

# Precision Medicine with Sulfonylureas: From Clinical Studies to Bedside Practice

V Mohan<sup>1</sup>, Mathew John<sup>2</sup>, Soumik Goswami<sup>3</sup>, Mohan Magdam<sup>4</sup>, Saket Kant<sup>5</sup>, MV Vimal<sup>6</sup>, S Amarnath<sup>7</sup>

## Abstract

Precision medicine is part of personalized therapy that is based on an individual's genetic/epigenetic imprints, lifestyle, and environmental characteristics. Recent advances in understanding of the genomic landscape in diabetes mellitus have identified genetic polymorphisms associated with the risk of diabetes mellitus along with other related complications such as cardiovascular risk or hypoglycemia, in turn, spurring the development of precision medicine in prevention and management of diabetes mellitus. Here we will discuss the various genetic polymorphisms that are currently being explored for the development of precision medicine with sulfonylureas, such as glimepiride, for management of people with diabetes.

## Introduction

Understanding the underlying etiology of type 2 diabetes mellitus has been driven by advances in the knowledge of human genetics, biomarkers, epigenetics, large clinical trials, and mechanistic studies, all of which have provided new insights into the pathophysiology, progression, susceptibility, and development of complications of the disease.<sup>1</sup> The rising prevalence of diabetes mellitus along with the insufficiency of the conventional therapeutic options in wholesome management of the disease have necessitated the search for alternative prevention and treatment strategies for diabetes mellitus. Ideally, such new therapeutic options should be better tailored to suit individuals for increased effectiveness and tolerability. It is a well-accepted fact that precision medicine based on various sources of data will improve the prevention and therapy of multifactorial diseases like type 2 diabetes mellitus.<sup>2</sup> Type 2 diabetes mellitus and its associated complications are regarded as polygenic and complex diseases that result from interactions of several genetic and environmental factors. The genetic basis was examined in a GWAS study, where 128 distinct association signals were detected at 113 loci.<sup>3</sup>

## Sulfonylureas (SUs) in Precision Medicine

Sulfonylureas undergo metabolism in the liver mainly by the CYP2C9 enzyme.<sup>4</sup> Gene polymorphisms of the CYP2C9 enzyme lead to impaired metabolism of SUs, which, in turn, might lead to hypoglycemia.<sup>5</sup> In a case study it was shown that a marked sensitivity to SUs was observed in patients with diabetes with *HNF1A* mutation.<sup>6,7</sup> This finding was later validated in a randomized controlled trial that served as the first example of personalized medicine in the treatment of diabetes mellitus. It has been suggested that the SU-induced closure of the ATP-sensitive potassium ( $K_{ATP}$ ) channel bypasses the key sites of beta-cell dysfunction that are upstream of the  $K_{ATP}$  channel, thereby, leading to increased insulin secretion. SUs serve as the first-line treatment due to the presence of activating mutations in *ABCC8* and *KCNJ11* genes that prevent the closure of  $K_{ATP}$  in response to glycolysis-generated ATP in case of some specific people with neonatal diabetes mellitus.<sup>1,8-10</sup> Therapeutic response to SUs is also affected by genetic polymorphisms

in the *TCF7L2* gene, which increases the risk of type 2 diabetes mellitus. The underlying mechanism involves impairment of insulinotropic role of incretin hormones.<sup>11</sup> In fact, a study by Srinivasan *et al*, indicated that altered integrin signaling is an important underlying mechanism for increasing risk of type 2 diabetes mellitus through *TCF7L2* variation. This gene variation in turn, affects acute response towards SU and metformin treatments.<sup>12</sup> In the following sections, we will discuss the genetic variations that have been explored for precision medicine in patients with diabetes.

## Gene Variation Mimicking SU Therapy

*ABCC8 p.A1369S* is a common missense mutation in the gene encoding a component of the SU receptor, which promotes closing of the target  $K_{ATP}$  channel during SU therapy and leads to enhanced secretion of insulin, thereby, mimicking the effects of SU therapy. Based on individual data from 1,20,286 participants in the UK Biobank, Emdin *et al*. studied the association of this gene variant with type 2 diabetes mellitus, cardiometabolic traits, and coronary heart disease. It was found from the study that this gene variant was associated with lower risk of type 2 diabetes mellitus, increased body mass index (BMI), and lower waist-to-hip ratio adjusted for BMI. In addition, it was also associated with reduced risk of coronary heart disease, which indicated that genetic mutation that mimics SU therapy might reduce the risk of coronary heart disease.<sup>13</sup>

This adds to the long-term efficacy, benefits beyond glycemic control and safety data for SUs.

<sup>1</sup>Chairman and Chief Diabetologist, Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu; <sup>2</sup>Consultant Endocrinologist and Managing Partner, Providence Endocrine and Diabetes Specialty Centre, Trivandrum, Kerala; <sup>3</sup>Consultant Endocrinologist, Department of Endocrinology, NRS Medical College, Kolkata, West Bengal; <sup>4</sup>Consultant Endocrinologist, Poona hospital and Aditya Birla Hospital, Pune, Maharashtra; <sup>5</sup>Sr. Consultant, Department of Endocrinology, Max Super Speciality Hospital, Shalimar Bagh, New Delhi; <sup>6</sup>Consultant Endocrinologist, Aster MIMS, Calicut, Kerala; <sup>7</sup>Medical Affairs, Diabetes and Cardiovascular, Sanofi India Ltd.

**Table 1: Gene mutations/polymorphisms associated with the safety and efficacy of SUs**

Gene mutation	Involvement of SUs
HNF1A	Marked sensitivity to SUs
ABCC8 p.A1369S	Mimics the effect of SU therapy, increasing insulin release
KCNJ11	Neonatal patients can be switched over from insulin to SU therapy
HNF4A	Can be managed with SU therapy
CYP2C9*3 and CYP2C9*2	At higher risk of hypoglycemia when treated with SUs, such as glimepiride
POR*28	Shows better response to SU treatment by affecting CYP2C9 alleles

*HNF1A*: Hepatic Nuclear Factor 1 Alpha; *ABCC8*p.A1369S: ATP binding cassette subfamily C member 8, with A1369S mutation; *KCNJ11*: Potassium Voltage-Gated Channel Subfamily J Member 11; *HNF4A*: Hepatic Nuclear Factor 4 Alpha; *CYP2C9*\*3 and *CYP2C9*\*2: Genetic variants of Cytochrome P450 2C9 (*CYP2C9*); *POR*\*28: Genetic variant of Cytochrome P450 Oxidoreductase (*POR*).

### Precision Medicine with SUs in Neonatal Diabetes Mellitus

The occurrence of diabetes mellitus under six months of age is defined as neonatal diabetes, which mostly occurs due to an underlying monogenic defect, i.e., resulting from mutation(s) in a single gene. At present, more than 20 genetic causes are accountable for neonatal diabetes mellitus. In a large international cohort study on 1020 neonatal diabetes patients, more than 80 percent cases had a known genetic diagnosis. Mutations in *KCNJ11* and *ABCC8* account for 40% of these patients.<sup>14</sup> The *KCNJ11* and *ABCC8* genes, encode  $K_{ATP}$  channel, and are found in majority of neonatal diabetes mellitus patients.<sup>8-10</sup> This, in turn, leads to impairment of endogenous insulin release by preventing beta-cell depolarization that results from the closure of the  $K_{ATP}$  channels. The earliest cost-effectiveness analysis in precision medicine focused on the use of SU therapy in permanent neonatal diabetes mellitus patients. It was estimated that genetic testing in such cases would implement significant quality of life benefits at ten years.<sup>2</sup> In a clinical study on 49 patients with diabetes mellitus under six months of age harboring heterozygous activating mutations in *KCNJ11* gene, 44 patients (90%) could be successfully switched over from insulin to SU therapy.<sup>15</sup> Sulfonylurea therapy can be initiated in infants with newly diagnosed neonatal

diabetes mellitus, in case the test results of molecular genetic diagnosis are delayed.<sup>16-19</sup>

### Precision Medicine with SUs for MODY

Maturity-onset diabetes of the young (MODY) is caused by a range of single gene defects, each of such defects is responsible for one of the 11 types of MODY, such as MODY3 results from mutation in hepatocyte nuclear factor (*HNF*)-1a while MODY1 results from mutation in *HNF-4a* genes, respectively.<sup>3</sup> Insulin secretion is impaired in MODY1 and MODY3 and they are often misdiagnosed as type 1 diabetes mellitus. Under such circumstances, exogenous insulin therapy is prescribed. However, it has been found that treatment with SUs restores the secretion of endogenous insulin. Furthermore, switching to SUs from insulin is preferred for a number of reasons, including safety and reduced treatment burden.<sup>2</sup> In fact an additional advantage of SU mediated insulin release is the decrease in glucagon secretion and this endogenous insulin reaching portal circulation being more effective for decreasing hepatic glucose output.<sup>20</sup> It has been found that MODY1 can be managed with SU treatment, although eventually insulin therapy may be required. In case of MODY3, insulin therapy is not required as the genetic defect can be rectified with SU therapy, which makes the beta-cell to secrete insulin.<sup>17</sup> It has been observed that the MODY subtypes with dysregulation in beta-cell function (like *HNF4A*, *HNF1A*) or ATP-sensitive potassium channel (*ABCC8*) are most sensitive to SU treatment.<sup>21</sup>

### Gene Polymorphism of CYP2C9 Enzyme and Precision Medicine With SU

Primarily metabolism of SUs takes place in the liver by the cytochrome P450 2C9 enzyme encoded by the *CYP2C9* gene. Although a majority of the population carries a normal version of this enzyme, some carry polymorphisms of the gene with reduced function, termed \*2 and \*3. Overall, 6% of the population carries two reduced-function polymorphisms, as a result of which they are predicted to poorly metabolize SUs.<sup>22</sup>

A clinical study by Ragia *et al*

revealed that when people with type 2 diabetes mellitus carrying the *CYP2C9*\*3 polymorphism are treated with SUs, including glimepiride, they are at increased risk of hypoglycemia, possibly due to the impaired metabolism of SUs. The study proposed that *CYP2C9* could be used as a tool for predicting the adverse effects of SUs in people with type 2 diabetes mellitus.<sup>5</sup> In another similar study by Dujic *et al* on 1770 patients, the effects of a P450 oxidoreductase (*POR*) gene variant, *POR*\*28 were studied on *CYP2C9* (combined *CYP2C9*\*2 and *CYP2C9*\*3 genotypes) activity in the context of SU-induced hypoglycemia and the efficacy of SUs in the treatment of type 2 diabetes mellitus. The results indicated that the interaction between *POR* and *CYP2C9* genes may be important determinants of both adverse effects and efficacy of SU therapy.<sup>4</sup>

### Genetic Basis for Resistance/Poor Response to SU Therapy

It has been observed that Glu23Lys polymorphism (E23K) in *KCNJ11* gene is associated with increased risk of therapeutic failure of SUs. Another variant of the *ABCC8* gene with SNP at Ser1369Ala has been reported to be associated with altered antidiabetic efficacy of SU in Chinese population. Again, SNPs of the *ABCC8* gene in exon 16 (-3C/T) and exon 31 (Arg1273Arg) are reported to affect SU efficacy in European Caucasians. KATP channels with K23/A1369 risk haplotype were significantly less responsive to SU therapy including glimepiride. Carriers of the risk GG genotype of rs163184 variation in *KCNQ*, and the Arg (972) variant of *IRS-1* also associated with increased risk of SU therapy failure.<sup>23</sup>

Table 1 enlists the various gene mutations that have been identified to be involved in diabetes and their function in the context of SU therapy.

### Conclusion

Precision medicine is likely to become a major area in the therapy of diabetes mellitus.<sup>24-26</sup> Given the insufficiency of conventional antidiabetic therapies, along with the added complexity of their side-effects, precision medicine appears to be the ideal therapy for patients with diabetes. Sulfonylureas including glimepiride have been found to be efficient as precision medicine in the treatment of different types of

diabetes mellitus. Identification of genetic polymorphisms in such patients has aided the appropriate choice or inappropriateness of SUs in the therapy of patients with diabetes. With more clinical studies in the coming years, SUs are likely to be prominent members of precision medicine in the treatment of diabetes.

#### Conflict of Interest

SA is an employee of Sanofi India. All other authors report no conflicts of interest.

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#### Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, reviewed and have given their approval for the final version to be published.

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## References

- Gloyn AL, Drucker DJ. Precision medicine in the management of type 2 diabetes. *Lancet Diabetes Endocrinol* 2018; 6:891–900.
- Fitipaldi H, McCarthy MI, Florez JC, et al. A global overview of precision medicine in type 2 diabetes. *Diabetes* 2018; 67:1911–1922.
- Xie F, Chan JC, Ma RC. Precision medicine in diabetes prevention, classification and management. *J Diabetes Investig* 2018; 9:998–1015.
- Dujic T, Zhou K, Donnelly LA, et al. Interaction between variants in the CYP2C9 and POR genes and the risk of sulfonylurea-induced hypoglycaemia: A GoDARTS Study. *Diabetes Obes Metab* 2018; 20:211–214.
- Ragia G, Petridis I, Tavidou A, et al. Presence of CYP2C9\*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. *Pharmacogenomics* 2009; 10:1781–1787.
- Anuradha S, Radha V, Mohan V. Association of novel variants in the hepatocyte nuclear factor 4A gene with maturity onset diabetes of the young and early onset type 2 diabetes. *Clin Genet* 2011; 80:541–549.
- Anuradha S, Radha V, Deepa R, Hansen T, Carstensen B, Pedersen O, et al. A prevalent amino acid polymorphism at codon 98 (Ala98Val) of the hepatocyte nuclear factor-1alpha is associated with maturity-onset diabetes of the young and younger age at onset of type 2 diabetes in Asian Indians. *Diabetes Care* 2005; 28:2430–2435.
- Jahnavi S, Poovazhagi V, Mohan V, Radha V. Neonatal diabetes and hyperinsulinemia: The Indian experience. *J Neonatol* 2013; 27:15–23.
- Varadarajan P, Ananthanarayanan K, Mirna K, Suresh J, Venkatesan R, Mohan V. Clinical profile and outcome of persistent hyperinsulinemic hypoglycemia of infancy. *Pediatric Oncall* 2013; 50:759–763.
- Jahnavi S, Poovazhagi V, Kanthimathi S, Balamurugan K, Bodhini D, Jaivinder Y, et al. Novel ABCC8 (SUR1) gene mutations in Asian Indian children with Congenital hyperinsulinemic hypoglycemia. *Ann Hum Genet* 2014; 78:311–319.
- Heo CU, Choi CI. Current progress in pharmacogenetics of second-line antidiabetic medications: Towards precision medicine for type 2 diabetes. *J Clin Med* 2019; 8:pii: E393.
- Srinivasan S, Kaur V, Chamathi B et al. TCF7L2 Genetic Variation Augments Incretin Resistance and Influences Response to a Sulfonylurea and Metformin: The Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH). *Diabetes Care* 2018; 41:554–561.
- Emdin CA, Klarin D, Natarajan P, et al. Genetic variation at the sulfonylurea receptor, type 2 diabetes, and coronary heart disease. *Diabetes* 2017; 66:2310–2315.
- Lemelman MB, Letourneau L, Greeley SAW. Neonatal Diabetes Mellitus: An Update on Diagnosis and Management. *Clin Perinatol* 2018; 45:41–59.
- Pearson ER, Flechtner I, Njolstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; 355:467–477.
- Li X, Xu A, Sheng H, et al. Early transition from insulin to sulfonylureas in neonatal diabetes and follow-up: Experience from China. *Pediatr Diabetes* 2018; 19:251–258.
- Estampador AC, Franks PW. Precision medicine in obesity and type 2 diabetes: The relevance of early-life exposures. *Clin Chem* 2018; 64:130–141.
- Kanthimathi S, Jahnavi S, Balamurugan K, Ranjani H, Sonya J, Goswami S, et al. Glucokinase gene mutations (MODY2) in Asian Indians. *Diabetes Technol Ther* 2014; 16:180–185.
- Radha V, Ek J, Anuradha S, Hansen T, Pedersen O, Mohan V. Identification of novel variants in the hepatocyte nuclear factor 1 alpha gene in South Indian patients with maturity onset diabetes of young. *J Clin Endocrinol Metab* 2009; 94:1959–1965.
- Sola D, Rossi L, Schianca GPC, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci* 2015; 11:840–848.
- Kim SH. Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know? *Diabetes Metab J* 2015; 39:468–477.
- Pearson ER. Personalized medicine in diabetes: The role of 'omics' and biomarkers. *Diabet Med* 2016; 33:712–717.
- Semiz S, Dujic T, Causevic A. Pharmacogenetics and personalized treatment of type 2 diabetes. *Biochem Med (Zagreb)* 2013; 23:154–171.
- Mohan V, Unnikrishnan R. Precision diabetes: Where do we stand today? *Indian Journal of Medical Research* 2018; 148:472–475.
- Mohan V, Radha V. Precision Diabetes is Slowly Becoming a Reality. *Medical Principles and Practice* 2019; 28:1–9.
- Mohan V, Das AK, Mukherjee JJ, Seshadri K, Jha S, Kalra S. From Individualized to Personalized Medicine in Diabetes: An Expert Overview. *Journal of The Association of Physicians of India* 2019; 67:78–82.