

# Genetic approach in personalized medicine in type 2 diabetes

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## Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia commonly associated with insulin resistance at high risk of renal, neurological and cardiovascular complications. It is defined as a multifactorial etiology disease where genetic predisposition and lifestyle play an important role in pathophysiology and onset. Recently, genome wide association studies (GWAS) have been widely used to identify deregulated expression of T2DM related genes and genetic risk factors that can contribute, together with environmental and behavior factors, to T2DM onset. Since its dual feature, anti-diabetic effective therapy need to acknowledge the genetic contribution to T2DM pathophysiology. The pharmacological treatment of T2DM depends on blood glucose levels and/or glycated hemoglobin (HbA1c): well-compensated patients with normal HbA1c levels are, generally, treated with oral hypoglycemic drugs, such as metformin, associated with a diet that limits carbohydrate intake. Conversely, the uncompensated patient, with high levels of HbA1c is generally treated with insulin or other new generation drugs or a combination of them. Given the multifactorial nature of T2DM, recent studies have identified personalized therapy as a powerful means to refine the effectiveness of the therapy itself, paving the way for precision medicine.

## Diagnostic criteria and therapies in T2DM

In the last decade, Type 2 diabetes mellitus (T2DM) incidence have dramatically grown up worldwide [1], with serious consequences to global health. T2DM is a multifactorial disease where metabolic impairment is the common feature: it is clinically characterized by high blood glucose levels that can lead to an inadequate insulin secretion, insulin resistance and/or glucagon secretion impairment, often associated with comorbidity [2]. According to the ADA (American Diabetes Association) guidelines, T2DM diagnosis is based on plasma glucose criteria, either the fasting plasma glucose (FPG) value, or the 2-hour plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or glycated hemoglobin (HbA1c) percentage evaluation [3]. In particular, T2DM diagnosis requests FPG  $\geq 126$  mg/dl, OGTT  $\geq 200$ mg/dl and HbA1c  $\geq 6.5\%$  [3]. Pharmacological therapy is combined taking in account both FPG and HbA1c; moreover, ADA guidelines recommend life style modification coupled with drugs therapy depending on HbA1c percentage and/or body mass index levels: HbA1c levels less of 6.5%, in fact, requested changing in lifestyle coupled with only moderate metformin administration [4]. On the other hand, for HbA1c levels less than 7% therapy based on sodium-glucose transport protein 2 (SGLT-2) inhibitors, Dipeptidyl peptidase-4 (DPP-IV), or glucagon-like peptide 1-receptor agonist (GLP1-RA) may be suggested [4] while highly uncompensated T2DM patients showing HbA1c percentage from 8 up to 9%, need insulin treatment alone or in combination with other hypoglycemic drugs [4]. Despite the introduction of many novel anti diabetic drugs, such as gliflozin, whit promising results especially on cardiovascular complication preventions [5], or renal failure outcomes amelioration [6], non-responder patients to therapies are a serious challenge to face with [7]. A recent study highlighted how a significant percentage of newly

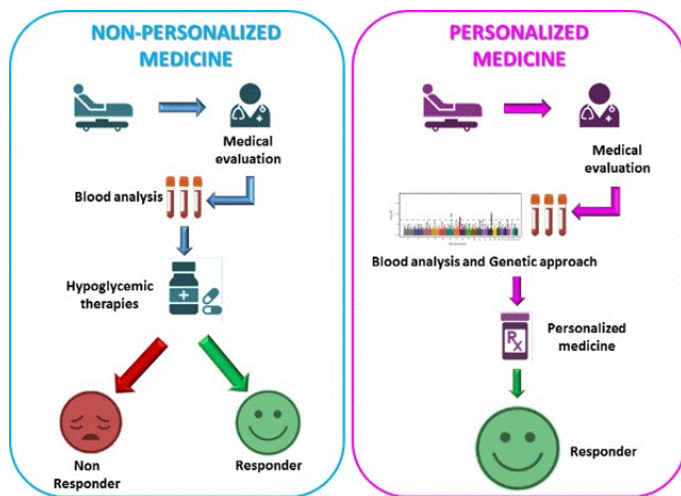
diagnosed patients resulted as metformin treatment non-responder [8]. Moreover, Heerspink and colleagues demonstrated how Dapagliflozin treatment failed to decrease urinary albumin-to-creatinine ratio in 46% of clinical cases [9]. Based on all these findings, a genomic approach could be useful to develop novel and more personalized therapies to treat the non-responders T2DM patients [10].

## GWAS approach in T2DM

The genetic component that characterizes the etiology of T2DM must be taken into consideration in developing the therapeutic plan for patients. Studies conducted on the genetics of T2DM using the genome-wide association studies (GWAS) technique, identified about 400 genetic loci strongly associated with T2DM [11]. GWAS is an observational study aimed to identify genetic variants across whole genome that can be related to a certain disease; it was developed in 2002 and recently became an important tool of genetics research [12,13]. GWAS analysis can be also used to determine the risk of developing disease [14,15]. Moreover, this technique identifies single nucleotide polymorphism (SNPs) that are associated with a large number of disorders [16]. Thirty-eight SNPs tightly associated with T2DM have been initially found [17], together with several SNPs linked with hyperglycemic state and high triglyceride conditions [18]. Nowadays, GWAS identified at least 143 genetic variants associated with T2DM [19]; moreover, in human islets 2,949 SNPs associated with *in vivo* cis-regulatory elements have been recently identified [20]. GWAS technique could potentially leading

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**Figure 1.** Schematic representation of personalized medicine rationale

to discover many new pharmacological targets for T2DM therapy. Recently polymorphisms in *SLC30A8* as affecting disease risk has been discovered in T2DM [21]. Thus, the common polymorphism *rs13266634*, associated with increased risk for developing T2DM, was associated with lowered beta cell function and a 14% increase in diabetes abundance [21]; it seems clear that a patient with this particular genetic setup will need a more precise therapeutic approach compared to a wild type genetic setup patient. Pharmacogenetic study on T2DM highlighted as mutations in *KCNJ11* gene encoding for ATP (Adenosine Triphosphate) sensitive potassium channel subunit Kir 6.2, reduces insulin secretion causing permanent neonatal diabetes onset; thus, patients with this mutation have more benefits in sulfonylureas therapy instead insulin [22].

### Personalized medicine in T2DM

Precision medicine is a customized approach that allows coupling patient with the best therapy taking in account his/her genetic profile environments and lifestyles leading to a personalized pharmacological intervention [23]. To achieve this goal, as previously reported, the genetic profile of diabetic subjects plays a pivotal role in avoiding ineffective therapies. In agreement, the GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) study demonstrated how the reduced allelic functions of the *OCT1* gene, encoding the organic cationic co-transporter -OCT, is directly correlated with the increased intolerance to metformin [24]. The rationale behind precision medicine is avoiding administration of an ineffective therapy that could not bring any benefit to the patient (Figure 1).

Moreover, it has also been suggested that the low allelic expression of the channels responsible for serotonin retention, is specifically correlated with the increased development of intolerance to metformin [25]. Based on these studies, metformin therapy would be contraindicated in patients who presented a genetic profile that included the reduced expression of the above mentioned alleles. Another study established as the presence of genetic polymorphisms, particularly *TCF7L2* polymorphism, could influence the response to DPP-IV inhibitors in diabetic patient [26]. Thus, antidiabetic therapy involving the use of DPP-IV inhibitors for T2DM patients with *TCF7L2* polymorphism, would invalidate or make less effective the prescribed therapy. Moreover, published data demonstrated the presence of genetic polymorphisms able to reduce the response to GLP-1-RA inducing T2DM [27]. This study confirmed uselessness to administrate GLP-1-RA therapy to a non-responder patient.

### Conclusions

Precision medicine associated with T2DM therapy is becoming the future prospect for the development of a strategy that takes into account the patient's genetic cluster. Further studies aimed to identify new genetic targets capable of influencing the response or tolerance to an antidiabetic drug are mandatory to develop a personalized approach, in order to avoid prescribing drugs whose efficacy may not be effective. Physicians and diabetologists need to work in synergy with geneticists in order to elaborate a more effective therapeutic approach that could be as personalized as possible.

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