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Understanding Metformin Response Variability: Genetic Variations Influencing Metformin Response in Middle Eastern Populations with Type 2 *Diabetes mellitus*

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Abstract: The efficacy of Metformin in managing type 2 diabetes varies widely due to genetic diversity, influencing pharmacogenomic responses. Recent studies, employing Genome-wide association research (GWAS), have identified genetic variants associated with Metformin response, revealing pathways like AMP-activated protein kinase (AMPK) and Ataxia Telangiectasia Mutated (ATM) involved in its mechanisms of action. Genetic variations in transporter genes like OCT1 and MATE2 affect Metformin absorption and glucose regulation. Collaboration through multicohort meta-analyses validates these findings, considering ethnicity and environmental influences. Despite these advancements, research on genetic determinants of Metformin response in Middle Eastern populations is limited. Studies from Lebanon, Egypt, Jordan, and Saudi Arabia highlight associations between genetic variations and Metformin response in type 2 diabetes. The Inclusion of diverse populations in genomic databases like the Genome Aggregation Database (gnomAD) and tools like the Ensembl genome browser enhances understanding of genetic diversity for personalized medicine. Greater inclusivity in genetic studies is crucial to improve research generalizability and advance personalized medicine in diverse populations, addressing disparities in genomic research representation. This underscores the need for a multifaceted approach to personalized diabetes management, integrating pharmacogenomic insights from diverse populations.

Key words: Metformin · Pharmacogenomics · Genome-Wide Association Research · Genetic Variation

INTRODUCTION

For the management of diabetes type 2, Metformin is advised as the first-line medication [1]. The response to Metformin varies widely, despite its widespread usage roughly a third of individuals on Metformin monotherapy do not achieve preliminary glycemic management [2, 3]. Many people lose their ability to respond to Metformin over time, which can occur for many reasons. Even while Metformin is largely considered effective and with a good safety profile, the exact processes through which it improves insulin sensitivity remain a mystery. A patient's responses to the antihyperglycemic agent Metformin, may be significantly influenced by genetic diversity, according to emerging research. The pharmacologic effect of Metformin and interindividual variations in response can be understood using a variety of methods, with pharmacogenomics providing a unique and powerful medically beneficial instrument. Identifying new therapeutic targets for the management of diabetes may potentially be feasible with an improved comprehension of the genes and mechanisms influencing Metformin response [4, 5].

To comprehensively investigate the genetic predisposition of diabetic patients, it became imperative to establish comprehensive databases encompassing all existing single-nucleotide polymorphisms (SNPs). This extensive repository of genetic variations serves as a critical resource for researchers, allowing them to delve deep into the genetic underpinnings of diabetes.

Advancements in Genomic Research Techniques: Simultaneously, there was an indispensable need to pioneer innovative genotyping techniques that yielded

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high efficiency but were also budget-friendly. This call for methodological innovation stems from the intricate and diverse genetic landscape associated with diabetes, necessitating the capacity to analyze a vast array of genetic markers in an affordable and expedited manner.

One noteworthy advancement in this realm is the emergence of the collaborative consortium's large-scale genome-wide association research (GWAS). This groundbreaking technique exemplifies collaboration across research institutions and leverages the collective expertise and resources of multiple centres to conduct extensive and in-depth genetic association studies on a genome-wide scale. It is an exemplar of scientific synergy and technological progress, revolutionizing the way we unravel the genetic underpinnings of complex diseases like diabetes [6]. Genome-wide association research (GWAS) represents a significant stride in the field of genetics, particularly with the establishment of large-scale collaborative efforts by multicenter consortia. This approach involves examining the entire genome to identify genetic variations associated with specific traits, diseases, or drug responses. Unlike candidate gene studies that focus on a specific genes, GWAS scans the entire genome for variations, providing a more comprehensive and unbiased view of the genetic landscape [7].

Multicenter consortia have played a crucial role in advancing GWAS, pooling resources and data from diverse populations to enhance statistical power and increase the likelihood of identifying relevant genetic markers. These collaborative efforts often involve researchers from different institutions, fostering a collective approach to understanding the underlying genetics of various conditions. Within the framework of drug response, including studies related to Metformin or cisplatin, GWAS has the potential to uncover genetic factors influencing individuals' variations in toxicity and effectiveness of drugs [8]. By analyzing large cohorts of patients, researchers can identify common genetic variants associated with drug response patterns. This information not only contributes to our understanding of the underlying biology but also holds promise in efforts to progress customized medicine, where treatment strategies could be customized according to a person's genetic composition. The success of GWAS relies on variables including the size and makeup of the population under examination, as well as the availability of high-quality genomic data. Ongoing advancements in technology and collaborative efforts within the scientific community continue to drive the success of GWAS, offering valuable insights into the complex interplay between genetics and drug response. As researchers investigate further into the genomic intricacies, GWAS remains a powerful tool in unraveling the mysteries of genetic influence on health, disease, and pharmacological outcomes [9].

In diabetic individuals taking Metformin, the DARTS (Diabetes Audit and Research in Tayside Scotland) study conducted the initial and exclusive research of genome-wide associations (GWAS) [10]. In a robust clinical trial, a cohort of 10,000 individuals diagnosed with diabetes actively participated, their medical profiles closely scrutinized alongside another group of 8,000 control participants who had their electronic health records readily available for analysis. This comprehensive study sought to unravel the intricate nuances of Metformin response, a commonly prescribed medication for managing diabetes. What emerged from this research was a profound revelation of substantial interindividual variability in how different patients responded to Metformin.

Within this diverse pool of individuals, there were stark disparities in terms of how their HbA1C levels, a crucial indicator of long-term blood sugar control, were affected by Metformin treatment. While some patients experienced a remarkable drop of nearly 4% in their per cent HbA1C levels, signifying an excellent response to the medication, others exhibited no change or even experienced significant increases in their HbA1C levels post-medication. This wide spectrum of responses underscores the complexity of diabetes management and the need for personalized treatment strategies tailored to individual patient profiles.

Furthermore, the study identified a specific genetic variation located on chromosome 11 and demonstrated a strong and statistically significant correlation with the ability to respond to Metformin. This finding opens a new avenue of exploration in the field of personalized medicine for diabetes. Specifically, the ataxia telangiectasia mutated gene (ATM) located in this genetic region emerged as a strong candidate gene of interest. Understanding how genetic variations within the ATM gene may influence Metformin response can potentially pave the way for more precise and tailored treatment approaches for diabetic patients. This breakthrough has the potential to revolutionize diabetes management, ushering in an era of customized medicine, which considers a person's genetic composition to provide more effective and efficient therapeutic procedures [11, 12].

Insights into Metformin's Pharmacogenomics:

Unraveling Complex Mechanisms: The mutation in chromosome 11 has been reproduced in subsequent meta-analyses and it is known now that it contains seven

genes [13, 14]. The ATM gene, which is accountable for coding the serine/threonine kinase, might control the activity of enzymes that are implicated in the body's reaction to Metformin. Even though the researchers' in vitro research demonstrated that ATM was essential for AMPK activation by Metformin [12]. Subsequently, it has been firmly established that the small chemical compound employed in vitro cellular tests to inhibit ATM is also an inhibitor of OCT1, as documented in 2012. This revelation is of particular significance because OCT1 serves as the primary transporter responsible for facilitating the entry of Metformin, a commonly prescribed medication for diabetes, into hepatic cells and the liver.

The intersection between ATM and OCT1 in this context leads to a crucial implication: when the ATM inhibitor is applied, it inadvertently interferes with the function of OCT1. As a result, Metformin's ability to enter the cells is hindered. This interference significantly complicates the interpretation of the results obtained from the tests conducted. In essence, the dual role of the chemical inhibitor, affecting both ATM and OCT1, creates a confounding factor in the experiments, making it challenging to discern the specific effects of Metformin on ATM activation. The interference of the ATM inhibitor with the primary Metformin transporter in hepatic cells underscores the importance of meticulous experimental design and the need to account for potential off-target effects when conducting studies in the field of pharmacology and molecular biology [15].

The Diabetes Prevention Program DPP and its following longitudinal DPP Outcomes Study (DPPOS) is another experiment [16]. The effectiveness of Metformin in diabetes prevention has yielded intriguing findings from the Diabetes Prevention Program research group. Their research unveiled variations in Metformin's impact on different subgroups of participants. Metformin was found to be less successful in elderly individuals but more so in Individuals suffering from obesity, suggesting that age and body weight influence its preventive effects. Furthermore, the study revealed an intriguing connection between Metformin-induced weight loss and its benefits, particularly in obese participants, indicating that weight loss contributes significantly to the medication's efficacy [17]. Notably, even after discontinuation of Metformin, the decline in the prevalence of diabetes continued for at least a decade, suggesting enduring metabolic changes or lifestyle improvements. Additionally, Metformin proved its effectiveness in lowering the prevalence of diabetes in women who had previously experienced gestational *Diabetes mellitus*, demonstrating its potential in high-risk groups. While Metformin had limited effects on blood pressure and lipid levels, it did significantly raise high-density lipoprotein (HDL) levels and enhance low-density lipoprotein (LDL) particle size, potentially benefiting cardiovascular health. These findings underscore the multifaceted role of Metformin in diabetes prevention and suggest exciting avenues for further research in the field [15].

The UK Prospective Diabetes Study (UKPDS) stands as among the first and most renowned trials that played a pivotal role in establishing the effectiveness of Metformin, as elucidated in 1998. This landmark study provided compelling evidence regarding Metformin's impact on diabetes management. It was revealed that Metformin led to a noteworthy reduction in the average percentage of glycated haemoglobin (HbA1C) by 1%. This effect was particularly pronounced in obese participants, shedding light on the medication's potential advantages in this subgroup.

One of the striking features of Metformin, as observed in the UKPDS, was its ability to regulate blood glucose levels without gaining weight. A substantial number of individuals experienced modest weight loss while on the medication. This unique attribute sets Metformin apart from some other diabetes treatments and is especially beneficial for those who are overweight. Moreover, the UKPDS findings had significant implications for overall health outcomes. The study revealed a reduction in the risk of mortality attributed to diabetes and other adverse outcomes. This suggests that Metformin not only helps manage blood sugar levels but also contributes to a decrease in diabetes-related complications and associated mortality. Importantly, meta-analyses have corroborated these findings, indicating that individuals using Metformin exhibit lower rates of cardiovascular-related mortality compared to those using alternative diabetic medications, even when achieving similar levels of glycemic control. This underscores the potential cardiovascular benefits associated with Metformin use. However, it's worth noting that the positive effects of Metformin on HbA1C were observed to diminish over time, highlighting the need for ongoing monitoring and potential adjustments in diabetes management strategies. The UKPDS study, with its enduring influence, not only confirmed Metformin's role in diabetes treatment but also paved the way for further research into its multifaceted effects and long-term implications for individuals living with diabetes [4].

The Global A Diabetes Outcome Progression Trial (ADOPT) further reinforced The effectiveness of

Metformin as a treatment for diabetes, but it also unveiled a noteworthy trend of declining effectiveness over time [15]. These findings indicate that early and late instances of Metformin effectiveness waning may be attributed to distinct mechanisms, both of which are likely influenced by multiple factors. This suggests that understanding the dynamics of Metformin response is a complex puzzle, with different variables at play in different stages of treatment.

To comprehend more deeply in the pharmacogenomics of Metformin, researchers have undertaken investigations focused on the interplay between its pharmacokinetics (how the drug moves in the body) and pharmacodynamics (how it exerts its effects) in individuals from diverse ethnic backgrounds who exhibit known differences in variations in transporter genes. Significant contributions to this area of research by demonstrating decreased cellular absorption of Metformin engineered to express naturally occurring variations that change amino acids of the OCT1 transporter, a key player in Metformin transport. They also translated these in vitro findings into clinical insights by showing that healthy individuals carrying heterozygous OCT1 variants experienced a decreased response to Metformin and exhibited altered pharmacokinetics. This highlights the consequences of genetic differences in transporters on how individuals respond to the drug.

Additionally, an intriguing discovery has been made in the form of a promoter region mutation in the *SLC47A2* gene, specifically the rs12943590 variant, known as MATE2. This genetic alteration has been linked to a modified response to Metformin concerning its influence on human glucose levels. It further underscores the intricate interplay between genetic variations and Metformin's pharmacological actions, offering insights into personalized medicine and tailoring therapeutic approaches determined by a person's genetic structure [18, 19].

The mentioned research underscores the significance of human pharmacogenomics methods, which involve integrating data from long-term Metformin clinical trials with shorter-term studies that focus on understanding the drug's pharmacokinetics and acute reactions in the body. This comprehensive approach aims to provide a deeper insight into the genetic factors influencing Metformin's effects.

Preliminary findings from these studies have indicated that genes responding to Metformin's actions are associated with well-established pathways such as AMP-activated protein kinase (AMPK), a crucial regulator of the homeostasis of cellular energy, as well as newer pathways like the Ataxia Telangiectasia Mutated (ATM) pathway. These findings suggest that Metformin's mechanisms of action involve a complex interplay with various genetic pathways, shedding light on its multifaceted effects. To solidify these findings and gain a more comprehensive understanding, a high-powered multicohort meta-analysis is needed. Such an analysis would not only confirm the observed genetic variants and pathways but could also potentially uncover novel genetic factors and pathways with clinical relevance. This collaborative approach, pooling data from multiple sources, enhances the statistical power and generalizability of the findings. However, it's crucial to consider and control for confounding variables that can influence the outcomes of these studies. Variables such as ethnicity, differences in research design, patient age, environmental factors, and clinical endpoints need to be carefully addressed. These factors introduce variations that can significantly impact the observed genetic associations and clinical responses. Acknowledging and accounting for these confounding factors is essential to ensure the accuracy and reliability of the research outcomes. The research highlights the need for a multifaceted approach to studying Metformin's pharmacogenomics, combining long-term clinical trials with shorter-term pharmacokinetic and acute reaction studies. It also emphasizes the importance of conducting high-powered multicohort meta-analyses to validate and extend these findings. Ultimately, the intricate interaction between environmental and genetic variables underscores the importance of adopting different research strategies and accounting for the influence of confounding variables in advancing our understanding of Metformin's actions in the human body [15].

Genes connected to Metformin's glycemic management with the strongest correlations exist in recognized transporter genes (Table 1).

Examination of Genetic Variations Impacting Metformin Response: Numerous previous studies have concentrated on elucidating the connections between various genetic factors and their impact on pharmacological responses. In the context of Metformin, one of the pivotal genes involved is *SLC22A1*, which primarily encodes the organic cation transporter 1 (OCT1). Notably, OCT1 exhibits a high degree of polymorphism, particularly concerning its involvement with Metformin. This extensive genetic polymorphism of OCT1 plays a central role in the observed interindividual variability in Metformin responses among patients with Type 2

Table 1: A List of Known Genes affecting the Pharmacokinetics of Metformin and the Identification of Certain Pharmacodynamic Genes Connected to the Therapeutic Response to the Drug.

Gene	Transporter Protein	An overview of the impacts	References
SLC22A1	OCT1	Decreased function alleles associated with decreased Metformin efficacy on early lipid and A1C responses; diabetes incidence	[20-22]
SLC22A2	OCT2	There were no correlations with clinical results; only modifications to Metformin PK were noted.	
SLC22A3	OCT3	There were no correlations with clinical results; only modifications in Metformin PK were noted.	
SLC47A1	MATE1	Elevated A1C response to Metformin; elevated diabetes incidence	[18,20]
SLC47A2	MATE2	Reduced efficacy with Metformin; variations in A1C	[18,23]
SRR	Serine racemase	Connected to alterations in FPG, PPG, and CHO	[24]
ATM	Serine/threonine kinase; SNP in large LD block with 6 other genes	Metformin therapy efficacy measured by A1C	[14,25]
LKB/STK11	AMPK upstream kinase	Ovulation reduction in women taking metformin for polycystic ovarian syndromes; diabetes incidence.	[20]
PRKAA1, PRKAA2, PRKAB2	AMPK subunits	Incidence of diabetes	
ABCC8-KCNJ11	Subunit of b-cell potassium channel	Incidence of diabetes	

CHO, cholesterol; FPG, fasting plasma glucose; LD, linkage disequilibrium; PK, pharmacokinetics; PPG, postprandial plasma glucose. [15]

Diabetes (T2DM). The genetic variations within OCT1 have been closely associated with the diverse responses to Metformin treatment. Specifically, certain individuals with a loss-of-function variant in the OCT1 gene exhibit lower Metformin responses. This genetic aspect contributes to the complexity of pharmacological reactions to Metformin, underlining the importance of understanding genetic factors in tailoring treatment strategies for individuals with T2DM [26,27].

Research conducted in 2007 revealed that four functional variants, specifically rs12208357, rs72552763, rs34059508, and rs34130495, were associated with a diminished ability of Metformin to reduce blood sugar levels in healthy human volunteers undergoing an oral glucose tolerance test (OGTT). This suggests that these genetic variations may impact the efficacy of Metformin in regulating blood glucose [21].

In a separate study in 2011, reduced functional variants of (OCT1), which includes rs72552763, rs12208357, rs34059508, and rs34130495, were linked to trough Metformin concentrations and improvements in glycated haemoglobin (HbA1C) levels following six months of Metformin treatment. This study involved 151 individuals with Type 2 Diabetes (T2DM) participating in the prospective multicenter South Danish Diabetes Study.

Furthermore, in a study involving 1,915 Metformin-tolerant and 251 Metformin-intolerant T2DM patients, it was discovered that allelic variants of OCT1, including rs12208357, rs72552763, rs34130495, rs55918055, and rs34059508, were associated with Metformin intolerance, likely due to higher Metformin accumulation in enterocytes. Additionally, three other OCT1 variants, namely rs622342, rs628031, and rs594709, which were identified in subsequent studies, were found to generally decrease the efficiency of Metformin.

These findings highlight the crucial role of genetic variations in OCT1 in influencing Metformin responses, efficacy, and tolerance, underscoring the need for personalized approaches to Metformin treatment in individuals with T2DM based on their genetic profiles. The influence of genetic factors on Metformin response has been explored across various groups in different studies. There was research conducted in this regard. Notably, it was observed that while Metformin blood levels remained unchanged, individuals carrying the *SLC22A1* alleles rs12208357 and rs72552763 had a lower accumulation of the medication in their livers, as demonstrated in a study in 2007. Interestingly, a previous study suggested that OCT1 gene polymorphisms might not significantly alter the therapeutic efficacy of Metformin. Similarly, the GoDARTS study, encompassing 1,531 individuals with Type 2 Diabetes (T2DM), found no association between the two OCT1 polymorphisms rs12208357 and rs72552763, which are most prevalent in people of European descent and glycemic response to Metformin. It's worth noting that the lack of a significant relationship between these polymorphisms and Metformin response was found in this study. However, it is important to recognize that certain OCT1 polymorphisms do indeed influence Metformin response. Nevertheless, limitations such as small sample sizes and the co-administration of other anti-hyperglycemic drugs within

some study groups have contributed to discrepancies across various studies.

The transcription factor 7-like 2 (TCF7L2) gene, in conjunction with genes responsible for encoding transporter proteins that affect responses in individuals with Type 2 Diabetes (T2DM), is intricately linked to T2DM by impacting glucose regulation and insulin production. Another study reported that TCF7L2 variants are linked to a more rapid decline in pancreatic β-cell function, higher glycemic levels, and reduced insulin production [28]. This underlines the complexity of genetic factors and their role in T2DM and the response to Metformin therapy [29-31].

In addition to the effects on insulin and glycemic control, other studies have suggested that carriers of TCF7L2 variants may experience alterations in their plasma metabolic profiles, particularly in phospholipids. This observation raises the intriguing possibility that changes in phospholipid metabolism may contribute to metabolic abnormalities even before the onset of glucose intolerance, further emphasizing the multifaceted nature of T2DM development. The TCF7L2 gene, particularly the rs7903146T genotype, has emerged as a significant genetic factor associated not only with Type 2 Diabetes but also with obesity, as indicated by studies conducted supported these findings underscore the pivotal role of TCF7L2 in the pathogenesis of T2DM and its relationship to metabolic disorders like obesity [32, 33]. Recent research has shed light on the multifunctional role of the TCF7L2 gene as a downstream effector of the Wnt/β-catenin signalling pathway. This gene regulates various activities, including adipogenesis and its involvement in diseases like Type 2 Diabetes. This deeper understanding of TCF7L2's role in these biological processes contributes to our knowledge of the intricate genetic and molecular mechanisms underpinning T2DM and related metabolic conditions [29-34].

Physiological investigations have provided valuable insights into the role of genetic variants, such as the rs290487 variant, in insulin resistance. It has been found that the rs290487 variant is associated with insulin resistance, suggesting that Wnt signalling pathways are involved in the development of insulin resistance. This connection underscores the relationship between genetic factors and the physiological mechanisms that underlie insulin regulation.

From this research, it appears that there is a lack of information about the molecular pathways, and further functional investigations on the pharmacodynamics of Metformin are required (Table 2).

As was already indicated, OCT2 is solely responsible for the tubular secretion of Metformin, which is predominantly removed by the kidneys. Numerous academic studies have established that people have OCT2 genetic polymorphism. OCT2 genetic variation has been discovered to modify Metformin action, firmly supporting the role of these genes in regulating Metformin responsiveness. Only a few research have found a connection between OCT2 genetic polymorphism and Metformin efficacy and clearance; other studies have not. In a narrative review 13 genetic polymorphisms (SNPs) of OCT2 from different ethnic groups were reported, and

Table 2: List of Known Gene Variations for Metformin that are Highly Associated with the Clinical Response to the Drug [35].

Gene	Db SNP ID	Cohort	Reference
SLC22A1 (OCT1)	rs1867351	Han Chinese	[30]
	rs4709400	153 T2D	
	rs628031	124 Control	
	rs2297374	256 healthy Brazilian	[36]
	rs622342	125 Chinese	[36-38]
		63 Lebanese patients	
		256 Brazilian health	[36]
	rs12208357	256 healthy Brazilian	[36]
	rs72552763		
	rs34059508		
	rs34130495	371 Danish T2D patients	[39]
	rs461473		
	rs34104736		
	rs594709	267 T2D Chinese patients and182 healthy subjects	[40]
SLC22A2(OCT2)	rs315978	2,994 Participants in Diabetes Prevention Program	[20]
	rs662301		
	rs316019	125 Chinese participants	[36, 37, 41]
		256 Brazilian adults	
		91 Korean subjects	
	rs201919874	400 Pakistani patients	[42]

Table 2: Continue

Gene	Db SNP ID	Cohort	Reference
SLC22A3 (OCT3)	rs3127602	258 White Europeans	[43]
	rs520685	25 Korean subjects	[44]
SLC29A4 (PMAT)	rs10234709	258 White Europeans	[43]
	rs2685753	91 Korean subjects	[45]
	rs3889348		
	rs4720572		
	rs4299914		
	rs6971788		
SLC47A1(MATE1)	rs2289669	267 T2D Chinese patients and 182 healthy subjects	[37-41]
		125 Chinese subjects	
		256 Brazilian subjects	
		91 Korean subjects	
	rs8065082	2,994 DPP	[20]
	rs2453583		
	rs2120274	258 White Europeans	[43]
	rs2252281	125 Chinese subjects	
		256 Brazilian subjects	[36, 37]
SLC47A2(MATE2)	rs4621031	258 White Europeans	[43]
	rs34399035	371 Danish T2D Patients	[39]
	rs12943590	256 Brazilian subjects	[36]
		91 Korean subjects	[41]
	rs34834489	91 Korean subjects	[45]
	rs138244461	400 Pakistani patients	[42]

they have been linked to Metformin pharmacokinetics and pharmacodynamics. The SNPs were rs7757336, rs316019, rs201919876, rs17588242, rs10755577, rs17589858, rs3127573, rs2928035, rs316024, rs316026, rs316025, rs662301, rs533452 [46].

The most extensively researched genetic variant was discovered to be rs316019. It displayed a range of impacts in various populations, either good, negative or no effect. In the conducted investigations involving Chinese, European Americans, and African Americans, the effects of rs316019 on the action of Metformin were statistically significant. The Metformin clearance, AUC, and $t_{1/2}$ varied between genotype groups. A significant contributor was decreased renal and tubular Metformin clearance. The genetic variant rs316019 showed that Metformin had a positive therapeutic impact (pharmacodynamic) in the Jordanian group. In the Danish and Caucasian populations, the OCT2 genotypes had no impact on Metformin clearance [45].

The rs10755577, rs17588242, rs17589858, rs2928035, rs3127573, rs316024, rs316025, rs316026, rs533452, rs662301 show no significant link with renal Metformin clearance yet there was no statistically significant evidence discovered to support *SLC22A2* genetic variants' effect on glycemic control [46].

Several investigations have failed to find any evidence connecting OCT2 mutations and Metformin response [25,26]. Furthermore, investigations have shown that the polymorphism rs8192675 in the *SLC22A2* gene, which codes for the glucose transporter (GLUT2), particularly the C allele, is required for limiting Metformin activity [29].

Similarly, there is a minimal association between Metformin responsiveness and variations in the gene encoding the transporter MATE1. A frequent variant (266T.C; rs2252281) in the promoter region of *SLC47A1* (MATE1) was found to have a minor allele frequency (MAF) of 25%. As a result of the 266C allele's disruption of an enhancer element and creation of a repressor binding site, MATE1 expression is likely to be downregulated and Metformin levels are likely to increase in hepatocytes. During an oral glucose tolerance test, the C allele of rs2252281 was linked to a considerably stronger response to Metformin's ability to reduce blood glucose levels [18].

There are inconsistent reports regarding how Metformin reacts to other variations of the *SLC47A1* gene, which produces MATE1 [25, 39]. Following a six-month Metformin regimen, studies have revealed that homozygous carriers of the *SLC47A1* rs2289669 A-allele exhibit a greater decrease in HbA1C than carriers of the more prevalent G-allele. About 20% of T2DM patients experienced a bigger two-fold (0.55 percent) decline in HbA1C levels than the other individuals [48]. Nevertheless, the Metformin Genetics Consortium's meta-analysis of trials involving over 8,000 T2DM patients

revealed no proof of a connection between the MATE1 transporter gene and glycemic response to Metformin [25, 48].

Genetic Variations Influencing Metformin Response in Middle Eastern Populations with Type 2 *Diabetes mellitus*: In the Middle East, genomic investigations are scarce concerning Metformin response in individuals with Type 2 *Diabetes mellitus* (T2DM).

A Lebanese study conducted in 2020 focused on sixty-three T2DM patients taking Metformin, who underwent genetic testing for the rs622342A>C mutation in the *SLC22A1* gene and were closely monitored over six months. The study aimed to assess how this genetic variant influences the response to Metformin treatment. Results revealed distinctive pharmacokinetic profiles in patients with the CC genotype of the rs622342A>C mutation in *SLC22A1*. Specifically, individuals with the CC genotype exhibited higher maximum concentrations of Metformin in the bloodstream and a greater area under the plasma concentration-time curve, indicating potential variations in Metformin absorption and distribution associated with this genetic variant. The study also examined clinical outcomes, focusing on reductions in fasting blood sugar (FBS) and glycated haemoglobin (HbA1C) percentages. Significant differences in Metformin response were observed among patients with different rs622342A>C genotypes, suggesting an influence of this genetic variation on the medication's therapeutic efficacy. Despite variations in Metformin pharmacokinetics and clinical outcomes, the study did not find substantial effects of the rs622342A>C mutation on serum levels of lactate or creatinine. This suggests that while the genetic variant may impact how the body processes and responds to Metformin, it may not significantly affect specific biomarkers related to lactate metabolism or kidney function. The Lebanese study underscores the diversity in how patients with Type 2 Diabetes respond to Metformin treatment and indicates a possible association between the rs622342A>C mutation in the *SLC22A1* gene and variations in Metformin pharmacokinetics and clinical results. This emphasizes the significance of taking individual genetic factors into account when tailoring diabetes treatment approaches for enhanced and personalized care [38].

In another study conducted in Egypt, researchers investigated the impact of genetic variants in MATE1, MATE2, and OCT1 on the action of Metformin in the context of T2DM. The study included 100 patients diagnosed with T2DM and 40 healthy individuals who served as controls. Notably, the diabetic patients in the study had recently received their diagnosis and were not undergoing any treatment at the time of the investigation. The researchers employed advanced molecular techniques, such as real-time PCR and a Sequence Detection System, to genotype three specific single nucleotide polymorphisms in the participants' genes: MATE1 (rs2252281), OCT1 coding variants (rs12208357) (related to the *SLC22A1* gene), and MATE2 (rs12943590). These genetic variations were examined to understand how they might influence Metformin's effectiveness and the clinical outcomes in individuals with type-2 diabetes.

The study revealed several key findings, first there were significant differences observed in the distribution of genetic variants, particularly in MATE2 ($p<0.05$) and OCT1 ($p<0.005$), between the control group and the patients with type-2 diabetes. The most prevalent genotypes among the patients were GG (54%) for MATE2 and CC (62%) for OCT1. Second, patients with specific genetic alleles exhibited variations in their glycemic control. Those with CC alleles and TT alleles tended to have better glycated haemoglobin levels compared to patients with CT alleles, indicating that specific genetic profiles may be associated with improved blood sugar management in response to Metformin.

The study also identified differences in random blood glucose levels based on the presence of specific genetic variants. Patients carrying the CG allele of the OCT1 SNP had higher random blood glucose levels compared to those with the CC allele, highlighting the potential impact of genetic variations on glucose regulation, these findings emphasize the influence of genetic factors, particularly MATE2 and OCT1 variants, on the effectiveness of Metformin and its impact on glycemic control in patients with type-2 diabetes [49].

In a study conducted within the Jordanian population, researchers delved into the interplay between specific genetic variations within the *SLC22A1*, *SLC22A2*, and *SLC22A3* genes and their influence on the pharmacogenetics of Metformin in Jordanian individuals diagnosed with type 2 diabetes. The study enrolled 212 eligible Jordanian diabetes patients who provided blood samples for SNP genotyping and HbA1C level assessment.

Noteworthy discoveries from this investigation encompassed several key aspects. First, the analysis of 21 different single nucleotide polymorphisms in the *SLC22A1*, *SLC22A2*, and *SLC22A3* genes unveiled associations between these genetic variants and the

responses of individuals to Metformin treatment. Secondly, a significant link ($p<0.05$) emerged between lower mean HbA1C levels, a crucial marker of long-term glycemic control, and a specific variant, rs12194182, situated within the *SLC22A3* gene. This correlation was particularly pronounced in patients harbouring the CC genotype for this variant, suggesting a genetic predisposition for improved diabetes management with Metformin.

Furthermore, through the application of multinomial logistic regression analysis, the researchers uncovered substantial associations ($p<0.05$) between diverse factors, encompassing body mass index (BMI), age at diagnosis, and SNP genotypes within the *SLC22A1*, *SLC22A2*, and *SLC22A3* genes, with glycemic control. These findings collectively imply that not only genetic variations, but also clinical and demographic variables play pivotal roles in shaping individual responses to Metformin therapy. This comprehensive understanding paves the way for more personalized and tailored approaches to diabetes management, holding the potential to enhance clinical outcomes significantly [50].

Except for a 2019 publication, there exists a dearth of information in Saudi Arabia concerning genetic variations that influence the response to Metformin in individuals with Type 2 Diabetes (T2DM). The primary objective of this study was to investigate how *SLC22A1* rs628031 and rs461473, as well as ATM rs11212617 polymorphisms, impact the susceptibility to T2DM within the Saudi Arabian population. This inquiry considered a range of factors about the glycemic control of T2DM, including body mass index (BMI), fasting blood glucose levels, glycated haemoglobin (HbA1C) concentrations, and triglyceride levels.

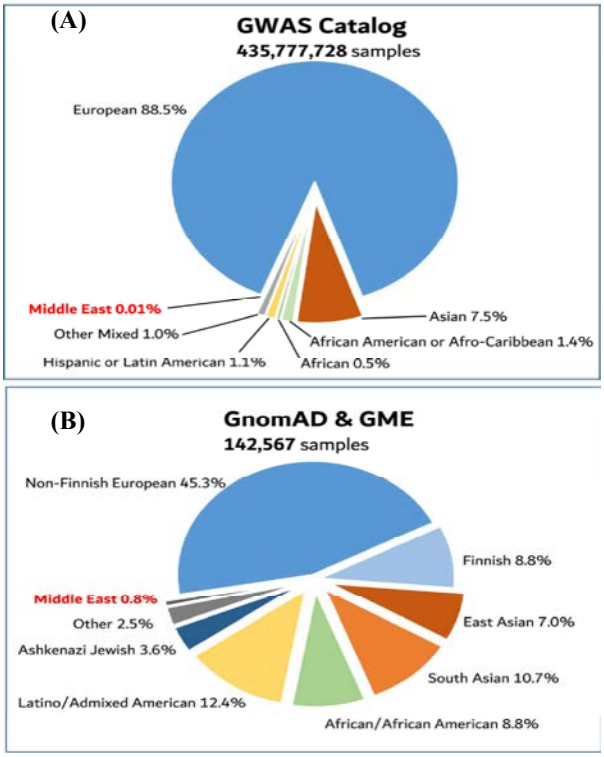
The study yielded noteworthy findings. It identified significant associations between T2DM and BMI, as well as HbA1c levels. Specifically, high HbA1C levels and the G/G and A/G genotypes of the *SLC22A1* rs628031 and rs461473 variants were found to be significantly correlated with the presence of T2DM. This indicated that, among the evaluated *SLC22A1* variations, the G allele was associated with an increased risk of developing T2DM.

Additionally, elevated HbA1C levels and the A/A and A/C genotypes of the ATM rs11212617 variant were also significantly correlated with the presence of T2DM. The relative risk analysis identified the A allele as the risk allele within the T2DM cohort [51].

Genom AD and Ensembl Genome Browser and Their Role in Enhancing Genetic Research Diversity: The Genome Aggregation Database (gnomAD) is a comprehensive resource that compiles and uniformly processes a vast amount of genetic data from both whole genome sequencing (15,708 individuals) and exome sequencing (125,748 individuals). This data repository is designed to systematically catalog genetic variations present in both coding and noncoding regions of the human genome. Notably, it plays a crucial role in capturing and documenting genetic diversity and variation, offering insights into the genomic landscape. It's important to acknowledge that the genomic studies conducted in the Middle East differ notably from European genomic studies. This variation in study populations reflects the rich diversity of genetic backgrounds and ancestry across different regions of the world.

The Genome Aggregation Database (genomAD) is a large and publicly accessible database that aggregates and provides genomic and genetic variation data from a wide range of populations. GenomAD is a valuable resource for researchers, clinicians, and geneticists studying human genetics and genomics. The gnomAD collection has expanded to encompass an impressive 241 million minor variants and structural variants (SVs). This extensive dataset provides researchers with a unique and comprehensive resource to assess the tolerance of genes to various forms of genetic variation. It also serves as a valuable tool for the clinical interpretation of genetic variations, aiding in the understanding of their potential implications for health and disease [52]. Notably, gnomAD comprises data from populations beyond those of European ancestry, including non-European Asians (with significant representation from South Asians and East Asians), Latinos, Ashkenazi Jews, and Africans or African Americans. Collectively, these diverse groups make up approximately 43 percent of the individuals in the gnomAD database, emphasizing the importance of inclusivity and representation in genomics research. This diversity enhances the applicability and relevance of genetic research findings across various populations, furthering our understanding of human genetic variation and its impact on health and disease.

Regarding the Ensembl genome browser is a pivotal platform for genomic research, integrating data from landmark projects like the 1000 Genomes Project and gnomAD (Genome Aggregation Database). By incorporating data from the 1000 Genomes Project, Ensembl enables researchers to explore human genetic variation across diverse populations, accessing allele frequencies and linkage disequilibrium patterns within the context of the reference genome. Moreover, Ensembl



(A) - Distribution of sample ancestries in the GWAS Catalog as of June 14, 2020 [9].
(B) - Distribution of sample ancestries in the Genome Aggregation Database (gnomAD v2.1) and the Greater Middle East (GME) various

Fig. 1: Genomic data representation.

provides access to gnomAD data, facilitating the examination of allele frequencies and variant annotations across populations. With its extensive genomic annotations, comparative genomics resources, and user-friendly interface, Ensembl serves as a vital tool for genomic exploration and interpretation, supporting advancements in genetics and genomics research. This integration of large-scale sequencing data within Ensembl empowers researchers to uncover insights into the genetic basis of human health and disease.

The concern about the limitations of precision or genomic medicine is well-founded, given the historical bias in many large-scale genomic studies, which have predominantly included participants of European descent. This lack of diversity in genetic research can indeed impede the applicability and effectiveness of genomic medicine for a broader population [53].

As of June 14, 2020, the data from the GWAS Catalog and the GWAS Diversity Monitor highlight the substantial disparity in genomic research representation, with 88.5 percent of genome-wide association studies (GWAS) conducted on Europeans, while only 7.5 percent included Asians, and a mere 4 percent incorporated individuals of African, Latin American, and other ancestries. This lack of diversity is a significant limitation when attempting to generalize research findings to more diverse populations (Fig. 1).

Addressing this issue and making precision medicine beneficial for a wider range of individuals can be achieved by several means. First, expanding the size of research cohorts is crucial to ensure that findings are statistically robust and applicable to various genetic backgrounds. Second, a concerted effort should be made to diversify the genetic data by including individuals from underrepresented ancestries. This approach will enhance the relevance of genomic research and its clinical applications for a more inclusive and global population. In the Middle East, there is a rich tapestry of diverse populations with unique genetic backgrounds. The history of migration, hybridization, and the coexistence of different ethnic and cultural groups, including Arabs, Jews, Armenians, Kurds, and others, presents a valuable opportunity for genomic research to become more representative and inclusive. Embracing the genetic diversity of this region can contribute to a more comprehensive and equitable approach to precision medicine.

Efforts to address these disparities and promote diversity in genetic research are essential for ensuring that precision medicine benefits not just a "few" but a broader and more representative cross-section of the global population, ultimately improving healthcare outcomes for all [54].

CONCLUSION

Based on the multitude of research findings presented, it becomes evident that there is still a substantial gap in our understanding of the molecular pathways and the intricacies of Metformin's pharmacodynamics. While studies have made significant progress in identifying genetic factors that influence Metformin response and the physiological mechanisms involved, there is a need for further in-depth functional investigations.

The existing body of research has illuminated the genetic variations associated with Metformin response, the potential role of specific genes like OCT1 and TCF7L2, and their impact on insulin regulation, glycemic control, and metabolic profiles. However, the specific molecular pathways through which Metformin exerts its effects and

how these pathways interact with genetic factors remain areas of active exploration.

To gain a more comprehensive understanding of Metformin's pharmacodynamics, future research should delve into the intricate molecular mechanisms that underlie Metformin's actions in the body. This may involve exploring how Metformin interacts with various cellular pathways, signaling systems, and genetic factors. Moreover, investigations into the interplay between these elements will be vital to unravel the full picture of Metformin's mode of action.

While the existing research has shed light on certain aspects of Metformin's pharmacodynamics, there is a pressing need for further functional investigations to bridge the knowledge gap and provide a more holistic understanding of this widely used diabetes medication. This ongoing research is critical for enhancing the precision and effectiveness of Metformin treatment and for developing targeted therapies for individuals with Type 2 Diabetes [15].

It is critical to gather all the data into one review to analyze the effects of numerous SNPs in connection to Metformin clearance and response. For patients with T2DM, extensive research is required to understand the interindividual variation with different *SLC22A2*, and *SLC47A1* gene variations and to individually tailor the treatment regimen [46].

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