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Association of Angiotensin-Converting Enzyme (ACE) and Glutathione S-Transferase (GST) Gene Polymorphisms with Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy accounts for the most serious microvascular complication of diabetes mellitus. It is suggested that the prevalence of diabetic nephropathy will continue to increase in future pretense a major challenge to the healthcare system resulting in increased morbidity and mortality. It occurs as a result of interaction between both genetic and environmental factors in individuals with T2DM-Type 2 diabetes mellitus. Genetic susceptibility has been offered as an important factor for the development of diabetic nephropathy, and various research efforts are being executed worldwide to identify the susceptibility gene for diabetic nephropathy. Several single nucleotide polymorphisms have been found in various genes giving rise to various gene variants which have been found to play a role in genetic susceptibility to diabetic nephropathy. The risk of developing diabetic nephropathy is increased several times by inheriting risk alleles at susceptibility loci of various genes like ACE, GST, TNF-α, COL4A1, eNOS, GLUT, etc. The identification of these genetic variants at a biomarker level could thus, let the detection of those individuals at high risk for diabetic nephropathy which could thus help in the treatment, diagnosis and early prevention of the disease. The present review discusses about the ACE-Angiotensin Converting Enzymeand GST-Glutathione S Transferase gene variants associated with diabetic nephropathy.

KEYWORDS: ACE, GST, Genetic polymorphisms, Diabetic nephropathy

INTRODUCTION

T2DM is a complex syndrome prominent to various metabolic dysfunctions. These metabolic dysfunctions apparent characteristic long-term complications in the form of various microvascular diseases, including diabetic nephropathy, retinopathy, and neuropathy. Diabetic nephropathy is one of the major secondary complicationsof diabetes mellitus affecting almost 40% of the diabetic patients. Diabetic nephropathy is clinically characterized by proteinuria, declining glomerular filtration rate, hypertension ultimately leading to renal failure, requiring dialysis or transplantation. Various risk factors like, hyperglycemia, increased blood pressure, and genetic alterations may prompt an individual to diabetic nephropathy in the near future (1). It is now a scientifically verified fact that apart from the above risk factors, thereis a strong association between an individual's genetic make-ups in his predisposition to diabetic nephropathy. In this context, Andersen *et al* (2) have shown that 35% of the patients with T2DM develop nephropathy, irrespective of glycemic control. Identification of genetic components of diabetic nephropathy is the most important area of diabetes research because interpretation of genes (alleles) associated with diabetic nephropathy will influence all efforts toward an understanding of the disease at molecular and mechanistic levels, its related complications, cure, treatment and prevention. Association studies of candidate genes for diabetic nephropathy are being conducted all around the globe to identify the biomarkers genes which may predispose a diabetic individual to the risk of diabetic nephropathy. Among the genetic factors involved, single nucleotide polymorphisms in the genes associated with diabetic nephropathy was found to have a major impact on the disease outcome. These gene polymorphisms studies are thus conducted to identify at-risk patients and design therapeutic strategies to prevent the outcome of such complication in his later future.

Developmental Risk Factor of Diabetic Nephropathy

Before the widespread aggressive treatment of blood pressure and hyperglycemia, between 25% and 40% of T2DM patients developed diabetic nephropathy over the course of 25 years' and risk factors that differentiate this subgroup from patients who maintain normal renal function are systemic hypertension, glycaemic control, gender (M>F), genetic factors, hyperlipidaemia, dietary protein intake and smoking.

Predictors of Diabetic Nephropathy

On the other hand, most recent studies have abortive to

demonstrate any significant impact of glycemic control on progression of nephropathy in T2DM. In kidney disease most reputed promoters of progression in blood pressure has been a close relation of glomerular filtration rate in T2DM (3).

Serum cholesterol concentration has been shown to be another forecaster of progression of nephropathy in both types of diabetes. the above-mentioned factors, led scientists to postulate and investigate about genetic factors leading to this dreadful complication is a fairly large number of diabetics goes on to develop nephropathy .

Strategies for identifying susceptibility genes

There has been incomplete success in identifying genetic variants that modify the hazard of developing diabetic nephropathy. In view of the complication involved, it is not surprising that although investment of significant resources. Both have led to the discovery of many chromosomal and gene regions that may confer susceptibility to Diabetic Nephropathy have been two strategies commonly used to identify Diabetic Nephropathy susceptibility loci: one is linkage analysis another is association analysis. The study of familial clustering of the disease powerfully suggests that genetic factors are implicated in the development of DN, while segregation analyses point to the survival of susceptibility and have established that the onset and progression of DN are inclined genetically (5-6).

Angiotensin converting enzyme (ACE) gene Polymorphisms

Angiotensin converting enzyme (ACE) gene is one of the most studied gene to be occupied in the pathogenesis of diabetic nephropathy as well as micro- and macro-albuminuria and development from micro- to macro-albuminuria.The above polymorphism is one of the most calculated polymorphism in diabetic nephropathy. Genetic factors are likely to be important in diabetic nephropathy.Some studies have found the DD(Deletion/Deletion) genotype to be associated with an increased risk of diabetic nephropathy and a rapid decline of GFR in T2DM (7). The frequency of ACE allele is differentiated might and ethnic group putting connecting result related to the role of ACE polymorphisms in diabetic nephropathy(8). DN in progress dissimilar renal function changes with glomerular hyper filtration and hyper perfusion increase glomerular filtration rates (GFR). DN is manifested with microalbuminuria that consequently can progress to macroalbuminuria (9). DN in progress dissimilar renal function changes with glomerular hyper filtration and hyper perfusion increase glomerular filtration rates (GFR) The ACE is a key feature of rennin angiotensin system (RAS) that play critical role in blood pressure homeostasis. In patients who build up macroalbuminuria, there is a progression from micro- to macro-albuminuria, decline of renal function and hypertension (10). Due to the control of genetic factors and metabolic control in pathogenesis of DN-Diabetic Nephropathy, its development varies among diabetic patients (11) The role of ACE I/D(Insertion/Deletion) polymorphism growth of DN to ESRD (End Stage Renal Disease) in T2DM patient has been well-known by a latest meta-analysis (12) create protective role for the D allele of ACE touching diabetic nephropathy.

Glutathione S - Transferase gene polymorphisms

In the family of GST enzyme are articulated as dissimilar isoform coded by a selection genes isolatedmostly on differentchromosome (13). Additionally most of these genetic loci accepted to have polymorphic genes (14). A few studies have exposed that polymorphisms of GST genes lead to modify in the appearance of the enzyme, either qualitatively or quantitatively (15) and hence can provide individuals prone to a range of diseases including CKD (Chronic Kidney Disease). Along with all the genetic polymorphisms described in this class of enzymes, the GSTM1 and GSTT1 are most considerable because these genes are reported to be deleted consequential in lack of the exacting isoforms of the enzyme.Studies on Indians, while few, show an elevated prevalence of these the occurrence of GSTM1 and GSTT1 null variants have been expose to be particularly high in various genetic variants in normal population (16). The association of GSTM1 and GSTT1 deletionswith nephropathy (17). (Glutathione S- Transferase mu1 and Glutathione S- Transferase theta1). A current study on Indian population evaluating the association between GST gene polymorphism and susceptibility to end stage renal disease (ESRD) initiates significant relationship of both GSTM1 null and GSTT1 null genotypes with ESRD- End Stage Renal Disease (18). The polymorphic GST gene with respect to diabetic nephropathy initiates that GSTM1 and GSTT1 double hopeful genotype seems to have a protective role on the susceptibility to expansion of nephropathy in patients with T2DM. GSTM1 and GSTT1 double deletion appears to be a risk factor for development of nephropathy in T2DM.

DISCUSSION

Diabetic nephropathy is actually the most common cause of kidney failure. It is now a scientifically proven fact that there is a strong association between an individual's genetic makeups in his predisposition

to diabetic nephropathy. Multiple genes are involved in pathogenesis of diabetic nephropathy, with several allelic polymorphisms having demonstrable effects in the development and progression of the disease thus contributing to the overall risk. Elhawary NA et al (19) show that the polymorphism of the *ACE* gene is not significantly associated with diabetic nephropathy in Egyptian ethnicity, while HadjadjS et al (20), Parchwani DN et al (21) in their studiesshows that ACE gene is significantly associated with DN in France and West Indian ethnicity. Apart from this the prevalence of GSTM1 and GSTT1 null variants have been shown to be remarkably high in different population groups from all over the globe. Studies on Indians, although few, show a high prevalence of these genetic variants in normal population. Studies in the area of diabetic nephropathy are not only few but also inconsistent in their results. While Fujita etal (18) found no association of GSTM1 deletion with diabetic nephropathy in Japanese T2DM patients and Orlewski J et al (22) also found the same in Poland ethnicity; Yang etal (23) showed that GSTT1 null genotype was a risk factor for development of diabetic nephropathy in the Chinese. Kim et al (16) found that GSTM1 null genotype is associated with development of nephropathy in Type 2 diabetes in the Korean population (table 1).

CONCLUSION

This review is based on the study of ACE I/D and GST gene polymorphisms in various populations and it was found that GST gene polymorphisms are not associated with onset and progression of diabetic nephropathy while conflicting results from various studies reported to the association of ACE I/D polymorphism in the development of Diabetic Nephropathy.

S. No.	Gene	Ethnicity	Case/Control (n)	Significance	References
1.		France	1057/1127	Y	[22]
2.	ACE	West India (Gujrat)	309	Y	[21]
3.		Egyptian	220/60	N	[23]
1.	GST	Japanese		N	[18]
2.		Poland	874/966	N	[20]
3.		Chinese		N	[19]
4.		Korean		Y	[16]

n: Numbers, Y: Yes, N: NO

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