

Special Article - Diabetic Nephropathy

Candidate Genes for Diabetic Nephropathy in Mexican Population

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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 specific for every population [1,2].

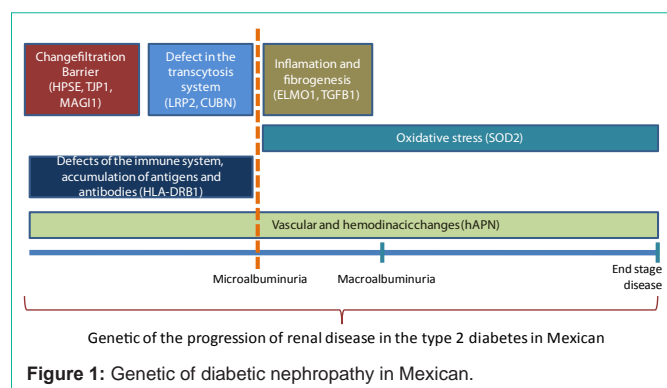
Glomerular filtration barrier

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.



Inflammation and fibrogenesis

TGF- β 1 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- β 1 869 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 *MAGI1* gene 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).

References

- Flores-Alvarado LJ, Ramirez-Garcia SA, Ferman PD, Davalos NO, Chavéz C, Cruz-Bastida J, et al. Molecular Heterogeneity of Type 2 Diabetes Mellitus in Mexican Population and its Impact of the Public Health on Policies in Primary Care. *Med Chem.* 2014; 4: 791-797.
- Rosales RC, López JJ, Núñez NY, González AE, Ramirez-Garcia SA. Type 2 diabetes nephropathy: a thresholds complex trait and chromosomal morbid map. *Rev Med Inst Mex Seguro Soc.* 2010; 48: 521-530.
- Ramirez-Garcia SA, Carrillo C. Detección molecular de una variante en la secuencia del gen HPSE que codifica para el dominio del sitio activo de heparanasa y el desarrollo de insuficiencia renal en pacientes con Diabetes mellitus tipo 2. *Bioquímica.* 2009; 34: 58.
- Flores-Alvarado LJ, Villafán-Bernal JR, Cabrera-Pivaral CE, Castro J, Ramirez-Garcia SA. Exploration of gene variations in the transcytosis system as a policy proposal for the personalized therapy in type 2 diabetes mellitus. *J Med Therap.* 2017; 1: 1-3.
- Carrillo C, González Manuel, Ramirez-Garcia SA. Detección molecular de una variante de secuencia del gen que codifica para megalina y el desarrollo de insuficiencia renal causada por diabetes mellitus tipo 2. *Bioquímica.* 2009; 34: 59.
- Carrillo C, Barajas L, García G, Godínez S. Haplotype of megalin gene and the susceptibility by diabetic nephropathy in Jalisciense population. XVI National meeting of the Group study of diabetes mellitus A.C.
- Ma J, Guan M, Bowden DW, Ng MC, Hicks PJ, Lea JP, et al. Association Analysis of the Cubilin (CUBN) and Megalin (LRP2) Genes with ESRD in African Americans. *Clin J Am Soc Nephrol.* 2016; 11: 1034-1043.
- Carrillo C, González M, Godínez S. Detección molecular de variantes de secuencia del gen que codifica para cubilina y el desarrollo de insuficiencia renal causada por diabetes mellitus tipo 2. *Bioquímica* 2007; 32: 73.
- Tzur S, Wasser WG, Rosset S, Skorecki K. Linkage disequilibrium analysis reveals an albuminuria risk haplotype containing three missense mutations in the cubilin gene with striking differences among European and African ancestry populations. *BMC Nephrol.* 2012; 31; 13: 142.
- Ovunc B1, Otto EA, Vega-Warner V, Saisawat P, Ashraf S, Ramaswami G, et al. Exome sequencing reveals cubilin mutation as a single-gene cause of proteinuria. *J Am Soc Nephrol.* 2011; 22: 1815-1820.
- Valladares-Salgado A, Angeles-Martínez J, Rosas M, García-Mena J, Utrera-Barillas D, Gómez-Díaz R, et al. Association of polymorphisms within the transforming growth factor- β 1 gene with diabetic nephropathy and serum cholesterol and triglyceride concentrations. *Nephrology (Carlton).* 2010; 15: 644-648.

12. Nannipeeri M, Posadas R, Williams K, Polit E, Gonzalez VC, Stern M, et al. Association between polymorphism of the atrial natriuretic peptide gene and proteinuria; a population based study. *Diabetologia*. 2003; 46: 429-432.
13. Palomo S, Gutiérrez ME, Díaz M, Sánchez, Valladares A, Utrera D, et al. DD genotype of angiotensin-converting enzyme in type 2 diabetes mellitus with renal disease in Mexican mestizos. *Nephrology*. 2009; 14: 235-239.
14. Ortega LE, Gómez A, Rodríguez E, Figueroa B, Farías VM, Higareda AE, et al. Angiotensin-1 converting enzyme insertion/deletion gene polymorphism in a Mexican population with diabetic nephropathy. *Med Clin*. 2007; 129: 6-10.
15. Ascencio-Montiel Ide J, Parra EJ, Valladares-Salgado A, Gómez-Zamudio JH, Kumate-Rodríguez J, Escobedo-de-la-Peña J, et al. SOD2 gene Val16Ala polymorphism is associated with macroalbuminuria in Mexican type 2 diabetes patients: a comparative study and meta-analysis. *BMC Med Genet*. 2013; 14: 110.
16. Ascencio-Montiel Ide J, Parra EJ, Valladares-Salgado A, Gómez-Zamudio JH, Kumate-Rodríguez J, Escobedo-de-la-Peña J, et al. SOD2 gene Val16Ala polymorphism is associated with macroalbuminuria in Mexican type 2 diabetes patients: a comparative study and meta-analysis. *BMC Med Genet*. 2013; 14: 110.
17. Ramirez-Garcia SA, Flores-Alvarado LJ, Topete-González LR, Charles-Niño C, Mazariegos-Rubi M, Dávalos-Rodríguez NO. High frequency of ancestral allele of the TJP1 polymorphism rs2291166 in Mexican population, conformational effect and applications in surgery and medicine. *Cir Cir*. 2016; 84: 28-36.
18. Topete-González LR, Ramirez-Garcia SA, Charles-Niño C, Villa-Ruano N, Mosso-González C, Dávalos-Rodríguez NO. [Polymorphism g.37190613 G>A of the ELMO1 gene in the Mexican population: potential marker for clinical-surgical pathology]. *Cir Cir*. 2014; 82: 402-411.
19. Liu CT, Garnaas MK, Tin A, Kottgen A, Franceschini N, Peralta CA, et al. Genetic association for renal traits among participants of African ancestry reveals new loci for renal function. *PLoS Genet*. 2011; 7: e1002264.
20. Flores-Alvarado LJ, Dávalos-Rodríguez NO, García-Cruz D, Madrigal-Ruiz PM, Ruiz-Mejía R, Aguilar-Aldrete ME, Villa-Ruano N, Ramirez-Garcia SA. (CAG)_n polymorphism of the ATXN2 gene, a new marker of susceptibility for type 2 diabetes mellitus. *Rev Panam Salud Publica*. 2016; 40: 318-324.
21. Vergel-Ávila Eduardo, De La Garza-Ibarra B A, Carrillo C. Asociación del gen MAG1 con niveles séricos elevados de glucosa en ayuno en población adulta de Guadalajara México. *Archivos de Ciencia*. 2015; 7: 74.
22. Pérez-Luque E, Malacara JM, Olivo-Díaz A, Aláez C, Debaz H, Vázquez-García M, Garay ME, Nava LE, Burguete A, Gorodezky C. Contribution of HLA class II genes to end stage renal disease in mexican patients with type 2diabetes mellitus. *Hum Immunol*. 2000; 61: 1031-1038.