



## REVIEW ARTICLE

### Genetics of Type 2 Diabetes: A Review

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#### Abstract

Diabetes Mellitus (DM), one of the most non-communicable diseases, is increasing day by day in an alarming way. More than 140 million people are suffering from diabetes throughout the world. It is not a single disease entity, but rather a group of metabolic disorders sharing the common underlying feature of hyperglycemia. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both. The chronic hyperglycemia and attendant metabolic deregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels. The pathophysiology of diabetes is not fully elucidated. Insulin secretory dysfunction and insulin resistance or both is main candidate for this metabolic disorder, moreover various genetic and environmental factors may also involve in this process. Racial variations play also an important role as evidenced by various studies. However, the interrelationships between the molecular and metabolic mechanisms in these parameters contributing this life threatening disease still remain a mystery to the scientists. [*Journal of Current and Advance Medical Research 2019;6(1):59-63*]

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#### Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin

which produces by its own<sup>1</sup>. Diabetes mellitus results from a deficiency in the amount of insulin released from the pancreas in response to glucose (type I) or from a decrease in the ability of muscle and fat cells to respond to insulin (type II)<sup>2</sup>. In both

types, the regulation of blood glucose is impaired, leading to persistent hyperglycemia and numerous other possible complications in untreated patients<sup>3</sup>. Most of the people in the world with diabetes mellitus have type II; however, the underlying mechanism of this form of the disease is not well understood.

## Diabetes Mellitus

Diabetes mellitus (DM) is not a single disease entity, but rather a group of metabolic disorders sharing the common underlying feature of hyperglycemia<sup>4</sup>. Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both. The chronic hyperglycemia and attendant metabolic dysregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels<sup>5</sup>. Diabetes is a leading cause of end-stage renal disease, adult-onset blindness, and non-traumatic lower extremity amputations worldwide<sup>6</sup>. Worldwide, more than 140 million people suffer from diabetes, making this one of the most common non-communicable diseases<sup>7</sup>. The number of affected individuals with diabetes is expected to double by 2025. The countries with the largest number of diabetics are India, China, and the United States<sup>7</sup>.

Type 2 diabetes mellitus (T2DM, previously known as non-insulin-dependent diabetes mellitus or NIDDM) is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic  $\beta$ -cells ("relative insulin deficiency"). Approximately 80% to 90% of patients have type 2 diabetes<sup>8</sup>.

## Genetics of type 2 diabetes

Several studies have found that genetic components play an important role in pathogenesis of type 2 diabetes. Several prospective studies and cross sectional studies have reported that positive family history among first degree relatives confers an increased risk of type 2 diabetes and the risk is greater when both parents are affected<sup>9</sup>. A study on twins has demonstrated that concordance estimate for type 2 diabetes is high in monozygotic compared to dizygotic and the rate increases with duration of follow up. Also, diabetes prevalence varies substantially among different ethnic groups, and this observation of substantial variation of disease prevalence across ethnic groups that share a similar environment, supports the idea that genetic factors contribute to disease predisposition<sup>10</sup>. Data

from multiple laboratories support that genetic factors predispose to development of type 2 diabetes by reducing insulin sensitivity and insulin secretion which deteriorate in parallel in most human type 2 diabetes cases<sup>11</sup>. Current studies have identified variants in 11 genes (TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX) to be significantly associated with the risk of type 2 diabetes independently of other clinical risk factors and variants in 8 of these genes were associated with impaired beta-cell function. Among these genes, expressed in pancreatic cells and involved in impairment of insulin secretion, the transcription factors 7-like 2 (TCF7L2), is the locus with the highest risk of type 2 diabetes (HR 1.5)<sup>12</sup>. This corresponds to an attributable risk of 25%, due to an average single allele frequency 18-30% in Northern Europeans. Still the value of genetic information decreased by duration of follow up and eventually only increases the receiver operating characteristics (ROC) achieved by clinical risk factors from 0.74 to 0.75 ( $p < 0.0001$ ). So far genetic information is of interest for research purposes only<sup>13</sup>.

## Role of Genetics in the Development of Diabetes

T2D is a polygenic, multifactorial disease and the risk for T2D is thought to be influenced by many genes with minor effects together with environmental factors. Until recently, genetics of T2D had limited success with only a few truly verified genes. Until 2007, the dissection of genetic predisposition to T2D was performed by linkage using microsatellites and candidate gene association studies<sup>14</sup>. With GWAS and large meta-analyses several novel T2D genes have finally been identified and verified, the function of which still remains to be elucidated<sup>15</sup>. Many genes have been proposed as candidate genes for T2D but only few susceptibility genes have been convincingly associated in several studies, including *PPARG*, *KCNJ11*, *TCF7L2* and *WFS1*. Many other genes have been associated with T2D in some studies but not in others, including *IRS1*, *CAPN10*, *ADBR3*, *PPARGC1A*, *ENPP1* and others<sup>16</sup>. Many of these genes have been investigated as candidate genes because of their biological function. Common polymorphisms in *MODY* genes, such as *TCF2*, *GCK*, *HNF1 $\alpha$*  and *HNF4 $\alpha$*  have also been implicated in the development of T2D<sup>17</sup>.

## *IRS1*

Insulin receptor substrate 1 (*IRS1*) is one of the proteins involved in signal transduction of the

activated insulin receptor by phosphorylation on its tyrosine residues<sup>18</sup>. A common polymorphism G972R (rs1801278), located close to the tyrosine phosphorylation motifs, has been associated with T2D in some but not in all studies<sup>19</sup>. A meta-analysis of 27 studies shows modest association with T2D, but this association could not have been confirmed by current large study or GWAS for T2D. The same polymorphism has also been associated with insulin resistance in obese but not in lean individuals<sup>20</sup>. Also the expression of *IRS1* mRNA has been reported to be lower in skeletal muscle from insulin resistant non-diabetic subjects. Mice lacking the *IRS1* display mild insulin resistance and hyperinsulinemia but do not develop diabetes. Tissue specific knock-out experiments indicate a role for *IRS1* in insulin signaling in skeletal muscle, adipose tissue and pancreatic  $\beta$ -cells<sup>21</sup>.

### ***PPARG***

The peroxisome proliferator-activated receptor gamma gene (*PPARG*) encodes a transcription factor highly expressed in adipose tissue and involved in adipocyte differentiation. *PPARG* is also a target of the anti-diabetic, insulin sensitizing drugs thiazolidinediones (TZD)<sup>22</sup>. This gene has been widely studied because it is important in adipocyte and lipid metabolism. In addition, it is a target for the hypoglycemic drugs known as thiazolidinediones<sup>23</sup>. One form of the *PPAR $\gamma$*  gene (Pro) decreases insulin sensitivity and increases T2D risk by several fold. Perhaps more importantly is that this variant is very common in most populations<sup>24</sup>. Approximately 98% of Europeans carry at least one copy of the Pro allele. Thus, it likely contributes to a considerable proportion (~25%) of T2D that occurs, particularly among Caucasians<sup>25</sup>. The minor Ala-allele in *PPARG*, (Pro12Ala, rs1801282) has been associated with lower BMI, increase in insulin sensitivity and reduced risk of T2D. This association has been confirmed by several recent GWAS for T2D<sup>26</sup>.

### ***KCNJ11***

A common, non-synonymous SNP (E23K, rs5219) in the potassium channel, inwardly rectifying, subfamily J, member 11 (*KCNJ11*) has been associated with T2D in several large studies and this finding was confirmed by several recent GWAS<sup>27</sup>. The gene encodes the Kir6.2 subunits of the inwardly rectifying KATP-channel. The KATP channels in pancreatic  $\beta$ -cells consist of four pore forming Kir6.2 subunits surrounded by four regulatory sulfonylurea receptor 1 (SUR1) subunits

and regulate insulin secretion by coupling metabolism to electrical activity<sup>28</sup>. The E23K polymorphism affects ATP sensitivity of the KATP-channel; homozygous KK-genotype carriers show two fold reduced sensitivity to ATP<sup>29</sup>. The KATP-channels are targets for sulfonylureas, drugs used to treat diabetes by closing the channel and triggering insulin secretion. Activating mutations in *KCNJ11* are known to cause neonatal diabetes and inactivating mutations neonatal hypoglycemia<sup>30</sup>.

### ***TCF7L2***

The association between polymorphisms in *TCF7L2* and T2D was first discovered in 2006 by Grant and colleagues when investigating a region linked to T2D on chromosome 10q25<sup>31</sup>. This association did, however, not explain the linkage to this region. The association has thereafter been confirmed by several studies, including all GWAS and *TCF7L2* is therefore considered the strongest susceptibility gene for T2D<sup>32</sup>. *TCF7L2* encodes a transcription factor involved in the Wnt signaling pathway but the mechanism by which it contributes to the pathogenesis of T2D is poorly understood<sup>33</sup>. Several studies have shown that an intronic SNP in *TCF7L2* is associated with impaired insulin secretion and  $\beta$ -cell function but not insulin action. It has been suggested that the impaired insulin secretion can be mediated by an impaired incretin effect<sup>34</sup>.

### ***WSF1***

*WSF1* was identified as a candidate gene for T2D in a study of 83 candidate genes for  $\beta$ -cell function and T2D. Meta analysis of 11 studies confirmed rs10010131 as a susceptibility variant for T2D with genome-wide significant p-value ( $p = 5.4 \times 10^{-11}$ )<sup>35</sup>. *WSF1* encodes wolfram, a membrane glycoprotein regulating calcium homeostasis in the endoplasmic reticulum. Mutations in *WSF1* cause the Wolfram syndrome, characterized by diabetes insipidus, DM, optic atrophy and deafness<sup>36</sup>.

### ***UABCC8* (ATP binding cassette, subfamily C, member 8) U**

This gene encodes the high-affinity sulfonylurea receptor (SUR1) subunit that is coupled to the Kir6.2 subunits (encoded by *UKNJ11U*, also known as the potassium channel, inwardly rectifying subfamily J, member 11). Both genes are part of the ATP-sensitive potassium channel, which plays a key role in regulating the release of hormones, such as insulin and glucagon, in the beta

cell<sup>37</sup>. Mutations in either gene can affect the potassium channel's activity and insulin secretion, ultimately leading to the development of T2D. Interestingly, *ABCC8* and *KCNJ11* are only 4.5 kb apart, and not far from the *INS* gene. Variant forms of *KCNJ11* (Lys) and *ABCC8* (Ala) genes have been associated with T2D, as well as other diabetes-related traits<sup>38</sup>.

Because of the close proximity of these genes, current studies are evaluating whether they work in concert with each other, or rather have an independent effect on T2D susceptibility. Since *PPAR $\gamma$* , *ABCC8* and *KCNJ11* are the targets of drugs used routinely in the treatment of T2D, there are pharmacogenetic implications for maintaining good glycemic control<sup>39</sup>. Response to hypoglycemic therapy may actually be related one's genotype. Thus, genetic testing may not only help determine who is at high risk for developing T2D, but also be useful in guiding treatment regimens for T2D<sup>40</sup>.

### **CAPN10 (calpain 10)**

*CAPN10* encodes an intracellular calcium-dependent cysteine protease that is ubiquitously expressed<sup>41</sup>. A haplotype that was initially linked to T2D included an intronic A to G mutation at position 43, which appears to be involved in *CAPN10* transcription.

Two amino acid polymorphisms (Thr504Ala and Phe200Thr) have also been associated with T2D risk. However, it has been suggested that the coding and noncoding polymorphisms do not independently influence T2D risk, but instead contribute to an earlier age at diagnosis<sup>42</sup>. Physiological studies suggest that variations in calpain 10 activity effects insulin secretion, and therefore, susceptibility to T2D. Studies from different ethnic groups indicate that the contribution of this locus to increased T2D risk may be much larger in Mexican-American than Caucasian populations<sup>43</sup>.

### **Other genes involved in T2D Diabetes**

In recent times, six new gene regions (*SLC30A8*, *CDKAL1*, *CDKN2A*, *IGF2BP2*, *FTO*) suspected to be involved in T2D were identified by GWAS<sup>44</sup>. None of these regions contains previously known obvious candidate genes, thereby showing the ability of GWAS to uncover new pathophysiological pathways<sup>45</sup>. Meta-analysis of the three large GWAS for T2D revealed additional six loci (*JAZF1*, *CDC123/CAMK1D*, *TSPAN8/LGR5*,

*THADA*, *ADAMTS9*, *NOTCH2*) with genome wide significant association<sup>40</sup>.

### **Conclusion**

The pathophysiology of diabetes is not fully elucidated. Insulin secretory dysfunction and insulin resistance or both is main candidate for this metabolic disorder; moreover, various genetic and environmental factors may also involve in this process. Racial variations play also an important role as evidenced by various studies. However, the interrelationships between the molecular and metabolic mechanisms in these parameters contributing this life threatening disease still remain a mystery to the scientists.

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