1c estimation we used Gen X haemoglobin A1c-Direct kit of Gen X special live series provided by Proton Biologicals, India Pvt. Ltd. The kit for calculation of results apply IFCC calibrated values using the equation NGSP=(0.0915 X IFCC) + 2.15 expected values. (NGSP units in % while IFCC units were in mmol/mol Hb). Low-density lipoprotein (LDL) was calculated using Friedewald's formula [16]. Body mass index (BMI) was calculated as weight in kg/height in m^2. All experiments were performed in accordance with the ethical standards of the Helsinki Declaration and all the assays were performed following the standard manufacturer's protocols.

Genomic DNA was extracted from peripheral blood leucocytes using the standard phenol-chloroform extraction method. The *KCNJ11 (E23K, rs5219)* and *SDF-1β (G801A, rs1801157)* polymorphisms were genotyped in controls and cases using polymerase chain reaction and restriction fragment length polymorphism. PCR amplification was carried out in a reaction mixture of 20 µl containing 0.5U Taq DNA Polymerase, 20 mM Tris HCl, 80 mM KCl, 4 mM $MgCl_2$, 10 pmol/l of each primer, approximately 100–150 ng of genomic DNA and nuclease free water in T100 Thermal Cycler (Biorad, U.S.A.). The PCR conditions and primers used for *KCNJ11* and *SDF-1β* genes were in accordance with primers and PCR protocols described elsewhere [7,17]. Amplified products were further digested with BanII (5U) and MspI (5U) restriction enzymes and ultimately resolved on 2% and 3% agarose gels for *KCNJ11* and *SDF-1β* genes, respectively (as shown in Figures 1 and 2).

Statistical analyses were performed with SPSS version 12 software (IBM Corp., Chicago, Illinois, U.S.A.). Variables were tested for normality using the Kolmogorov–Smirnov test. Variables with a normal distribution were expressed as mean with standard deviation. The genotyping data were compared between cases and controls using Chi-square test. *P*-values ≤0.05 were considered as significant. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to test the relative risk for association.

Results

Cases and controls were matched for age (46 and 45 years, respectively, $p = 0.079$) and sex (101 males/99 females and 102 males/98 females, respectively, $p = 0.920$). Clinical and biochemical parameters of cases and controls are shown in Table 1. As expected, all indices were significantly more adverse in the cases (all $p < 0.001$).

The genotype distribution of both *KCNJ11* and *SDF-1β* genes were in good agreement with the predicted

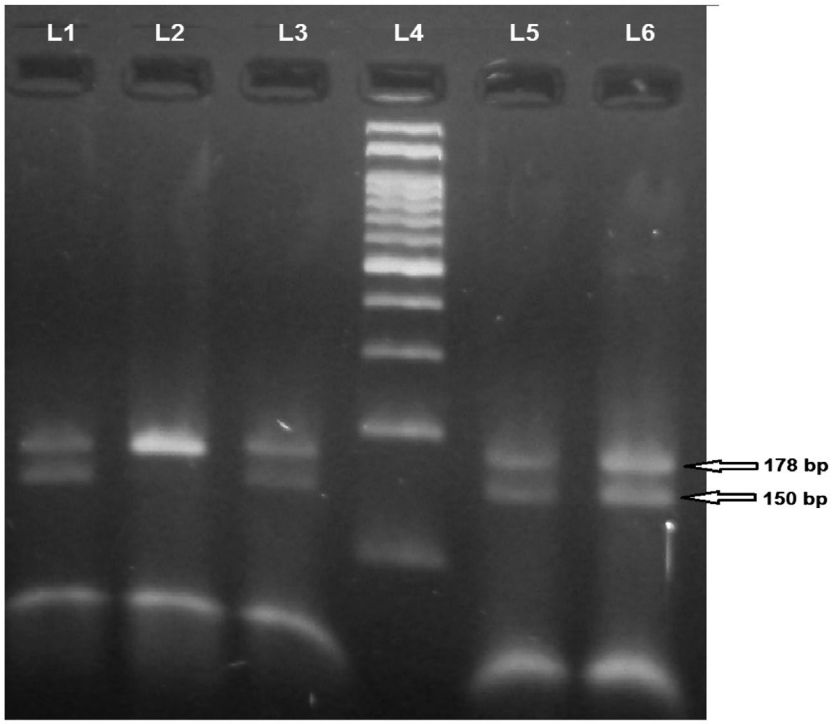

Figure 1. The 3% Agarose gel picture of *BanII* digested products of *KCNJ11*gene.
Notes: Lane 2 shows the mutant KK genotype corresponding to two bands of size 178 and 32 bp; Lane 1, 3, 5, and 6 shows EK genotype corresponding to four bands of 178, 150, 32, and 28 bp; whereas Lane 4 shows a 100 bp ladder (Bands corresponding to size 32 and 28 bp are not visible in the gel due to very small size).

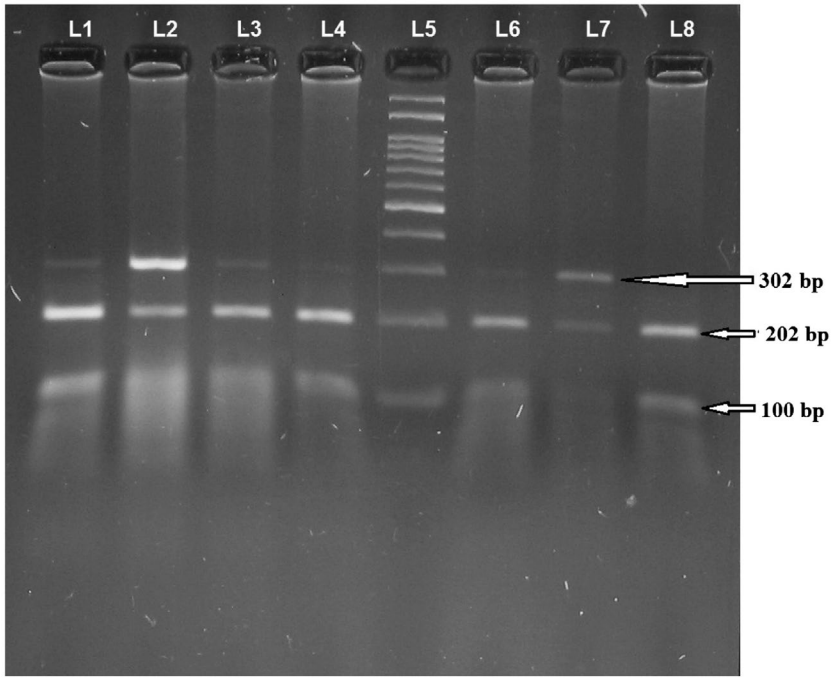

Figure 2. The 2% Agarose gel picture of *MspI* digested products of *SDF-1β* gene.
Notes: Lane 1, 3, 4, 6, and 8 shows the wild type GG genotype corresponding to two bands of size 202 and 100 bp; Lane 2 and 7 shows AG genotype corresponding to three bands of 302, 202, and 100 bp; whereas Lane 5 shows a 100 bp ladder.

Hardy–Weinberg equilibrium. The frequencies of EE, EK, and KK genotypes of *KCNJ11* were n = 42 (21%), n = 141 (70.5%), and n = 17 (8.5%), respectively, in the cases and n = 62 (31%), n = 119 (59.5%), and n = 19 (9.5%) in healthy controls (p = 0.05). The frequencies of E and K were n = 225 (56.25%) and n = 243 (43.75%), respectively, in cases and n = 243 (60.75%) and n = 157 (39.25%), respectively, in controls (p = 0.196). Distribution of *KCNJ11 (E23K, rs5219)* genotypes according to dominant, recessive, and additive models showed significant differences in dominant and additive models between diabetes cases and controls (Table 2).

The frequencies of AA, AG, and GG genotypes of *SDF-1β* gene were $n = 9$ (4.5%), $n = 101$ (50.5%), and $n = 90$ (45%), respectively, in cases, and $n = 6$ (3%), $n = 144$ (72%), and $n = 50$ (25%), respectively, in healthy controls ($p < 0.001$). The frequencies of A and G alleles in cases and controls were $n = 119$ (29.75%) and $n = 281$ (70.25%) vs. $n = 156$ (39%) and $n = 244$ (61%), respectively ($p = 0.006$). Distribution of *SDF-1β (G801A, rs1801157)* genotypes according to dominant, recessive, and additive models showed significant differences in dominant and additive models between cases and controls (Table 2).

Discussion

Type 2 diabetes is a genetically heterogeneous disease: in twins about 26% of this risk can be attributed to genetic factors [18], whilst in unrelated probands this falls to 20% [4]. The pattern of inheritance suggests that multiple genes and different combination of genes are involved in the development of diabetes.

Polymorphisms in *KCNJ11* result in neonatal diabetes and congenital hyper-insulinaemia, wherein the *E23K (rs5219)* polymorphism is linked with diabetes susceptibility where the K allele plays an important role in insulin secretion through reduction of ATP sensitivity of the KATP channel and suppression of insulin secretion [19,20]. In the past decade, a number of case-control studies have been conducted to investigate the association between the *KCNJ11 (E23K, rs5219)* polymorphism and diabetes in different populations, although results have not been in full agreement [2,4,6–9], possibly because of samples size and/or the genotype model used. Our data in the general, dominant and additive models is similar to results from a Mauritanian population, where a similar association was observed in the general model (OR/95% CI 2.08,1.09–3.97, $p = 0.026$) and under the dominant model (OR/95% CI 2.49, 1.12–5.55, $p = 0.026$) [21]. On comparing our results with other studies, we found a major difference in the frequency distribution of EE, EK, and KK genotypes in our diabetes subjects compared to Iranian (15, 50, 35%), South Indian (46.3, 28.2, 25.5%), and Indo-Trinidadian (32.73, 50.6, 16.67%) subjects [7,22,23]. In addition, E and K allele frequencies of our subjects were different from those observed in the Iranian population (40, 60%) but were similar to those in South Indian (60, 40%) and Indo-Trinidadian (58, 42%) diabetics [7,22,23]. The frequencies of E and K alleles of our control subjects were also similar to frequencies observed in controls from Iran (62.5, 37.5%) and South India (65, 35%) [7,22]. We observed a significant association of the *KCNJ11 (E23K, rs5219)* polymorphism with diabetes in our cases, in agreement with studies from East Asians [24], Japanese [25], Chinese [26], Iranians [7], North-western Indians [27], and Tunisians [28]. However, it failed to concur with a studies of Mauritanians of African descent, Lebanese, and the Han population of Qingdao, which showed no such association [21,28,29].

The *SDF1–3′* G(801)A allele increases the expression of *SDF-1β*. Individuals carrying this allele have higher levels of SDF-1β protein [30]. To date, only one study of *SDF-1β (G801A, rs1801157)* polymorphism with diabetes has been reported, which failed to show an association of *SDF-1 β* gene polymorphism with diabetes [31]. In our study, the frequency of AA genotype was 4.5% in our cases, similar to the frequency of AA genotype observed

Table 1. Comparison of biochemical parameters in diabetes cases and controls.

Variables	Controls ($N = 200$)	Cases ($N = 200$)
BMI (kg/m2)	20.6 [4.2]	23.8 [4.9]
SBP (mmHg)	120 [7]	127 [18]
DBP (mmHg)	80 [4]	84 [11]
PPBS (mmol/L)	7.1 [0.6]	14.0 [2.1]
FBS (mmol/L)	4.1 [0.3]	9.7 [4.8]
RBS (mmol/L)	6.3 [1.1]	11.9 [5.3]
Creatinine (μmol/L)	50 [10]	70 [10]
HbA1C (%)	5.6 [0.1]	7.9 [0.1]
Cholesterol (mmol/L)	9.2 [1.4]	11.4 [2.8]
Triglyceride (mmol/L)	6.9 [1.4]	9.6 [3.9]
HDL (mmol/L)	3.0 [0.5]	2.3 [0.3]
VLDL (mmol/L)	1.3 [0.3]	2.0 [1.7]
LDL (mmol/L)	5.4 [1.1]	7.0 [3.9]

Notes: Data are mean (standard deviation). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PPBS: Post prandial blood sugar; FBS: fasting blood sugar; RBS: random. blood sugar; HbA1C: glycated hemoglobin; HDL: high-density. lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein.

Table 2. Genotypes of *KCNJ11 and SDF-1β* in diabetes cases and healthy controls.

Model	Genotype	Controls (*n*, %)		Cases (*n*, %)		Odds ratio (95% CI)	*p*
(a) KCNJ11							
Recessive	KK	19	9.5	17	8.5	0.88 (0.44–1.76)	0.737
	EE+KK	181	90.5	183	91.5	Reference	
Dominant	EE	62	31.0	42	2.0	0.59 (1.07–2.66)	0.022
	EK+KK	138	69.0	158	79.0	Reference	
Additive	EK	119	59.5	141	70.5	1.63 (1.07–2.46)	0.021
	EE+KK	81	40.5	5,	29.5	Reference	
(b) SDF-1β							
Recessive	AA	6	3.0	9	4.5	1.52 (0.53–4.36)	0.43
	GG+AG	194	97.0	191	95.5	Reference	
Dominant	GG	50	25.0	90	45.0	2.45 (1.61–3.75)	<0.001
	AG+AA	150	75.0	110	55.0	Reference	
Additive	AG	144	72.0	101	50.2	0.40 (0.26–0.60)	<0.001
	GG+AA	56	28.0	99	49.5	Reference	

in Iranian diabetics (4%) [31]. The frequency of GG genotype observed in our diabetics subjects was significantly higher than our controls, in agreement with the earlier reported Iranian study where the frequency of GG genotype was higher in diabetes cases (33.3 and 23.5%) as compared to controls (10, 23%, respectively) [31]. The frequency of A allele in our cases was higher than the frequency observed in Iranian diabetics (15.3%) [31]. In case of G allele, we observed a higher frequency in our cases as compared to Iranian cases (34.8%) [31].

Although the leading cause of diabetes is obesity and lack of exercise [3], these do not account for all disease, and genetic factors are being increasingly recognised as having a role [2,4,6]. This work represents an advance in biomedical science because it shows that the dominant and additive genotype models, but not the recessive model, of *KCNJ11 (E23K, rs5219)* and *SDF-1β (G801A, rs1801157)* polymorphisms are linked with diabetes.

Summary table

What is known about this subject?

- Various polymorphisms in candidate/susceptibility genes such as *TCF7L2, GNB3, KCNJ11, SDB-1β*, and *PPARG* with diabetes disease risk and progression have been reported
- A number of risk alleles for diabetes and mutations in several genes may add up and predispose an individual to increased risk of disease.

What this paper adds

- The distribution of *KCNJ11 (E23K, rs5219)* genotypes according to dominant, recessive, and additive models shows significant differences in dominant and additive models between diabetes cases and controls.
- Distribution of *SDF-1β (G801A, rs1801157)* genotypes according to dominant, recessive, and additive models showed significant differences in dominant and additive models between cases and controls.
- The recessive model of *KCNJ11 (E23K, rs5219)* and *SDF-1β (G801A, rs1801157)* cannot discriminate diabetics from healthy controls.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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