Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Genetic Factors of Diabetic Nephropatia in Patients with Type 2 Diabetes Mellitus

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GJMR-F Classification: NLMC Code: WJ 340

Strictly as per the compliance and regulations of:

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I. Introduction

Recently, the increasing prevalence of diabetes mellitus (DM) is alarming worldwide. For the most part, an increase in the incidence is due to type 2 diabetes, which accounts for 80-90% of all cases of this pathology [26, 31]. The need for an active solution to this problem is dictated by the following unfavorable factors: "rejuvenation" of type 2 diabetes, a significant percentage of mortality disability due to the development of early and late complications of diabetes, like diabetic nephropathy (DN). It is recognized that it is diabetes type 2 the leading pathology, which leads to an increase in the frequency of cardiovascular diseases and vascular accidents in different countries and populations [3]. Gradually developing late complications of diabetes, such as retinopathy, nephropathy, polyneuropathy and angiopathy, lead to a significant decrease in the patient's quality of life, and in many cases to severe disability, causing blindness, chronic renal failure, diabetic foot - the main cause of high amputation in patients. Despite the significant progress of the pharmaceutical industry, which led to the appearance on the medical market of a wide variety of high-quality pharmaceuticals, the number of patients who do not reach the recommended treatment goals remains high. The unfavorable situation with type 2 diabetes predetermined the development and adoption in 2007 of common international treatment approaches. By decision of the 2007 consensus, the target level of glycated hemoglobin should not exceed 7%. For the first time, the need was indicated for the prompt and timely correction of the treatment regimen in the long-term absence of a decrease in glycated hemoglobin to non-diabetic values [3, 10, 11].

Subsequently, it was noted that achieving compensation for diabetes mellitus and stable maintenance of the target values of glycated hemoglobin prevents the development of late complications in all patients. The study of this controversial situation led to the possibility of genetic justification of the predicted complications. Since diabetes mellitus type 2 is not a genetically mediated disease, its debut and progression up to the development of complications are associated with many genes and their complex interaction with each other and with environmental factors. The result of new advances in molecular genetics, immunology and some other related disciplines was the development by the WHO Expert Committee on diabetes, taking into account the proposals of the American Diabetes Association, a new, improved classification of diabetes (WHO, 1999). Unlike the previous one, in the new classification the class of "impaired glucose tolerance" was excluded, the name "insulin-dependent" and "insulin-independent" diabetes mellitus for type 1 and type 2 diabetes was changed. In the subsection "Genetic defects of p-cell function", it was suggested include diabetes MODY 1, 2, 3, 4, 5, 6 and some other monogenic types of diabetes, in the pathogenesis of which. The cause of the disease caused by a violation of a particular gene is clearly established. The following types of insulin resistance have been attributed to the genetic defects of insulin: type A insulin resistance, leprechaunism, Rabson-Mendelhall syndrome, lipoatrophic diabetes and some other forms of diabetes resulting from the mutation of the insulin receptor gene [2]. The classification also includes the sections "Endocrinopathy", "Diabetes induced by drugs or chemical agents", "Infection", "Unusual form of immune-mediated diabetes", "Other genetic syndromes sometimes combined with diabetes" and "Gestational diabetes". Thus, the onset of diabetes includes a large number of diseases, which can be divided into diabetes of type 2, genetic syndromes associated with diabetes, and secondary forms of

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diabetes. The proportion of type 2 diabetes accounts for more than 95% of all diabetes, while as the second type in prevalence significantly dominates the first. In spite of the fact that type 2 diabetes develops more often in adult or even old age, there are cases in children. In the development of the disease in childhood, the main importance is attached to the genetic factor. Monozygous twins in 100% of cases are concordant for type 2 diabetes. Parents also in most cases have type 2 diabetes, especially when examined in terms of the glucose tolerance test [1, 2].

Type 2 diabetes is a multi factorial disease, the development of which is due to the mandatory interaction of genetic factors with the environment [2, 9]. However, the genetic basis and degree of importance of various environmental factors in both types are different. For the development of diabetes in both cases, many genes are responsible, i.e. type 1 diabetes and type 2 polygenic diseases. However, unlike type 1 DM, where there is an unfavorable combination of many normal genes, the debut of type 2 DM causes a combination of several pathological genes. It is assumed that type 2 diabetes develops in people who have mutations in the genes encoding the processes of synthesis, secretion and action of insulin [2]. Studies performed (I. I. Dedov et al.) Demonstrated that type 2 diabetes is inherited independently of friend, and nosologically it is an independent disease. The authors concluded that the system of genetic factors determining susceptibility to the two types of diabetes is different. The results of diabetes analysis in the families participating in the study showed that intra-familial similarity in the type of diabetes is largely due to genetic factors, as evidenced by the correlation in the type of diabetes between the probands and their relatives [2]. In the study of families on the subject of heredity according to type 2 diabetes, it was noted that the risk of diabetes in mono-gothic twins is about 70%, in children with one of the parents with type 2 diabetes, about 40%, while in both parents the risk increases to 70% [9, 29]. However, this study does not take into account that environmental risk factors in a given family are similar in nature. For example, brothers and sisters inside the uterine will be subjected to the same effects, which subsequently in the study cannot be taken into account. In other words, with the same genetic set and different effects of unknown environmental factors, the outcome will be different, which may indicate an exaggeration of the role of the genetic component in the development of type 2 diabetes, as assessed in earlier studies [9].

Externally environmental factors, which are the trigger for the development of the disease, also have a fundamental difference. In type 1 diabetes, a viral infection most often serves as a trigger, whereas in type 2 diabetes, lifestyle is fundamental: physical inactivity, improper over-feeding, leading to obesity, bad habits, urbanization, stress, low or high birth weight [2, 9].

Progress in genetics in the 1980s allowed to make attempts to determine the genetic loci that underlie this inherited pathology. Candidate genes, most likely responsible for the development of type 2 diabetes, have been empirically determined based on the pathogenesis and pathokinesis of diabetes. In the course of further research, many candidate genes did not confirm the assigned roles in the development of diabetes. Given the importance of environmental factors and their complex interaction with genes, it may be very difficult to assess the role of a specific genetic component or association of genes in the research.

The difficulty also lies in the fact that, unlike type 1 DM, where candidate genes are mostly concentrated in the HLA region, in type 2 diabetes the mutant genes can be located throughout the genome, increasing the number of different unpredictable variants of their interaction. Modern methods of genetic research, having a relatively low resolution, make it possible to identify genes that have a clear linkage with a specific defect or pathology. This allows you to actively study monogenic diseases, while methods are not quite suitable for identifying genes involved in complex polygenic disorders. Therefore, only two genes that are directly related to type 2 diabetes were identified: calpain-10 (CAPN10) and 7-like 2 transcription factor (T-cell specific, HMG-box) (TCF7L2). About 80% of people are carriers of the calpain gene -10, increasing the likelihood of developing diabetes in humans. Such a high percentage of carriage of the pathological gene and a much smaller number of people with diabetes once again prove the polygenic nature of type 2 diabetes and the undeniable significance of the influence of environmental factors. CAPN10 was the first open gene to have a clear connection with type 2 diabetes. Discovered in 1996 when analyzing the linkage of a locus on chromosome 2, it was originally called the NIDDM1 locus, since specific genes were not identified [7, 9]. In 2000, the CAPN10 gene was identified [9, 17]. The value of the gene in glucose metabolism is still unknown, but many research papers have shown the relationship of this gene with the debut of type 2 diabetes [9]. Calpain-10 is a protein encoded by the CAPN10 gene, and belongs to the family of calcium-dependent cysteine proteases. By organization, it is similar to calpains-5 and -6, being atypical due to the lack of calmodulin in the structure, the calcium binding domain.

The second gene, which has a clear connection with type 2 diabetes, is the TCF7L2 gene, located on chromosome 10. Initially, the relationship of the TCF7L2 gene with diabetes was established in the American, Icelandic and Danish populations. Subsequently, in many studies of GWAS (Genome-Wide Association Studies) in different ethnic groups, the role of one nucleotide polymorphism of the TCF7L2 gene in the onset of type 2 diabetes was proven. Now, the gene

TCF7L2 is the most accurate genetic marker of type 2 DM. GWAS data showed that the risk allele is in the 3rd intron of the gene. The TCF7L2 gene encodes a transcription factor that activates the β-cells of the islets of Langerhans. In studies of V. Lysenko, if there is a risk of an allele in the TCF7L2 gene, the amount of TCF7L2 protein in the β-cells increases, which leads to a violation of insulin secretion, incretion effects and an increased glucose production rate in the liver [22].

In the islets of the pancreas of a patient with type 2 diabetes, expression of TCF7L2 is increased fivefold (especially in homozygotes), and over expression of this gene reduces glucose-stimulated insulin production. These data were confirmed by several subsequent studies, which led to the conclusion about the possible etiology of type 2 diabetes. The debut of the disease occurs due to a decrease in insulin secretion by β-cells, possibly due to the impaired action of in cretins, which leads to a change in the insulin response to food intake [9, 15, 25].

In other studies of this gene, it was determined that alternative splicing of the TCF7L2 gene leads to the formation of multiple isoforms in different tissues of the body, which, in addition to impaired insulin secretion, causes a decrease in insulin sensitivity by target tissues, such as adipose tissue [9]. Recent studies also showed the relationship of the TCF7L2 gene not only with type 2 diabetes, but also with cancer [13, 14]. When searching for candidate genes of any pathology, as mentioned above, they are guided by knowledge of the etiology and pathogenesis of the disease, clinical manifestations, development and progression of complications. Scientists focused on known pathways of glucose metabolism, insulin secretion and insulin receptors, as well as lipid metabolism [9] to determine the candidate genes for type 2 diabetes. However, in practice it turned out that not all of the alleged genes responsible for the development of type 2 diabetes, confirmed their participation in the research. In this section, some candidate genes will be considered, the connection of which with type 2 diabetes was substantiated in the conducted studies.

It is known that it is known for its development of type 2 diabetes. It makes it possible to increase the sensitivity of muscle tissue and adipose tissue to insulin, that is, to reduce insulin resistance. The effect of thiazolidinedione is mediated by their potent agonist affect with gamma receptors activated by the peroxisome proliferator (PPARG). It is included in the group of transcription factors. It is the result of exposure to the cell nucleic receptors and the lipids [1]. The PPARG has been found to be a substitute for proline by 20%. Nevertheless, it is not ubiquitous that prevails [9]. HNF1A, HNF1B and HNF4A genes, which cause monogenic diabetes, i.e., MODY. It is noted that the population increases the incidence of type 2 diabetes. However, the role of the HNF1A, HNF1B and HNF4A genes is quite small in the case of polygenic diabetes. For example, the glucokinase gene can be diagnosed, for example, the glucokinase gene. It is not possible to make a diagnosis of diabetes. the correct diagnosis. In other studies, the role of genes was shown. Insulin receptor (IRS1 and IRS2), which is a signal transduction. It is noted that it is associated with a decrease in insulin resistance.

In addition, some connection with type 2 diabetes was found in the KCNJ11 gene, an ATP-sensitive potassium channel involved in the regulation of insulin secretion by pancreatic β-cells, and the WFS-1 gene encoding a defective protein that occurs in Wolfram syndrome, which is characterized by juvenile diabetes, optic nerve atrophy and deafness [2]. Unfortunately, the value of both the listed and many other candidate genes cannot be overestimated, as it has not yet been possible to reliably prove their confident connection with the development of type 2 diabetes.

Diabetic nephropathy (DN) is one of the most serious complications of diabetes, the frequency of which progressively increases with the duration of the disease. However, a paradox was also noted regarding DNF, in which patients with no clinical and metabolic compensation for diabetes with additional risk factors for DNF, such as hypertension, hypercholesterolemia and hypertriglyceridemia, kidney damage is minimal or significantly delayed. Other DNFs can quickly form even under conditions of careful metabolic and hemodynamic control. These dissociations indicate the likelihood of a genetic explanation for the development of nephropathy [7].

When studying the genetic background of DNF, the most important pathogenesis pathways of this complication were taken into account, including increasing the activity of growth factors and cytokines (transforming growth factor in (TGF-c)), growth hormone (GH), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF). The activation of various isoforms of protein kinase C, enhancement of the effects of renin, angiotensin, endothelin, and bradykinin, the formation of reactive oxygen species, activation of aldose reductase, and increased glucose metabolism by pathological pathways have also been studied [21].

The study of candidate genes associated with the listed pathogenesis pathways in different populations resulted in ambiguous and sometimes contradictory data. One of the most studied candidate genes for DNF can rightly be considered the ACE gene involved in the renin-angiotensin-aldosterone regulatory system. The ACE gene exists in two versions: one with normal sizes - option I, the other, denoted as option D, with a missing small segment, which determines the so-calledinsertional deletion (I/D, insertion/deletion -

insertion/absence of insertion) polymorphism. There is a relationship between the genotype of the ACE gene and the concentration of tissue agiotensin-converting enzyme (ACE). The highest enzyme activity is detected in D/D homozygotes, the lowest in homozygotes I/I, and intermediate in heterozygotes I/D [7].

The contribution of the polymorphism of the ACE I/D gene can be estimated using the latest major meta-analysis based on 47 studies published between 1994 and 2004 inclusive. For instance, the I/I polymorphism of the ACE gene has nephroprotective properties in Asian patients with type 2 diabetes, while in Caucasian patients with type 2 and type 1, this connection is not confirmed. It was also shown that with I/D polymorphism of the ACE gene there is a good response to treatment with ACE inhibitors, however, the nephroprotective effect is more pronounced with the I / I genotype (20, 23, 28). Some studies have shown that the response to treatment with ACE inhibitors and the nephroprotective effect is better pronouncedin homozygotes for genotype I/I [20, 28].

There is evidence to support the concept of genetic susceptibility to nephropathy in patients with type 2 diabetes. First, diabetologists have long recognized that a number of patients develop nephropathy despite apparently good glycemic control, and vice versa, some patients with chronic hyperglycemia, reflecting indistinguishable control diabetes seems to be spared from this complication. Secondly, if the development of nephropathy was directly related to the total glycemic load, the prevalence is expected to increase steadily with increasing duration of diabetes. However, the peak frequency of nephropathy occurs between 10 and 20 years after the onset of diabetes, with a decrease in the frequency after that, indeed, only 25–40% of patients with type 2 diabetes will develop nephropathy [5–8]. Third, several studies have demonstrated familial clustering of nephropathy [9, 10]; if two or more siblings have diabetes, the risk of developing a second nephropathy for the second sister is about three times greater if the first sister has diabetic kidney disease. In addition, diabetic offspring of parents with hypertension or cardiovascular disease often develops nephropathy, affecting the fact that genes that confer the risk of hypertension. The general population predisposes to kidney disease in patients with diabetes [11].

The discovery of genetic variants that underlie susceptibility to nephropathy can provide important information on this condition. Firstly, it would allow identifying patients with a risk of nephropathy soon after diagnosing diabetes, and not much later, when persistent microacumuria develops, by that time there is already an egological evidence of kidney damage. This has facilitated fast-targeted therapeutic interventions aimed at primary prevention rather than secondary treatment of nephropathy. Secondly, and, perhaps more importantly, if susceptibility options are located in genes that have not previously participated in diabetic nephropathy, this may lead to an improved understanding of its pathophysiology and the development of new treatments. In addition, it is possible that variants of the genetic susceptibility may be specific for type 2 diabetic nephropathy, but they may be common for type 2 diabetic nephropathy or indeed other forms of kidney disease.

Identifying variants of genes that predispose to diabetic nephropathy is a difficult task. Unlike monogenic disorders, in which a relatively rare mutation in one gene usually gives a very high risk of developing the disease, susceptibility to diabetic nephropathy will most likely be determined by a large number of relatively common alleles of variants, each of which individually gives a modest increase in relative at risk. Thus, the risk of developing nephropathy is the summation of the effects of alleles present at each susceptibility locus, interacting with each other and with environmental factors, such as long-term glycemic and blood pressure control. The most common forms of human gene changes are single nucleotide polymorphisms (SNP) are single base substitutions, insertions or deletions that occur with a frequency of at least 1% in a given population. It is estimated that more than 10 million SNPs in the human genome occur at an approximate frequency of one out of every 300 base pairs [12]. Additional genomes arise through inherited duplicated or deletions of short chromosome segments; each person, therefore, may be less or more than the standard two parental alleles for each gene, signs like a change in the number of the instance [13]. In addition, genetic and environmental factors also contribute to variations in epigenetic phenomena, such as DNA methylation, which can affect gene expression and the risk of developing diseases [14].

Type 2 diabetes mellitus is complicated with DN and then leads to chronic renal failure (CRF) accompanying chronic kidney disease (CKD). In consequence, it leads to hemodialysis.

CKD is defined as renal damage, which is characterized by structural or functional kidney abnormalities or glomerular filtration rate (GFR) $<$60 ml/min/1.73 m, with or without renal injury for at least three months, without taking into account its causes [2].DN is characterized by a set of diabetic pathophysiological changes that begin with glomerularhyperfiltration and hypertrophy of the kidneys, and then progress in proteinuria and contraction of GFR. Based on the level of urine albumin excretion in a didactic person. DN has two phases: initial nephropathy or microalbuminuria phase with urine albumin (GAE) excretion in the range of 20 to 199 μg/min (or 30-300 mg/24 h); and, clinical nephropathy or proteinuria phase with GAE$>$199 μg/min ($>$300 mg/24 h) or proteinuria $\geq$500 mg/24 h. Microalbuminuria is considered as arisk

factor for DN progression [3]. In approximately 20-30% of patients with types 1 and 2 DM develops DN; however, a smaller proportion of patients with type 2 diabetes will progress to the end stage of renal disease (ESRD). Because of its high prevalence, most patients requiring dialysis are type 2 diabetes. DN is the most common cause of ESRD in a number of countries [4, 5], but not all diabetic individuals will develop this complication. Those who do not develop NAM in the first 15 years after the onset of the disease appear to be genetically protected [6]. Many environmental factors have been identified as contributing to the development of NAM, while the role of other people remains to be clearly understood [7]. Known factors such as hyperglycemia, arterial hypertension and/or dyslipidemia play a role in the development of DN only in genetically predisposed persons. The hospitalization rates for all causes are three times higher in patients with CKD than in those without disease [8]. According to Pagano et al. [9], patients with type 2 diabetes with DN and peripheral arterial disease are 1,2 – 1,3 times more likely to be hospitalized [9]. In addition, ESRD is associated with an increase in mortality, mainly due to cardiovascular reasons [10]. Reduced renal function is itself a high mortality rate. Other associated risk factors such as hypertension and autonomic neuropathy may contribute to cardiovascular diseases [10]. Even patients with DN, initially characterized by microalbuminuria, already have an increased risk of developing cardiovascular diseases and higher mortality [11]. In accordance with accumulated evidence, the risk of DN and cardiovascular diseases begin when GAE values are still within normal limits [12]. Some authors consider albuminuria to be the main risk factor for cardiovascular events, and not only the simplest marker for DN of progress [13], since some patients develop fatal cardiovascular events even before the appearance of reduced kidney function. In the metropolitan area of Porto Alegri, southern Brazil, 25% of new patients need dialysis because of diabetes, and they show high mortality during the first two years on dialysis [14]. So far, it has not been clearly established that some patients with diabetes will progress loss of kidney function and will require dialysis, while others will maintain normal kidney function. The study focused on the search for potential genetic changes associated with CKD and EPR. In fact, genetic evidence was found in the case of control and communication and more recently in research. These studies support the assumption that, on the set, the progression and severity of the DN may be partly associated with genetic factors [15]. Identification of genes associated with DN will allow one to recognize those who are at a high level of development of this complication. It will also allow a better understanding of the mechanisms and progress of the DM. Early and more aggressive treatment may provide high risk to the patients. Therefore, it is associated with high disease and mortality. Achieving pharmacogenetic studies can help treatment of choice by choosing renoprotective drugs according to individual hopl types [16]. This review discusses key information available in the literature that confirms the importance of genetic factors in DN. Also summarized are some of the results of our recent geo-institutional research.

The mode of genetic transmission of DN is still controversial. Theoretically, as with other diseases, this can occur in three different forms, which will lead to the development of DN [6, 17]. Monogenic form: mutations in the gene with a dominant role. Oligogenic form: mutations/polymorphisms of several genes would contribute to an independent and cumulative way of increasing susceptibility. Polygenic form: changes in many DNA loci and each of them will have a small and cumulative effect on DN development. Considering that DN is a multi factorial disease, the mode of transmission is likely to be polygenic, as well asgeosynthetic interaction with other environmental factors and clinical data such as duration of DM, arterial hypertension, dyslipidemia, smoking will lead to DN growth. Researches about family aggregation are not clearly studied for mode of transmission, but they provide evidence this is a polygenic complex disease [6, 17]. On the other hand, studies using segregation analysis [18, 19] suggest that familial aggregation of NAM is mainly due to the action of the main genetic locus. This effect will correspond to a monogenic or oligogenic form, where few genes have a greater impact on the phenotype. Since several genes may be involved in the development of the DN, and many of them have not yet been identified, one cannot be absolutely sure about the exact pattern of heritability in most cases.

Genes that give susceptibility to DNcan be searched in different ways. A widespread method is the approach of genes of candidates. The search for candidate genes includes the study of polymorphisms in one or more genes that are potentially involved in the pathogenesis of the disease. This approach is useful even when the effect of a gene on the progression of the disease is small [17]. Candidate genes are often analyzed in case-control studies, comparing the frequency of polymorphic/mutations in candidate genes among patients with and without disease. This is a suitable study for the study of complex genetic transmission, and it is especially useful in situations where genetic influence is relatively small, and disease-related alleles are common among the population [17]. However, this approach is very sensitive to stratification of the population, which can lead to false associations. In light of this, it was proposed that these studies include obtaining very small valuesof p and be based on reasonable a priori assumptions. This approach allowed us to describe many polymorphisms associated with DN; however, the results of the study were inconsistent.

One of the most studied changes is the insertion / deletion of the angiotensin-converting enzyme [ACE] gene. Meta-analysis showed that the D allele is associated with a high risk of DN [20]. Another approach used to analyze candidate genes is a non-equilibrium transfer test (TDT). This test is not affected by population stratification, but information is required about individuals studied and their parents and only parents of heterozygotes are informative. The frequency of transmission of the risk allele is comparable to the expected 50%. Its main limitation is access to a person and his parents, especially for DN type 2, which has a late start in life. In the case, demonstrated that the gene ectoenzymenucleotidepyrophosphatephosphodiestera (ENPP1) is associated with the early development of ERSD in patients with DN [21], and using the TDT approach, we confirmed that this association was not caused by aratification [24]. Recently, candidate genes are being tested in prospective studies. This study design is less susceptible to survival than research related to disease control, but they are more expensive and time consuming. Alternatively, the authors study cohorts that have been for a long period of time [23]. The limitation of these studies is that they are not specifically designed for the genetic effect of a particular gene. The use of microchips made it possible to quickly and accurately analyze a large number of candidate genes and execute GWS based on single nucleotide polymorphisms (SNPs). GWS can identify chromosomal regions that contain genes that are potentially involved in the genesis of the disease being studied. Panels of microsatellite markers or SNP at intervals of ~10 centimorgans (cM) in the entire genome are genotyped in several generations of families of patients with DN, or not having DN affected. Markers that are most often found in family members with DN indicate the location of the functional variant associated with the disease, and in a non-equilibrium state of adhesion with the marker. Given the difficulty of finding a large family with several members affected by DN, an alternative approach is to compare the observed and expected frequency of markers in pairs of diabetic siblings and inconsistency for DN. The main advantage over the candidate approach is that this approach can detect chromosomal regions containing genes that were previously not known to be involved in the pathogenic presentation of NAM. However, it has the disadvantage only to remove determinative genes that have a moderate or large effect [24]. Using GWS, we identified three polymorphisms found on chromosomes 9q and 11p associated with DN in two different populations of patients with type 2 diabetes [25]. Studies of familial aggregation showed that some families are susceptible to DN [26-28]. Studies on siblings with type 1 or type 2 showed that DN of siblings is associated with an approximately 3-4-fold increase in the risk of DN with another brother [29, 30]. There appears to be genetic inheritance that contributes to the development of CKD. Forsblom et al. [31] showed that heritability (h2) in the UAE is about 30% when analyzing non-diabetic type 2 diabetic children in children [31]. This conclusion was confirmed by another study, in which it was found that after adjustments such as gender, age, obesity and DN, approximately 30% of the variability in the speed of albumin and creatinine is due to genetic factors [32]. The magnitude of the family association cannot be attributed only to exposure to similar risk factors, with the result that there is a genetic component [33]. Although proteinuria and loss of kidney function often occur simultaneously, there is evidence of different geo-information predispositions for each condition [15]. This may explain why some patients may have resistant protein-disease without the progression of loss of kidney function [34] and other patients have renal function without proteinuria or microalbuminuria [15, 35]. In genetic association studies, it is very important to defineclearly the phenotype of interest. Most studies of heritability use albuminuria or proteinuria as a DN marker. In fact, the loss of kidney function measured by GFR is strongly associated with an increase in OAE. However, it is important to note that a significant proportion of patients with DN develop kidney function loss, but they support albuminuria [35–37] and, conversely, some patients with clinical proteinuria maintain stable GFR for many years [38]. The abbreviation of OAE and GFR is genetically determined, but apparently independently [15]. Langefeld et al. [39] evaluated 310 families, including 662 patients with DN 2 type and found h2 0.35 for OAE and 0.69 for GFR [39]. These data were similar to those described in other studies, h2 creatinine concentration 0.63 among mono and dizygotic twins [35].

One approach to the identification of genes associated with DN is the study of candidate genes. There are many studies of candidate genes for DN, but the results are incompatible. The choice of gene to be studied depends on knowledge of its actions in DNA pathophysiology, such as those related to blood pressure control, the severity of proteinuria, or insulin resistance [21]. Below we present our experience with this approach. Patients with type 2 with Microalbuminuria have a high level of circulating fatty acids [50] in the serum compared with norminobuminuric patients. The intestinal absorption of long chain fatty acids is controlled by fatty acid binding protein 2 (FABP2). Thus, changes in the gene that codifies FABP2 may be candidates indicating a predisposition for DN. A54T polymorphism (rs1799883) in FABP2 is associated with an altered protein conformation, which leads to a greater affinity of FABP2 protein for intestinal fatty acids with a subsequent increase in serum. We genotyped this polymorphism in 1042 Brazilian patients with type 2 DN. The T-allele link was found at different stages of DN [28]. This

association was reproduced in an independent sample of 483 whites. American test subjects with type 2 diabetes [28]. Several studies have analyzed insertion / deletion (I/D) of polymorphism in the ACE gene, but the results of its association with DN in patients with type 2 DN were inconsistent, possibly due to ethnic differences in the populations under study [20]. In addition, several studies have used a longer duration of DN as a critical inclusion interval, which may predispose to survival bias, since possible genes associated with DN can also be associated with increased mortality. Therefore, we chose to investigate the potential link between the I/D polymorphism in the ACE gene and the development of DN in 982 Brazilian patients with type 2 DN, taking into account the duration of their disease. In patients 10 years or less from a disease with the D allele (DD/ID), the odds ratio (OR) was 2.66 (95% CI 1.12-6.58, p = 0.015) for initial DN and 3, 19 (95% CI 1.18–9.30, p = 0.012) for open dm. On the other hand, in patients with a longer duration of the disease, an increased risk for DN was associated with allele D [35]. Candidate genes for insulin resistance can also be considered candidates for the Duma, since insulin resistance is a common characteristic of patients with type 1 and type 2, which represent an increased OAE [21, 32]. Polymorphism in the ENPP1 gene, previously known as PC-1 was found to be associated with insulin resistance [33]. This association was confirmed using TDT, which showed that this association was not caused by population stratification [21]. GLUT1 gene polymorphisms associated with DNs were also considered. GLUT1 is a carrier of glucose in the kidney, and this has been associated with early kidney changes leading to proteinuria. We studied 230 patients (patients with DN 2, disease duration of at least 15 years and normoalbuminuria) and 262 cases (151 patients with persistent proteinuria and 111 with ESRD). Homozygotes for the Xbal (-) allele were associated with a discrete increased risk for DN when compared to other genotypes combined [OR 1.83 (95% CI 1.01-3.33)]. A significant difference in the distribution of genotypes among cases and controls was observed for the enhancer-2 SNP1 (p = 0.036). There was an excess of the AA genotype among cases (10.7%) compared with the control group (4.8%). These homozygous individuals are at risk for DN compared with the AG and GG genotypes mixed [OR 2.38 (95% CI 1, 16-4.90)] [23]. Other studies analyzed different genes and did not find a connection with the DN (Table 1). One of these studies showed that when patients stratified smoking, the T allele (p22phox C242T polymorphism; rs4673) was more common in ESRD smokers or resistant proteinuria than in patients with normal albumin-recipient (43% vs 32%, p=0.045). Repeated logistic regression analysis confirmed that CT and TT genotypes were independently associated with a greater risk of open DN among smokers (OR = 6.76; 95% CI 1.83-25.02) [36]. Our experience with candidate genes has allowed us to identify some genes that may be associated with the development and seriousness of DN.

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