Austin Journal of Nephrology and Hypertension

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Austin Publishing Group

Special Article - Diabetic Nephropathy

Candidate Genes for Diabetic Nephropathy in Mexican Population

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Received: June 24, 2017; **Accepted:** July 11, 2017; **Published:** July 26, 2017

Commentary

Dear editor, genetic markers for association studies for the renal disease are limited in the Mexican population. Different countries in the world have been explored metabolic pathways such as glomerular filtration barrier, carbohydrate metabolism, lipid metabolism, oxidative stress, hemodynamic and vascular factors, electrolyte and oligoelements, inflammation, fibrogenesis, genetic expression, intake and satiety, mainly [1,2]. These studies of the linkage and association, show more than 60 genes for predisposition, with locus in all chromosomes, except to Y chromosome, which is specifics for every population [1,2].

Glomerular filtration barrier

The first changes related with the diabetic nephropathy (DN) are initiated in the glomerular filtration barrier. For this function the gene markers encoding for the proteins related with this, are the mainly factors of the predisposition and prevention for the renal damage. In this sense the gene variation on HPSE genes is very important, because the HPSE encodes by the enzyme heparanase, which maintains the heparan sulfate in the basal lamina of the podocytes, preventing the passage of proteins, by the net carrier. The loss HPSE translates into glomerular proteinuria (high molecular weight) [3]. In the case of gene HPSE we did a preliminary study in Mexican Mestizos with diabetic nephropathy where we analyzed the polymorphism p.K307R, but we just have found an overdominant effect on T2DM, and we found not association with renal disease. However it has been explored, considering that one have to increase the population sample and corroborate in other population. Because this genetic marker has a locus at the region encoded by active site of the heparanase, it should be explored in different populations [1,3]. Physicians at first level should be clear that when a gene is mapped and has variants in regions coding for functional domains, these markers must be considered as a candidate for association studies. Thus variations such as that can be translated into different functional isoforms, which may have relation to the development of the phenotype; the kidney could have dysfunction at the basal lamina.

When proteins pass through the filtration barrier they can be recovered in the proximal re up take in the brush border epithelium of proximal tubule by the transcytosis system. This system consists of a heterogeneous group of proteins that recapture the proteins filtered through endocytosis; including meglin (encoded by the lrp2 gene) and cubilin (encoded by the CUBN gene) [4]. The dysfunction of this system among other pathologies with renal diseases has been resulted in tubular proteinuria (low molecular weight). Genetic variations in this system have already been explored in diabetic nephropathy; however the first studies of these genes as candidates were carried out in the Mexican population of Jalisco state. For *LRP2*, we analyzed the polymorphisms p.H498Q in exon 22 and p.R4220P as well as p.I4210L located at the exon 69. The polymorphism in exon 22 is not associated with overt nephropathy, but has an overdominant effect on T2DM. The haplotype 2-2 (CC-CC), exon 69 has a risk factor of 13.5 [1,5,6]. A novel LRP2 missense variant, rs17848169 (N2632D), was also significantly protective from T2D-ESRD (odds ratio, 0.47; 95% confidence interval, 0.29 to 0.75) [7].

The variants p.I2984V (rs1801239) and p.G3002E (rs1801240) of *CUBN* gene was also analyzed in overt diabetic nephropathy in a Mexican preliminary cohort. The polymorphism p.I2984V (rs1801239) is not associated with diabetic nephropathy [1,8]. Recently it was described the SNP rs1801239 (p.Ile2984Val) associated with albuminuria levels in diabetics. Also, this polymorphism has very high Linkage disequilibrium, three of them are missense mutations (p.Leu2153Phe, p.Ile2984Val, p.Glu3002Gly) [9]. Recently the SNP rs1801239 (I2984V) of the CUBN is associated with T2D-ESRD in blacks (odds ratio, 1.31) [7]. Therefore, in the Mexican population, it would be important to do replication studies of variants of the CUBN and LRP2 genes, since they are important markers of proteinuria [10], and we have already been demonstrated in other populations that contribute to the development of diabetes nephropathy.

Citation: Flores Alvarado LJ, Ramirez-Garcia SA, Ortega-Pacheco D, Ramírez-Bohórquez E, Castro-Juárez CJ, Ruiz-Mejia R, et al. Candidate Genes for Diabetic Nephropathy in Mexican Population. Austin J Nephrol Hypertens. 2017; 4(2): 1069.

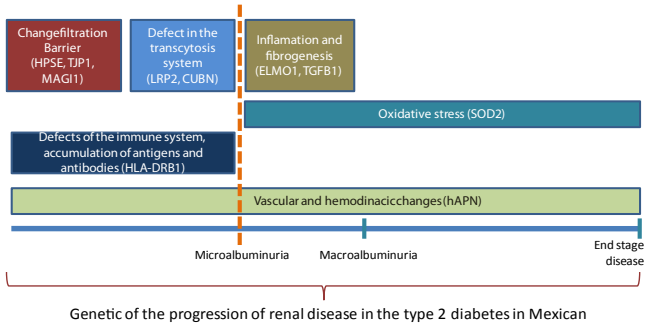

Figure 1: Genetic of diabetic nephropathy in Mexican.

Inflammation and fibrogenesis

TGF-β1 gene encodes for a proinflammatory cytokine and is also a regulator of fibrogenesis, which participates in the development of chronic kidney disease. The genetic studies on this pathogenic entity are limited in Mexican population. A study in population of méxico center show the 869 T→C and the 915 G→C polymorphisms were associated with diabetic nephropathy in (OR=4.073 and 1.818). The TGF-β1 869 T allele seems to confer protection against DN [11].

Vascular and hemodynamic factors

The renal failure is associated with the vascular function and is closely linked to rennin angiotensin aldosterone system, which used some molecular markers. Considering that this is a highly line of investigation studied in the world, studies are limited in Mexico. Only two works have been reported from this line of research: in a town from central of México, a study shows association between albuminuria and mutant alleles of polymorphism BstxI or ScaI from hANP gene; odds ratio of 0.60 and 0.51, suggesting that there are protective factors [1,12]. Another study from central and of western of México population where polymorphism ins/del from ACE gene (homozygous genotype D) shows association with incipient nephropathy and established kidney disease with odds ratios greater than 2.8 [1,13,14].

Metabolic stress

DN is the leading cause of chronic kidney disease; the risk factors for DN have not been clearly established. There is evidence indicating that oxidative stress is associated with renal damage. Macroalbuminuria is a predictor of DN, and it's related with oxidative stress [15]. The gene variation in the oxidative system. Superoxide dismutase 2 (SOD2), also known as manganese superoxide dismutase (MnSOD), is one of the major antioxidant defense systems against mitochondrial superoxide radicals. The polymorphism rs4880 (p.Val16Ala) in the *SOD2* gene has been predicted to cause a conformational change in the target sequence, which induces a 30-40% decrease in SOD2 activity due to less efficient transport of the protein into the mitochondrial matrix [15]. The carries homozygote C for this marker had significantly lower risks of macroalbuminuria than those with the TT genotype (OR=0.42) [15].

New candidate genes in mexican population

In the Mexican population it would be important to explore the association of the *ELMO1* and *TJP1* genes with diabetic nephropathy (determinants of homeostasis of the filtration barrier), considering that they are polymorphic markers in this population and it has already been validated as risk markers for renal disease [16,17]. At the level of regulators of carbohydrate metabolism, the *ATXN2* gene, is also associated with diabetes and determines the rate of filtration [18,19]. In these sense also MAGI1gene is a putative candidate. It has been proposed that this gene participates in the homeostasis of glucose and is part of the cytoskeleton of the podocytes. Variant c.12345C>T is polymorphic and is related to elevated fasting glucose levels which determines the progression of renal damage, for these reasons it could be associated with DN [20]. It would be worth retaking the allele DRB1*1502 from MHC class II genes, which in Mexican population was long ago found to be associated with end-stage renal disease, and to analyze the association with albuminuria [21].

Given the genetic diversity of the Mexican population and the complexity of diabetes mellitus type 2, it is necessary to look for more candidate genes that explore the risk of development for diabetic nephropathy (Figure 1).

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Austin J Nephrol Hypertens - Volume 4 Issue 2 - 2017
ISSN : 2381-8964 | www.austinpublishinggroup.com

Citation: Flores Alvarado LJ, Ramirez-Garcia SA, Ortega-Pacheco D, Ramírez-Bohórquez E, Castro-Juárez CJ, Ruiz-Mejia R, et al. Candidate Genes for Diabetic Nephropathy in Mexican Population. Austin J Nephrol Hypertens. 2017; 4(2): 1069.