ROLE OF CAPN-10, TCF7L2, PPAR GANDKCNJ11GENE IN TYPE 2 DIABETES MELLITUS (T2DM)

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by polygenic hyperglycemia caused by insulin secretion or insulin resistance. Several environmental factors and genetics interact to increase the risk of developing type 2 diabetes and its complications. Among the various factors associated with genetic T2DM polymorphism of the same nucleotide in several genes, it has been widely studied and showed that the resulting genetic variants have a positive or negative correlation with T2DM, which increases or decreases the risk of T2DM. In this review, we will focus on the Peroxisome proliferator-activated receptor gamma (*PPARG*), Potassium voltage-gated channel subfamily J member 11 (*KCNJ11*), Transcription factor 7-like 2 (*TCF7L2*), Calpain-10 (*CAPN10*) and their relationship with T2DM, studied in different ethnic groups. The products of these genes are involved in the biochemical pathway leading to T2DM. The polymorphisms of these genes are widely studied in individuals of different ethnic groups. The results show that the genetic variants of the *CAPN-10*, *TCF7L2*, *PPARG*, and *KCNJ11* genes can become a biomarker of risk for T2DM, and were studied in people from different ethnic groups. We tried to synthesize globally obtained results in the context of selected genes that could help researchers working in this area and ultimately it would be helpful to understand the mechanistic pathways of T2DM lead to early diagnosis and prevention.

KEYWORDS: Genetic polymorphism, CAPN-10, TCF7L2, PPARGandKCNJ11, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes refers to a group of metabolic diseases characterized by hyperglycemia based on defects in insulin secretion, insulin action or both (1). Hyperglycemia of chronic diabetes is associated with long-term damage, dysfunction and failure of multiple organs, particularly the eyes, kidneys, nerves, heart and blood vessels. Diabetes is currently the fastest growing epidemic and has been attributed to a collision between genes and the environment. Data on prevalence worldwide show that in 2013, 382 million people were living with diabetes and that this number will raise to 592 million by 2035 (2). India and China have the highest prevalence of diabetes at 65 and 98 million in 2013. More than 90% of these cases are considered Type 2 Diabetes Mellitus (T2DM). In Europe, about 8% of the population is affected by diabetes, of which 90% is due to T2DM, making T2DM the fastest growing disease in Europe and the world (2, 3).

The onset of T2DM is largely due to the global increase in obesity over the past 30 years, with more than 60% over 15 in the UK and overweight in the United States (BMI> 25) (4). This was attributed to a collision between genes and the environment. The social determinants of environmental factors vary among populations and have changed dramatically in recent decades.

A traditional, energy-rich lifestyle has been replaced by a sedentary western lifestyle with little or no exercise and a high-energy diet. In the meantime, genetic factors are developing more slowly over generations and tend to favor the selection of "prudent and energy-efficient" genotypes that could be useful for individuals in periods of unstable food supply by consuming energy in times of excess (5). this hypothesis provides an attractive explanation for obesity and T2DM outbreak, formal evidence for this hypothesis is lacking.

Advances in genomic technology have spawned a number of new genetic discoveries, including more than 2,000 common variants that contribute to the risk of complex diseases. While we have learned much, a new biology of the pathogenesis of these variants can explain only a small portion of the overall inheritance of diabetes, leaving many of the underlying mechanisms unknown. Various factors and their combined effects have been found to contribute to the development of T2DM such as environmental factors, obesity, lifestyle, family history, drugs, etc (6). Apart from these factors T2DM have a strong genetic component since it's a polygenic disease with multiple genes interacting with one another along with other

factors especially with various environmental factors contributing to disease susceptibility (7). The candidate gene approach in T2DM research helps the identification of these genetic variants that are associated with the evolution of the disease. Meta-analysis studies performed in several candidate genes around the world helps to the determination of susceptibility genes for a given Disease Table 1.

Variants	Nearest gene	Full gene name	OR-T2DM	References
rs2975760, rs3792267	*CAPN10*	Calpain 10	1.17	9,12
rs5219	*KCNJ11*	Potassium inwardly-rectifying channel, subfamily J,member 11	1.09-1.14	10,23,24, 25,26,28
rs1801282, rs13081389	*PPARG*	Peroxisome proliferator-activated receptor gamma	1.14-1.24	10,27,28
rs7903146, rs12255372, rs4506565, rs11196218	*TCF7L2*	Transcription factor 7-like 2 (T-cell specific,HMG-box)	1.4	10,18,28

Table 1. Genetic variants associated with T2DM.

In the case of a polygenic disease, however, the results may not be conclusive because gene-gene interactions, also Play an important role in the contribution of a gene.

The variant is deeper for a disease phenotype if this is the case the result of gene-gene interactions. A large number of the candidate genes have been studied over the past two decades and huge information is available from various associations studies conducted worldwide. In this report we will do it focus on the genes *CAPN-10, TCF7L2, PPARG*and*KCNJ11*and its association with T2DM studied in various ethnic groups as shown in Table 1, the products of these genes. They are involved in the biochemical pathway leading to T2DM while that of NET gene is involved in sodium–chloride dependent active reuptake of norepinephrine which in turn increases release of glucagon from pancreas thereby increasing blood glucose levels. *KCNJ11* gene product was found to regulate insulin secretion.

In T2DM, peripheral blood monocytes express more inflammatory cytokines than those from healthy subjects.

Calpain 10 (CAPN10)

CAPN10 encodes a cysteine protease belonging to the Calpain family, a large family of ubiquitous genes that play multiple roles in intracellular remodeling, post-receptor signaling or other intracellular functions. The first T2DM gene detected by linkage analysis was linked to T2DM in 1996 as the chromosome 2 locus (8). The locus was originally named NIDDM1, but the genes (or genes) were not identified. In 2000, the causal gene was finally identified as CAPN10 (9). Subsequent studies do not always support this conclusion, but broader Meta-analyzes have shown that CAPN10 variants are likely to be related to T2DM (10). Currently, the function of this gene in glucose metabolism is unknown and its association with T2DM, which is confirmed in several populations, is not always consistent (11-13).

Transcription factor 7-like 2 (*TCF7L2*)

TCF7L2 was detected as a T2DM susceptibility gene after mapping a strong 10q chromosome signal in the US-Mexico population (14). This area was closely mapped to the Icelandic population and confirmed in the American and Danish cohorts where the risk site was found in intron 3 of the *TCF7L2* gene (15). Communication between different DT2 and single nucleotide polymorphisms (SNP) in *TCF7L2* gene has been fully confirmed by numerous complex genome researches on association (GWAS) in various ethnic groups, and this gene is replicated on the T2DMM gene, and most of the risk genes strongly related at this time (16). We will discuss this gene later in the GWAS section of this review.

Peroxisome proliferator-activated receptor gamma(*PPARG*)

The *PPARG* gene was an attractive candidate gene for T2DM as it encodes the molecular target of thiazolidine, a class of widely-used antidiabetics. It was found that a shift from proline to arginine at position 12 in the *PPARG* gene resulted in a 20% increase in the risk of developing diabetes. This conclusion has been confirmed in several other populations and it has been found that other polymorphisms of this gene may play a role in some cases of diabetes (17). However; the importance of these mutations has not been replicated in all populations and the contribution of these polymorphisms to the overall prevalence of diabetes remains low (18, 19).

Potassium voltage-gated channel subfamily J member 11 (*KCNJ11*)

The *KCNJ11* gene encodes the Kir6.2 ATP channel, which plays an important role in the regulation of insulin secretion by beta cells. Activation of mutations in this gene is a known cause of neonatal diabetes. The missing polymorphism in *KCNJ11* was associated with T2DM and confirmed in further studies (20). The probabilistic ratio of T2DM development is about 1.2 in carriers of the risk allele, and this allele is also associated with a decrease in insulin secretion in different populations (21-26).

CONCLUSION

The incidence of diabetes is increasing rapidly worldwide, and available data show that prevalence is increasing in children and adolescents under the age of 30. This requires the urgent development of methods and techniques to combat this growing epidemic and

to identify high-risk people at an early stage so that T2DM could be prevented from taking appropriate preventive measures. In addition to environmental factors such as diet, ethnicity, family history, lifestyle, etc., genetic factors also have a profound effect on the development of T2DM and interact with environmental factors to predict an individual T2DM.

Several genetic linkages and association studies have identified several candidates for T2DM and ongoing research in this area to identify new gene variants that may play a role in the pathophysiology of T2DM genes. This Review summarizes the results of several global studies combining the CAPN-10, TCF7L2, PPARGandKCNJ11genes with T2DM, which can help researchers in this area and ultimately help understand the mechanisms of T2DM. CAPN-10, TCF7L2, PPARGandKCNJ11 can act as biomarkers of the risk of T2DM and play an important role in T2DM.

It can therefore be said that a proper understanding of the genetic background of T2DM facilitates the understanding of biochemical and molecular mechanisms, the development of potential biomarkers that can identify patients at an early stage and develop new treatments that aid in diagnosis and treatment, and finally the prevention of this disease.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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