Associations of Polymorphic Markers Aluins/Deli>DAce T-786C Gene Enos3 in Diabetic Nefropate Progressing for Type 2 Diabetes Mellitus

Ozimboy O Jabbarov*1, Botir T Daminov2, Kodirjon T Boboev3, Laylo D Tursunova1, Maxsuma X Tashpulatova1, Lola I Maksudova4

1Department of faculty and hospital therapy No.2, Farabi 2, Tashkent - 100109, Uzbekistan
2Department of Propaedeutics of Internal Diseases, Hospital and Faculty Therapy, Doctor of medicine, Bagishamal str., 223. Yunusabad region, Tashkent city - 100140, Uzbekistan
3Head of the Laboratory of Medical Genetics, Doctor of Medicine, Medical Care Department 138 Usman Nasyr street, Tashkent city - 100059, Uzbekistan
4Department of children’s infections, Bagishamal str., 223. Yunusabad region, Tashkent city - 100140, Uzbekistan

ABSTRACT

In the current study, the development of diabetic nephropathy identified the relationship between the polymeric marker of AC genes and the NS3 gene. One hundred twenty-nine patients with type 2 diabetes were tried. Patients in the principle gathering: 65 people with diabetes nephropathy preserved kidney function (33 patients), and kidney function weakness (32 patients), 64 patients with Diabetes were enduring more than 10-20 years, diabetic nephropathy preserved the chain of genotyping polymers carries out kidney function (31 patients). The study showed a link between eNOS3 genes in the development of diabetic nephropathy in Type 2 diabetes patients, supported by the ACE gene.

INTRODUCTION

Diabetic nephropathy (DN) is a microvascular complex of Diabetes, which develops under the control of a completely combined effect of work and hemodynamic substances (Colombo et al., 2003). In addition to the above elements, there are also genetic trends that interact with the clinical manifestation of this pathology. (Ezzidi et al., 2008) Despite the similar incidence of type 1 and type 2 diabetes, patients with type 2 diabetes are more likely to die from terminal kidney failure - 45% compared to 5–10% of type 1 diabetes (Dellamea et al., 2014).

Convenient recognition of this difficulty legitimately influences the adequacy of treatment, exhibits the significance and significance of the issue of reading hazard factors for DNA and shows the need to create enlightening techniques for its determination. (Dellamea et al., 2014)

To be able to diagnose and prevent DN early, it is necessary to identify markers associated with DN, which in turn will help to form danger groups for DN growth even in the preclinical step. (Ezzidi et al., 2009)

Also, it is of practical interest to study the progress of NAM for actual preventive procedures and reduction of chronic kidney failure (CRI). The cost of exceptional treatment at the terminal level of naturopathy is high. (Maslova et al., 2005; Villeneuve et al., 2014) In this way, the issue of kidney entanglements of Diabetes mellitus, notwithstanding clinical, has
obtained significant financial significance. (Hana, 2011)

Hereditary components dictate the danger of rising nephropathy before clinical preliminaries. Around 40–half of the patients by type 1 and type 2 diabetes later create DNA. Genetic plants can distress the growth of DM and 100 or work together with genes that cause heart disease. In contrast to possible genetic markers, this preventative pathology drug acts as one of the essential functions of the Medicines. (Koopal et al., 2015).

By creating such markers, physicians create risk groups for diseases. (Macisaac et al., 2014) They include an individual diagnosis or diagnosis (including the earlier clinical release of the disease) in some pathologies. (Maslova et al., 2005) The occupation of genetic signs in Diabetes relies upon the racial recurrence and racial and ethnic contrasts between the genotypes of the individuals considered. (Morshe et al., 2002). In recent years, the genetic risk of Diabetes and its complications has been widely discussed in insulin resistance genes, insulin-based genes, lipid metabolism-affected genes, angiotensin i-conversion enzyme (AC) polymorphism, and endothelial no-synthesis (NOS) (Ezzeidi et al., 2009; Hana, 2011).

As indicated by the present-day hypothesis, DNA creates under the total complex impact of reciprocal, hemodynamic and hereditary parts, the activity of which prompts the clinical appearances of pathology. In the pathogenesis of DN, the activation of the local renal renin-angiotensin system (RAS) is of great importance, which leads to the development of systemic and intracellular hypertension. (Ezzeidi et al., 2008) The mechanism of pathogenic effect of angiotensin II (AT-II) at DM is determined not only by vasoconstrictor action but also by proliferative, prooxidant and prothrombogenic activity, stimulation of cytokine synthesis, growth factors. Therefore, the genes encoding the components of the RAC gene of the angiotensin-converting enzyme (ACE) are of interest as candidates of diabetic nephropathy in patients with type 2 DM (Mustafina et al., 2001).

At present the pathogenesis of micro- and macrovascular complications of DM is dominated by endothelial dysfunction, accompanied by a deficit of vasodilators - nitrogen oxide (NO), and activation of local secretion of vasoconstrictors such as endothelin-1 (E-1). (Macisaac et al., 2014) In its turn, the gene of nitrogen oxide endothelial synthesise (eNOS3) participates in the production of the latter as candidate genes for diabetic nephropathy and CKD (Chronic kidney disease) of type 2 SD (Ng et al., 2005).

Nevertheless, the single density and properties of AC and eNOS3 genes, which cause activation of RAAS (renin-angiotensin-aldosterone system) and endothelial dysfunction, are of interest to the study as a candidate gene that controls the trend of vascular complications in type 2 diabetes. (Rizvi et al., 2014)

Explore and distinguish the connection between the AC quality and the INS3 quality as indicators of the turn of events and movement of patients with type 2 diabetes mellitus and decide the hereditary diagnostics of the Uzbek national hazard industrial facility. (Uryasiev and Shakhanov, 2017)

There are multiple variants of the AC, and Inose3 genes for type 2 diabetes and its macrobiotic and microvascular complications have not been previously studied in Uzbek nationalities. (Villeneuve et al., 2014)

The research objective is to evaluate the contribution of polymorphic markers AluIns/Del>D of the ACE gene and T-786C of the eNOS3 gene to the danger of diabetic nephropathy.

**MATERIALS AND METHODS**

One hundred twenty-nine patients at The Republican Scientific and Practical Center Nephrology, based at the TMA Multidisciplinary Clinic, was tested for the diagnosis of type 2D clinical lysis; The control group included 110 healthy Uzbeks in the “case-control” policy. Patients of the key group are spread as trails: disease duration ten years, diabetic nephropathy retains renal function (33 patients) and renal impairment (32 patients), permanent normal blood and urine tests over 10-20 years 64 patients, lipid Spectrum, glycemic outline, glycosylated haemoglobin, microlamination, strawberry filtration rate (CCD-EPI), endothelin-1 level plasma, resonance, SAMD and Doppler renal vessels were studied. The eNOS3 quality was completed by Applied Biosystems 2720 (USA) utilizing test frameworks from Lightech (Russia) as indicated by the maker’s directions. STATISTICA 6 was utilized for measurable handling of materials. Information is introduced as mean qualities with standard deviations (m. SD). The Kolmogorov - Smirnov rules tried the typical dissemination. The general danger of infection in transporters of specific alleles and genotypes was determined as a marker of the extent of positivity. The OR esteem was determined to utilize online clinical insights adding machine (http://med statistic.ru/calculators.html).

Genotype share was verified for anomaly from hard balance Weinberg. The correlation coefficient was
measured utilizing the Spearman method. Differences between $P<0.05$ considered statistically significant.

**RESULTS AND DISCUSSION**

The frequency of alleles and genotypes of AluIns/DelI>D ACE gene polymorphism in entire analyze patients in the principal, and manageable groups are shown in Figure 1.

![Figure 1: Frequency of AluIns/DelI>D polymorphism alleles and genotypes in the main and control groups of the ACE gene](image1)

According to the results obtained, the prevalence of genotypes I/I, I/D, D/D was 42.6%, 39.5%, 17.8%, and 34.5%, 46.4%, and 19.1% respectively. According to statistical calculations, there is no probability of disease development in D/D genotype carriers compared to I/I genotype carriers ($\chi^2$=0.1; $P=0.8$; OR=0.9; 95% CI 0.478-1.771). Genotype I/I was significantly higher in the control group than in the main group, at 42.6% and 34.5% respectively, and showed a protective function against disease progression by 1.4 times, but no positive difference was found ($\chi^2$ = 1.6; $P=0.2$; OR=1.4; 95% CI 0.833-2.382). Genotype I/D was significantly lower in the major group than in the control group by 39.5% and 46.4% respectively, and the probability of disease development was not observed ($\chi^2$ = 1.1; $P=0.3$; OR=0.7; 95% CI 0.452-1.266).

Genetic testing of alleles and genotypes of polymorphic marker AluIns/DelI>D on the ACE gene was compared with the main and control groups, and the probability of functional unpleasant allele D in the main group was not reliable OR = 0.8 (CI 95% 0.57-1.18), ($P>0.2$). The probability of participation of mutational homozygous DD-genotype, also causing the disease, was not found OR = 0.9 (CI 95% 0.47-1.77), ($P>0.8$). In addition, the heterozygous I/D genotype has no probability of OR = 0.8 (CI 95% 0.45-1.26), ($P>0.3$).

The initial I allele OR = 1.2 (CI 95% 0.84-1.75), ($P>0.2$) and I / I genotypes OR = 1.4 (CI 95% 0.83-2.38) showed their protective nature against disease progression, but no reliable statistical significance was obtained ($P>0.2$).

Similarly, the eNOS3 gene is shown in the eNOS3 gene and the frequency of the genotype and the genotype Figure 2 in all patients.

![Figure 2: Frequency of alleles and genotypes of eNOS3 gene polymorphism T-786S in all patients and control group](image2)

The alleles of the T786S eNOS3 gene were 70.1% and 79.5% in the main and control groups studying polymorphisms, respectively. The frequency of undesirable C allele was 29.8% and 20.4%. As per factual estimations, C-allele transporters are multiple times bound to experience the ill effects of this ailment than T-allele transporters ($\chi^2=5.5; P=0.02; or=1.6; 95\% CI 1.0844-2.524$). Allelic T ($=2 = 5.5; P = 0.02; or = 0.6; 95\% CI 0.3962-0.9222$) demonstrates that it protectively affects Disease movement.

The consequences is that the primary and control bunches indicated that the genotypes TT, TC and CC were 50.3%, 39.5%, 10% and 62.7%, 33.6% and 3.6%. As indicated by measurable computations, CC genotype transporters are 2.9 occasions bound to experience the ill effects of this infection than TT genotype transporters and have a dependable
factual importance ($\pi = 2 = 3.7; \ p = 0.05$; or $= 2.9$; 95% CI 0.9392–9.3906). Immune function was 50.3%, 62.7%, and disease advancement ($\pi = 2 = 3.7; \ p = 0.05$; or $= 2.9$; 95% CI 0.3594–13232), was significantly lower in the main team than in the genotype TT control team. Genotype was less influential group than TC control group, 39.5% and 33.6%, and did not play a significant role in the development of pathology ($\pi = 0.9; \ p = 0.3; \ or = 1.29$; 95% CI = 0.7592-19192). In our knowledge, we have shown a link between Inos3 gene C-light (CC genotype) infection among type 2 diabetes mellitus and diabetic nephropathy patients. The results are consistent with the information of local and foreign authors. Analysis of 32 research results published before 2016 according to a meta-analysis, three NOS3 polymorphisms link to DNA development were establish: / B / A, T-CC6C and G97T. Polymorphism 4B / A and T-786666C666666 showed a reliable correlation with all genetic models ($\pi = 12.77$ and 1.11-11.50).

These data and the consequences of our study lead us to the conclusion that the ENOS3 gene plays an important role in the DNA development of patients with type 2 diabetes in Uzbekistan (Uryasiev and Shakhanov, 2017). Consequent from the main and control rally showed that the distribution rates of the TT, TC, and CC genotypes were 50.3%, 39.5%, 10% and 62.7%, 33.6%, and 3.6%, respectively. According to statistical calculations, this disease of CC genotype carriers is 2.9 times more common than that of TT genotype carriers, and the difference between them has real statistical significance ($\pi = 2 = 3.7; \ p = 0.05$; or $= 2.9$; 95%) CI). 0.9392 - 9.3906). The TT genotype was significantly lower in the main team than in the control team, was 50.3%, 62.7%, and showed a function protector against disease advancement ($\pi = 2 = 3.7; \ p = 0.05; \ OR = 0.6; \ 95\% \ CI \ 0.3594-1.0132$). Genotype TC was significantly lower in the main group than in the control team, 39.5% and 33.6%, and played no significant role in the development of pathology ($\pi = 0.9; \ p = 0.3; \ OR = 1.29; \ 95\% \ CI \ 0.7592-19192$). Our test has shown a link between the infect of the eNOS3 gene and the alleles of mutant homozygous CC genotypes. Consequently, the alleles and genotypes of the polymorphic marker Alulns / Dell> D of the ACE gene did not show any predisposition to the disease in the primary and control groups. However, the genotypes of polymorphic marker Alulns / Dell> D of the ACE gene showed a shielding effect in the unfavourable manifestation of eNOS3 gene in the progression of DN in patients with diabetes mellitus type 2 of the Uzbek population. (Villeneuve et al., 2014)

CONCLUSIONS

The research has shown that the functionally unfavourable polymorphic marker T-786C of the NOS3 gene in the first and control groups, it was shown that the development of the disease involving the functionally unfavourable allele C causes the disease in the main group with a high probability OR = 1.6 (CI 95% 1.084-2.52), (p> 0.01). It was noted that homozygous CC genotype is also more likely to cause disease (OR> 2.9 (CI 95% 0.93-9.39)). (p> 0.05). The favorable T allele OR = 0.6 (CI 95% 0.39-0.92), (p> 0.01) and TT genotypes OR = 0.6 (CI 95% 0.35-1.01), (p> 0.05) demonstrated protective properties in response to disease progression. Similar results were repeated in other groups, and they had a probability of morbidity.

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Conflict of interest

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REFERENCES

Colombo, M. G., Paradossi, U., Andreassi, M. G. 2003. Endothelial nitric oxide synthase gene polymorphisms and risk of coronary artery disease. Clinical Chemistry, 49:389–395.
Dellamea, B. S., Pinto, L. C., Leitao, C. B. 2014. Endothel nitric oxide synthase gene polymorphisms and risk of diabetic nephropathy: systematic review and meta-analysis. *Bio Med Central Medical Genetics*, 15.

Ezzidi, I., Mtiraoui, N., Kacem, M. E. 2009. Identification of specific angiotensin-converting enzyme variants and haplotypes that confer risk and protection against type 2 diabetic nephropathy.

Ezzidi, I., Mtiraoui, N., Mohamed, M. B. 2008. Association of endothelial nitric oxide synthase Glu298Asp, 4b/a, and -786T>C gene variants with diabetic nephropathy. *Journal of Diabetes and its Complications*, 22:331–338.

Hana, T. 2011. Association between Apolipoprotein E-polymorphism and Ischemic Heart Disease Patients With or Without Type 2 Diabetes Mellitus: A Preliminary Study in Kuwait- Al-M. T. Hana. *Archives of Iranian Medicine*, 14:385–388.

Koopal, C., Koopal, Y., Graaf, F. V. D., Asselbergs, J., Westerink 2015. Influence of APOE-2 genotype on the relation between adiposity and plasma lipid levels in patients with vascular disease. *Int J ObesRelat Metab Disord*, 39(2):265–269.

Macisaac, J., Ekinci, E. I., Jerums, G. 2014. Markers of and risk factors for the development and progression of diabetic kidney disease. *Am. J. Kidney Dis*, 63:39–62.

Maslova, O. V., Suntsov, Y. I., Shestakova, M. V., Kazakov, I. V., Vikulova, O. K., Sukhareva, O. Y., Martynov, S. A., Trubitsyna, N. P. 2005. Prevalence of kidney damage in diabetes mellitus type 1 and type 2 in the Russian Federation. *Russian Federation // Diabetes*, pages 47–51.

Morshed, M., Khan, H., Akhteruzzaman, S. 2002. Association between angiotensin I-converting enzyme gene polymorphism and hypertension in selected individuals in the Bangladeshi population. *Journal of Biochemistry and Molecular Biology*, 35(3):251–254.

Mustafina, O. E., Shagisultanova, L. I., Nasibulin, T. R. 2001. Polymorphism of mini-satellite gene of endothelial nitric oxide synthase: research in the Volga-Ural region and analysis of associations with myocardial infarction and essential hypertension. *Genetics*, 4:1–7.

Ng, D. P., Tai, B. C., Koh, D. 2005. Angiotensin-I Enzyme insertion/removal and its relationship with diabetic nephropathy: A meta-analysis of the research reported between 1994 and 2004 and 14,727 is formed subjects. *Diabetologia*, 48(5):1008–1016.

Rizvi, S., Raza, S. T., Mahdi, F. 2014. Association of Genetic Variants with. *Diabetic Nephropathy World J Diabetes*, 5(6):809–825.

Uryasiev, O. M., Shakhanov, A. 2017. Role of Polymorphism in the formation of core code biosynthesis of nitrogen oxides - bronchial asthma and high blood pressure. *Kazan Medical Journal*, 98:226–232.

Villeneuve, S., Bryson, D., Marchant, N. 2014. Possible application of apolipoprotein E in Personalized Medicine. *Frontiers in Aging Neuroscience*, 3(6):154.