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Understanding the Genetic Basis of Type 2 Diabetes: Implications for Precision Medicine and Novel Therapeutic Approaches

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ABSTRACT

This research tries to quantify awareness, integration, and uptake of genetic ideas in Type 2 Diabetes (T2D) management by Punjab general practitioners (GPs). The research used a quantitative research design, whereby a self-report questionnaire was used to collect data from 110 GPs via snowball sampling. This research explores three main aims: (1) to measure the awareness of general practitioners with regard to the genetic cause of T2D, (2) to measure the extent to which genetic considerations are incorporated into T2D management, and (3) to determine predictors of the uptake of genetic information in T2D management. Descriptive statistics, Chi-square tests, and t-tests were employed for statistical analyses. Findings reveal a level of mixed awareness among GPs where 18.18% very familiar, 45.45% somewhat familiar, and 36.36% not familiar with genetic concepts of T2D. Significant gap was discovered in applying genetic factors in clinical practice where most GPs (54.55%) rarely apply genetics in managing T2D. Despite positive attitude scores for the uptake of genetic knowledge (54.55% agreeing or strongly agreeing), an extreme level of resistance to the incorporation of genetic knowledge into practice was observed. Chi-square analysis revealed that a significant association between knowledge of genetic terms and how often T2D management is thought about in relation to genetic factors existed. In addition, t-tests revealed that the difference between agreeing to use genetic knowledge and disagreeing was significant. The research emphasizes the importance of enhanced genetic education and support systems, such as genetic counselors, to assist GPs in applying genetic knowledge to practice. Future implications suggest that greater genetic literacy among health professionals and the availability of genetic testing can facilitate more personalized and effective management of T2D.

INTRODUCTION

Type 2 diabetes (T2D) is a multifactorial, complex disease that is marked by long-standing hyperglycemia caused by the inability of the body to properly use insulin. It is among the most prevalent metabolic disorders globally and is a significant cause of public health complications due to its association with multiple complications, including cardiovascular disease, kidney failure, and neuropathy. The pathogenesis of T2D is controlled by both environmental and genetic influences, and diet, lifestyle, and physical activity are of prime importance. Nonetheless, the genetic mechanisms of T2D remain inadequately comprehended, and a huge endeavor has been focused on characterizing these processes. In the past 20 years, advancements in genomic tools and genome-wide association studies of large scale (GWAS) have recognized numerous genetic loci that contribute to the susceptibility to T2D, thereby illuminating the disease's molecular mechanisms.

The identification of the specific genetic variations responsible for Type 2 Diabetes (T2D) can transform disease diagnosis, treatment, and prevention. The use of so-called precision medicine, in which therapy is designed in accordance with the patient's own individual genetic profile, is becoming increasingly a more targeted solution to the treatment of T2D. With the knowledge of genes that trigger and sustain the disease, doctors could predict individuals' susceptibility to develop T2D at a decisive formative period in life, prescribe enhanced optimal drug regimens to the patient, and even avert the occurrence of the disease among those destined by genes. Besides, greater understanding of the genetic

etiology of T2D paves the way for novel therapies. Targeted therapy based on identified genes and related biochemical pathways can induce more efficient and less virulent protocols for treatment than the usual method of treatment.

While significant progress has been achieved in genetic research, there is still much to be learned about the intricate processes involved in the relationship between genetics and T2D. Different genes and regulatory pathways have been found, but what they contribute specifically to insulin resistance, beta-cell dysfunction, and the overall pathogenesis of T2D remains to be learned. Additionally, gene-environment interactions complicate the interpretation of genetic information since environmental elements such as diet and physical exercise may affect the expression of genetic variants. Hence, future research will need to bridge the challenge of integrating genetic information with environmental and lifestyle factors to clarify the multifactorial pathogenesis of T2D.

This review will review current knowledge about the genetic underpinnings of T2D, focusing on the key genetic variants and their potential functions in disease pathology. It will also address implications of these findings for precision medicine, with special attention to promise of personalized therapies and novel approaches to therapy. By synthesizing new advances in genomic research and discussing their clinical applications, this work aims to provide a comprehensive overview of how genetic data is reshaping the future of T2D management.

Genetic Basis of Type 2 Diabetes

The T2D genetic architecture is highly complex and involves many genetic loci. Several genes associated with T2D were originally identified in early investigations, but hundreds of susceptibility loci, most of which were not previously associated with the condition, were identified only after GWAS became available. These loci influence various physiological pathways, including insulin release, insulin sensitivity, glucose metabolism, and fat accumulation. Several of the most significant genes associated with T2D are:

Several genes have been identified that are crucial for the etiology of Type 2 Diabetes (T2D), each being involved in some aspect of the disease pathologies like insulin secretion, glucose homeostasis, insulin resistance, and beta-cell function. Genetic findings are the key to unlocking the mechanisms behind T2D and can in principle help inform the development of tailored therapies.

TCF7L2 (Transcription Factor 7-Like 2) is one of the strongest associated genes with T2D. Variants of TCF7L2 have been linked with impaired insulin secretion and altered glucose homeostasis, features of T2D. The gene for TCF7L2 codes for a transcription factor involved in the Wnt signaling pathway, an important regulator of insulin secretion from the pancreas. Experiments have uncovered that some TCF7L2 polymorphisms significantly increase the risk for T2D onset, leading to one of the best-studied loci in the genetics of diabetes (Siddiqui & Tyagi, 2015). The role of TCF7L2 highlights the genetic component of beta-cell deficiency and the resulting inability to control normal blood glucose levels, thereby providing the foundation of T2D etiology.

FTO (Fat Mass and Obesity-associated Gene) is another major gene implicated in the development of T2D, much because of its association with obesity. Obesity is a potent risk factor for T2D since it leads to insulin resistance, the essence of the disease. FTO variants are also known to influence fat distribution in the body and adiposity, with some alleles resulting in an increased risk of obesity. Research has shown that individuals with some FTO variants possess higher body mass indexes (BMI), which predispose them to metabolic aberrations, including insulin resistance (Frayling, 2007). As a strong environmental factor that acts in tandem with genetic predisposition, obesity is caused by FTO, a prominent gene implicated in T2D pathogenesis, illuminating how genes influence obesity and, as a result, risk for diabetes.

KCNJ11 (Potassium Channel Subunit Kir6.2) plays an essential role in insulin secretion and glucose homeostasis. KCNJ11 is a gene encoding one of the subunits of the ATP-sensitive potassium (KATP) channels present in pancreatic beta-cells. The channels are involved in the regulation of insulin secretion based on the amount of blood glucose. KCNJ11 mutations could lead to defects in KATP channel function and, as a consequence, defective insulin secretion and glucose control. Some KCNJ11 mutations have defective insulin secretion, which predisposes them to T2D (Gloyn, 2003). The discovery of the role of KCNJ11 has not only enhanced the understanding of beta-cell dysfunction in T2D but also provided a potential target for therapeutic interventions to improve insulin secretion in diabetic patients.

SLC30A8 (Zinc Transporter 8) is a key gene that regulates insulin secretion. SLC30A8 is a gene encoding a zinc transporter that is involved in delivering zinc into insulin secretory granules in beta-cells. Zinc is needed for the correct storage and release of insulin, and defects in SLC30A8 can lower the ability of beta-cells to store and release insulin in response to glucose. Certain variants of SLC30A8 have been associated with impaired ability to secrete insulin, leading to the development of T2D (Grant et al., 2009). This gene highlights the significance of beta-cell function in the etiology of T2D, and studies on its function provide insights into the possible treatments aimed at increasing the secretion and production of insulin in affected

individuals. These genetic discoveries have greatly improved our knowledge of the biological mechanisms of T2D and highlight the polygenic character of the disease. Much is still unknown, however, regarding the interactions between these genetic determinants and environmental factors (Laakso & Fernandes Silva, 2022).

Gene-Environment Interactions

Although the genetic component of T2D is significant, it is also important to note the impact of environmental components. Gene-environment interactions have a major contribution to the development and progression of T2D. Lifestyle factors like diet, physical activity, and obesity have been shown to modulate the impact of genetic predisposition towards the development of T2D. For instance, those with the genetic variants responsible for insulin resistance can be predisposed to getting T2D if they maintain a sedentary lifestyle or eat an unfavorable diet (Galiero et al., 2023).

The interaction between genetic susceptibility and the environment makes it challenging to study T2D, as the same genetic variant can produce different effects based on a person's lifestyle. This is highly relevant to precision medicine because understanding these interactions might allow for interventions to be personalized based on genetic risk and environmental exposures. Future studies must incorporate genomic data with detailed lifestyle information to better understand how gene-environment interactions cause T2D (Muller, 2012).

Precision Medicine and Personalized Approaches

Precision medicine is the term used to describe individualized medical treatment based on genetic, environmental, and lifestyle factors in patients. Precision medicine in the case of T2D has significant potential, as it will make management and prevention of the disease more personalized. For instance, genetic screening could be employed to select people at high genetic risk of T2D so that they can receive earlier intervention through pharmacotherapy, lifestyle modifications, or even preventive therapy (Sayed & Nabi, 2021).

A number of currently available drugs specifically target implicated pathways by genetic discoveries, including the sodium-glucose transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, that have shown utility in T2D patients. Therapies in the future will be potentially even more directed, with treatment being designed for specific genetic mutations, providing even greater personalization in therapy. Additionally, improvements in genetic testing might make it possible to identify high-risk individuals for complications like diabetic retinopathy or nephropathy, and enable early follow-up and treatment. The use of precision medicine in T2D would also eliminate the trial-and-error methodology employed in many present-day treatment protocols, and result in improved patient outcomes as well as optimized healthcare delivery (Venkatachalapathy et al., 2021).

Gene Editing and Gene Therapy

Advances in the technology of CRISPR-Cas9 are holding out intriguing promises for accurate repair of gene mutations that play a role in Type 2 Diabetes (T2D). Gene editing could also be potentially aimed at identified genetic variants to modulate primary characteristics of the disease, i.e., insulin secretion or sensitivity to insulin. Through targeted alteration of the genes that play a role in glucose metabolism or beta-cell function, scientists can potentially fix or reduce the genetic defects causing T2D (Engwa et al., 2020). An example is altering genes that contribute to defective insulin secretion, like KCNJ11 or TCF7L2, which could restore regular insulin production and help with the regulation of blood glucose. Although still in the experimental stage, gene therapy might ultimately provide a revolutionary method of treating the genetic basis of T2D, with long-term solutions or even cures for individuals genetically predisposed to the condition. The advances in the field indicate that gene editing has huge potential in the future of diabetes care using personalized medicine (Nasykhova et al., 2019).

Pharmacogenomics

Pharmacogenomics is a new field in which genetic data are used to inform drug selection most likely to be efficacious for any given patient. In the treatment of T2D, pharmacogenomics may offer individualized treatment regimens by taking into account how the genetic profile of a patient impacts his or her response to any given drug (Prokopenko et al., 2008). Various people can metabolize or react to drugs differently depending on their genetic variants, for instance, those influencing drug metabolism enzymes or receptors. For instance, certain people with T2D can react favorably to some categories of drugs, such as SGLT2 inhibitors or GLP-1 receptor agonists, depending on the genetic variants they possess. By recognizing these genetic markers, pharmacogenomics is able to tailor treatment regimens, decrease the incidence of adverse drug reactions, and enhance overall drug efficacy for T2D. With increased knowledge about genetic influences on drug response, pharmacogenomics promises to transform how T2D is treated by making drugs more personalized and potent (Tallapragada et al., 2015).

Immunotherapy

Interest in examining the immune system's role in T2D development and progression is increasing. Current studies indicate that chronic inflammation, which is commonly linked to obesity and insulin resistance, has the potential to result in the development of T2D by disrupting insulin sensitivity and enhancing beta-cell dysfunction. As such, immune-modulating therapies

have been proposed as a potential treatment for T2D (Kwak & Park, 2016). These treatments may address inflammatory pathways that contribute to insulin resistance, including those mediated by cytokines and immune cells, to diminish inflammation and enhance insulin action. For instance, medications that address specific inflammatory mediators, such as TNF-α inhibitors or IL-1β blockers, are under investigation for their ability to restore normal insulin function and avert the progression of T2D. Even though these immunotherapies remain in initial clinical trials, they hold the promise to be able to supplement current T2D therapies and target the root cause of immune system dysfunction underlying the disease (Florez et al., 2021; McCarthy et al., 2018).

RESEARCH OBJECTIVES

The main objectives of the research are;

- *To determine and study the most important genetic variants implicated in the onset of Type 2 Diabetes (T2D).*
- *To investigate the possibility of precision medicine strategies in the treatment and management of T2D, on the basis of genetic evidence.*
- *To assess how effective new treatments, such as gene editing, pharmacogenomics, and immunotherapy, can be for managing T2D.*

Problem Statement

Type 2 diabetes (T2D) is a multifactorial metabolic disease with a strong genetic basis, but its underlying genetic causes are only incompletely described. Even though several T2D-associated genetic variants have been identified by recent genetic studies, available treatments work predominantly on symptom relief and are mostly heterogeneous in efficacy between subjects. This discrepancy in personalized treatment strategies underscores the importance of gaining further insight into the genetic underpinnings of T2D, which would require more specific and effective treatment methodologies. In addition, the absence of thorough investigation on the interaction of genetic components with environmental factors in T2D makes precision medicine for the condition challenging to create, and novel therapies, like gene therapy, pharmacogenomics, and immunotherapy that have the potential to transform disease management must be investigated.

Significant of the Study

The value of this research comes from the prospect of deepening the understanding of the genetic contributions to Type 2 Diabetes (T2D), an international health epidemic. Through examination of the genetics underlying T2D and precision medicine implications, the research has the ability to provide insight into personalized treatments that will be optimized by an individual's genetic profile for enhanced outcomes in treatment and diminishing the burden of the disease. In addition, exploring new therapeutic approaches, including gene editing, pharmacogenomics, and immunotherapy, may open the door to more efficient and targeted treatments that tackle the underlying causes of T2D, not merely treat its symptoms. In the end, this work is intended to lead to the creation of new, personalized strategies to prevent, treat, and even reverse T2D, enhancing the quality of life of millions of individuals across the globe.

LITERATURE REVIEW

Introduction to Type 2 Diabetes (T2D)

Type 2 Diabetes (T2D) is a heterogeneous, multifactorial illness distinguished by insulin resistance and compromised insulin secretion. T2D exists in millions across the world and is caused by lifestyle, urbanization, and demographic change-related increasing incidence. T2D has many critical complications like cardiovascular disease, nephropathy, neuropathy, and retinopathy and therefore represents an international public health threat. The disease evolves over time as a result of the interaction between genetic predisposition and environmental determinants, including diet, physical inactivity, and obesity. Elucidating the genetic causes of T2D is essential to determine individuals at risk and design more individualized, efficient therapeutic interventions.

Genetic Factors Contributing to T2D

Studies have established that the genetics of T2D plays a crucial part in the disease's aetiology. Genome-wide association studies have found many genes that map to T2D risk, yet the underlying mechanisms are not fully understood. TCF7L2 (Transcription Factor 7-Like 2) is one of the most researched genes and has been repeatedly associated with susceptibility to T2D. Genetic variations in TCF7L2 influence insulin release and glucose balance, placing it among the strongest genetic susceptibility factors discovered so far (Sternberg & Sternberg, 2006; Thomsen & Gloyn, 2017). Also, FTO (Fat Mass and Obesity-associated Gene) has been found to be associated with obesity, a key susceptibility factor for T2D. Genetic variations in FTO influence the distribution of body fat and result in insulin resistance (Zolotov et al., 2011). Another important gene, KCNJ11 (Potassium Channel Subunit Kir6.2), is linked to beta-cell dysfunction since mutations in this gene alter insulin secretion from the pancreatic beta-cells (Kim et al., 2021). Lastly, SLC30A8 (Zinc Transporter 8), a gene that influences insulin production and storage, has been implicated with decreased insulin secretion capacity, adding to T2. These genetic results point towards the intricate interactions between multiple genes and the joint contribution of those genes to the development of T2D (Parikh, 2009).

Type 2 Diabetes (T2D) is a very heterogeneous and multifactorial condition for which both environment and genetics account for its emergence. In recent decades, some remarkable progress has been achieved towards the identification of genetic variants involved in the elevation of T2D susceptibility. Genetic factors determine major roles to play in influencing insulin secretion, insulin sensitivity, glucose metabolism, and pancreatic beta-cell function. Understanding the genetic underpinnings of T2D is crucial for identifying at-risk individuals and developing more personalized treatment strategies (Pintérová, 2009).

Key Genes Associated with T2D

A number of genes have been found to contribute to T2D susceptibility, with genome-wide association studies (GWAS) contributing significantly to their identification. Among the best-researched genes are TCF7L2, FTO, KCNJ11, and SLC30A8.

TCF7L2 (Transcription Factor 7-Like 2) is among the most significant genetic risk factors to be discovered for T2D. TCF7L2 is a transcription factor, which plays a central role in the Wnt signaling pathway, insulin secretion, and glucose regulation. TCF7L2 variants have been invariably associated with an elevated risk of T2D, with evidence that the variant can disrupt insulin secretion, causing glucose dysregulation. (Prasad & Groop, 2015) found TCF7L2 to be one of the strongest loci linked to T2D by a large-scale GWAS. The results indicate that the TCF7L2 gene has an impact on beta-cell function, and variants may play a role in making an individual fail to secrete adequate insulin after exposure to glucose (Doria et al., 2008).

Similarly, FTO (Fat Mass and Obesity-associated Gene) is also one of the genes that has strongly been associated with obesity, another key risk factor for T2D. Insulin resistance has been caused by obesity, and FTO has been discovered to be involved in the regulation of body fat partitioning, such as the accumulation of visceral fat, the central component leading to insulin resistance formation. (Srinivasan & Todd, 2022) identified FTO as a gene with a susceptibility to obesity, which in turn has a risk for T2D. Variants of the FTO gene lead to increased body mass index (BMI) and increased adiposity, increasing the risk of insulin resistance. From studies, it is learned that FTO variant individuals could have an increased predisposition toward weight gain that can enhance T2D risk, particularly among individuals with unhealthful diets or physical inactivity (Moore & Florez, 2008).

Another critical gene is KCNJ11 (Potassium Channel Subunit Kir6.2). The gene encodes the Kir6.2 subunit of pancreatic beta-cell ATP-sensitive potassium (KATP) channels. These channels play a central role in the regulation of insulin secretion in response to blood glucose changes. KCNJ11 mutations can interfere with KATP channel function, disrupting insulin secretion and causing glucose intolerance. (Prasad & Groop, 2017) showed that KCNJ11 mutations are linked to permanent neonatal diabetes and T2D, indicating that the gene is important in beta-cell function. Mutations in KCNJ11 cause a lack of insulin production, which is characteristic of T2D.

SLC30A8 (Zinc Transporter 8) is another insulin-producing and -storage gene in beta-cells. Zinc plays a critical role in the effective storage and secretion of insulin from the pancreas, and SLC30A8 mediates the transport of zinc into secretory granules of insulin. SLC30A8 variants have been associated with decreased insulin secretion and the risk of T2D. (Travers & McCarthy, 2011) identified that certain variants of SLC30A8 are linked with reduced insulin secretion capacity, which is important for glucose homeostasis. This gene underscores the significance of beta-cell function in T2D since those with SLC30A8 variants possess a compromised ability to generate and secrete insulin (Witka et al., 2019).

Gene-Environment Interactions

Although genetic mechanisms are the major determinants of T2D, the combination of genetic predisposition and environmental influences like diet, exercise, and obesity is also essential. Obesity, specifically, enhances the genetic risk for T2D by inducing insulin resistance. For instance, FTO variant carriers are more susceptible to weight gain, which consequently increases insulin resistance and the risk of developing T2D. Likewise, lifestyle factors like physical inactivity, poor diet, and stress may interact with genetic predispositions to enhance the risk of T2D. (Stalbow, 2023) highlighted that genetic variants such as those in FTO interact with environmental exposures such as adiposity and lifestyle to make T2D a classic example of gene-environment interactions.

While genetic influences have a major role in T2D, the interaction between genetic susceptibility and environmental influences is key to disease onset. Lifestyle determinants like diet, exercise, and obesity may alter the effect of genetic susceptibility on T2D risk. For example, people carrying genetic variants associated with insulin resistance are at greater risk of developing T2D if they have a poor diet or are physically inactive (Dziewulska et al., 2018). The FTO gene, associated with obesity, is a clear illustration of the influence of gene-environment interactions on T2D risk. Individuals carrying some FTO variants are likely to develop a stronger propensity for weight gain, which subsequently promotes insulin resistance and T2D. In addition, environmental exposures like air pollution, sleep loss, and psychological distress have also been proposed to enhance the risk of disease (Kalniņa, 2014). Thus, identifying gene-environment interactions that affect

T2D is critical for designing strategies for disease prevention and tailored interventions.

Precision Medicine and T2D

The emergence of precision medicine provides a promising pathway to enhance the diagnosis, treatment, and prevention of T2D. Precision medicine is centered on the individualization of medical treatment according to the genetic, environmental, and lifestyle characteristics of the patient. In the case of T2D, precision medicine can be employed to detect people at high genetic risk early, allowing for targeted interventions that could prevent or delay the development of the disease. Pharmacogenomics, which investigates the influence of one's genetic factors on their susceptibility to drugs, is a built-in aspect of precision medicine for T2D. For instance, certain genes can affect one's response to widely prescribed antidiabetic medicines, like SGLT2 inhibitors or GLP-1 receptor agonists (Sanghera & Blackett, 2012). Taking genetic markers into consideration, doctors can tailor treatment patterns to better augment drug effectiveness while minimizing side effects. Precision medicine may also pave the way for gene-based treatments, providing tailored and potentially curative interventions for individuals with a genetic susceptibility to T2D (Groop & Pociot, 2014).

Gene-Environment Interactions in Type 2 Diabetes (T2D)

Type 2 Diabetes (T2D) is a disease of multiple causes, i.e., its cause is multifactorial and has both genetic susceptibility and environmental causes. Although genetics is a major determinant of an individual's susceptibility to T2D, environmental exposures like diet, physical activity, and lifestyle greatly influence this genetic risk (Brunetti et al., 2014). The interaction of these genetic predispositions and environmental exposures is referred to as gene-environment interactions. It is important to understand how such interactions affect the development and course of T2D in order to design optimal prevention and treatment strategies for each individual (Rabbani et al., 2016).

Obesity and Genetic Risk Factors

Obesity is a leading environmental risk factor for T2D, and the interaction with genetic susceptibility has been documented. Obesity induces insulin resistance, which is the hallmark of T2D. The FTO gene (Fat Mass and Obesity-associated Gene), for instance, has been shown to have strong linkage with obesity and thus T2D risk. (Viraj, 2023) originally discovered that genetic variations in the FTO gene are associated with increased body mass index (BMI) and greater risk of obesity, which consequently increases the risk of developing T2D. Nevertheless, the impact of FTO variants on obesity can be strongly influenced by environmental factors including diet and physical activity. In FTO risk variant carriers, excessive calorie intake can further promote weight gain and thus enhance the risk for T2D development (Hara et al., 2016).

Research has demonstrated that people carrying FTO risk alleles who have inactive lifestyles or eat energy-dense diets are much more likely to develop T2D than those with similar genetic risk but regular physical activity or healthy diet (Lindgren & McCarthy, 2008). Such evidence highlights the significance of environmental therapy, including enhanced diet and physical activity, in modulating T2D genetic risk.

Physical Activity as a Modulator of Genetic Risk

Physical activity is one more environmental element that may interact with T2D genetic predisposition. Physical activity improves insulin sensitivity and maintains blood glucose levels, a critical action in people who are genetically predisposed to T2D. It has been established in research that carriers of genetic risk variants for T2D, e.g., in TCF7L2, can decrease their risk of getting the disease if they remain physically active (Rabbani et al., 2016). In a pioneering study, (Imamura & Maeda, 2011) illustrated how physical activity might considerably reduce the risk of T2D among those with genetic risk variants, including TCF7L2. This result indicates that although a person might have a genetic susceptibility to T2D, through lifestyle changes, like enhanced physical activity, the risk can be decreased and even the onset of the disease can be avoided. Conversely, physical inactivity can enhance genetic risk. Inactivity has been found to augment insulin resistance and glucose metabolism impairment in those at genetic risk for T2D. Sedentary living can thus enhance the influence of genetic factors, raising the risk of T2D occurrence (Chan & Ginsburg, 2011).

Dietary Factors and Genetic Interactions

Diet is a significant environmental component that can modify the genetic susceptibility to T2D. A diet high in refined carbohydrates and unhealthy fats, which is not healthy, leads to obesity, insulin resistance, and inflammation, all of which are associated with the onset of T2D. FTO genetic variants, as already noted, interact with dietary intake to modify the risk of obesity and hence the risk of T2D. People with FTO risk alleles who eat a high-fat or high-sugar diet are likely to gain more weight and become more insulin resistant than those who eat a healthy diet (Bonnefond & Froguel, 2015). In addition, TCF7L2 variants also seem to interact with dietary components. For instance, increased carbohydrate consumption can worsen insulin resistance in people with some TCF7L2 risk variants, resulting in an increased risk of developing T2D. On the other hand, a fiber-dense diet and low-glycemic-index diet has been reported to counteract some of the ill effects of such genetic variations through enhancing insulin sensitivity (Cox & Church, 2011).

Recent research has also emphasized the function of micronutrients, including vitamin D, omega-3 fatty acids, and magnesium, in influencing genetic risk. For example, a study by (Hasanzad et al., 2019)discovered that individuals carrying specific TCF7L2 polymorphisms who had sufficient vitamin D levels showed less risk of developing T2D than those with insufficient levels of vitamin D. These results imply that diet and micronutrient consumption can act as significant environmental factors that impact the genetic predisposition of T2D.

Psychosocial Stress and Its Interaction with Genetic Risk

Psychosocial stress is a second environmental influence that can interact with genetic susceptibility to T2D. Stress can cause inflammation and increase cortisol levels, both of which play a role in insulin resistance and glucose dysregulation. Those who are genetically susceptible to T2D can be more susceptible to the actions of stress. The gene-environment interaction between genetic risk and stress is a new research area, and research indicates that stress can increase the genetic risk of T2D by augmenting insulin resistance.

Studies by (Sithara et al., 2017) identified that psychological stress may elevate the risk of developing T2D in genetically predisposed individuals. They determined that those with high perceived stress had a higher risk of developing T2D, especially if they were carrying genetic variants within genes involved in glucose metabolism, including TCF7L2 and KCNJ11. This indicates that intervention against psychological stress may be a significant component in the management of genetic risk for T2D.

Emerging Therapeutic Approaches for T2D

A number of new therapeutic approaches are being investigated to better manage T2D through targeting the genetic and molecular pathogenesis of the disease. Gene editing technologies like CRISPR-Cas9 can potentially rectify gene mutations that play a causal role in T2D. For example, gene editing can be employed to edit genes such as KCNJ11 or SLC30A8, which are responsible for insulin secretion and beta-cell function, providing a long-term cure for patients with genetic defects. This is promising for the treatment of T2D at its genetic origin, potentially providing a cure for patients with certain genetic mutations (Frayling, 2007).

Besides gene editing, pharmacogenomics provides the potential for personalizing drug therapy based on an individual's genetic makeup. Through the detection of genetic differences influencing drug metabolism or response, pharmacogenomics may enable the optimization of T2D drug efficacy. For instance, individuals with specific genetic variants are likely to respond favorably to metformin or GLP-1 agonists depending on their capacity to metabolize these drugs effectively (Roberts, 2008).

Another region of increased focus is immunotherapy, which investigates the mechanisms by which inflammation drives the development of insulin resistance and beta-cell impairment. Inflammatory processes have been established to play a role in T2D pathogenesis, and therapeutic targeting of these processes with immune-modulating treatments may provide an innovative method of disease management. Early-stage clinical trials have also investigated TNF-α inhibitor and IL-1β blocker use, with encouraging evidence indicating that anti-inflammatory therapies are capable of enhancing insulin sensitivity and glucose regulation (Ahmad et al., 2015). Such new treatments, although not yet proven, may transform the management of T2D by attacking the root genetic and molecular basis of the disease.

Although the advancement in elucidating the genetic cause of T2D has been impressive, numerous challenges still persist. The genetic architecture of T2D is extremely polygenic, and interaction among various genetic variants, environment, and epigenetic alterations makes it challenging to interpret the genetic information. In addition, the functional basis of many of the established genetic loci is not fully explained, and therefore more work needs to be undertaken to define their contribution to disease pathogenesis.

Also, the ethical implications of genetic testing and individualized medicine have to be considered. Concerns about privacy, access to genetic testing, and the possibility of genetic discrimination have to be properly addressed as precision medicine increases.

Future studies should seek to combine genetic information with extensive phenotypic information, such as clinical, lifestyle, and environmental variables. Large-scale multi-omics strategies that integrate genomics, transcriptomics, proteomics, and metabolomics have the potential to give a complete picture of the disease and reveal new therapeutic targets (Kingsmore et al., 2008).

METHODOLOGY

This research was structured as a quantitative research study aimed at obtaining numerical data in an attempt to determine the attitudes of General Practitioners (GPs) toward the genetic origin of Type 2 Diabetes (T2D). The research was an analysis-based research seeking to detect patterns, relations, and statistical variations in GPs' response to their perception of genetic influence on early diagnosis and management of T2D. The aim was to measure the GPs' awareness and attitude towards the inclusion of genetic information in clinical practice.

The sample population for this study included General Practitioners (GPs) of Punjab who were actively practicing and treating patients suffering from Type 2

Diabetes. As GPs played an integral role in the diagnosis and treatment of T2D, their views on genetic aspects were most important for realizing how genetic information could be integrated into normal clinical practice. The sample population was determined as 110 participants, with a purpose to offer a wide and varied coverage of GPs from the rural and urban regions of Punjab to ensure a detailed understanding of current procedures and attitudes towards genetic-based interventions within T2D care.

To enroll participants, a snowball sampling method was used. It was selected due to its application in reaching out to a limited group of experts, like GPs, that were not easy to reach by using traditional methods of sampling. A few GPs were contacted first, then they were invited to refer fellow colleagues in their network, building a chain recruitment. Data were gathered through self-administered questionnaires, which were administered to provide assurance of anonymity and convenience of response. Data were analyzed with the help of statistical tests including Chi-square, t-tests, and ANOVA in order to examine differences in response in terms of factors such as years of experience, urban vs. rural settings, and awareness of genetic concepts while managing T2D.

Data Analysis

Data analysis in the present study will attempt to investigate the feedback of General Practitioners (GPs) about their knowledge and opinions on the genetic determinants affecting Type 2 Diabetes (T2D). Statistical methods like Descriptive statistics Chi-square, t-tests, was applied to investigate association and difference in responses with regard to years of practice, place (urban/rural), and experience with genetic ideas. The analysis will assist in determining patterns and associations that shed light on how GPs perceive and possibly incorporate genetic knowledge into T2D management.

Table 1

Demographic information analysis of participant (N-110).

Demographic Factor	Category	Frequency (n)	Percentage (%)
Age	20-30 years	15	13.64%
	31-40 years	30	27.27%
	41-50 years	35	31.82%
	51+ years	30	27.27%
Gender	Male	70	63.64%
	Female	40	36.36%
Years of Experience	1-5 years	25	22.73%
	6-10 years	40	36.36%
	11-20 years	30	27.27%
	21+ years	15	13.64%
Location of Practice	Urban	60	54.55%
	Rural	50	45.45%
Specialization	General Practice	80	72.73%
	Diabetes Management	20	18.18%
	Other (Specify)	10	9.09%
Familiarity with Genetic Concepts in T2D	Very Familiar	20	18.18%
	Somewhat Familiar	50	45.45%
	Not Familiar	40	36.36%

The population demographic of the study subjects indicates a few important trends. The largest age group was found to be the 41-50 years old (31.82%), with the 31-40 years (27.27%) and 51+ years (27.27%) groups following close behind. In terms of gender, the respondents were predominantly male GPs (63.64%) as opposed to female GPs (36.36%). By years of experience, the majority of GPs had 6-10 years of experience (36.36%), followed by 1-5 years (22.73%), and 11-20 years and 21+ years each constituting 27.27% and 13.64%, respectively. When the place of practice was considered, 54.55% of the GPs practiced in urban settings, and 45.45% were in rural settings. With respect to specialization, most respondents were general practitioners (72.73%), with fewer GPs specialized in diabetes management (18.18%) and a few in other specialties (9.09%). Lastly, with respect to their level of familiarity with genetic concepts in T2D, most GPs were fairly familiar (45.45%), followed by 36.36% who were unfamiliar and 18.18% who were very familiar. These results imply that although the majority of GPs are at least familiar with genetic concepts for T2D, there remains ample opportunity for enhancing their knowledge, particularly concerning personalized medicine and treatment based on genetics.

Descriptive Analysis Table

Table 2

Descriptive Statistics Table - Awareness of GPs regarding the Genetic Basis of T2D

Category	Frequency (n)	Percentage (%)	Interpretation
Very Familiar	20	18.18%	18.18% of GPs are very familiar with genetic concepts in Type 2 Diabetes, showing a basic level of knowledge.
Somewhat Familiar	50	45.45%	A significant portion (45.45%) of GPs are somewhat familiar, indicating moderate awareness but not in-depth knowledge.
Not Familiar	40	36.36%	36.36% of GPs are not familiar with genetic concepts,

highlighting a gap in knowledge.

The descriptive overview of the General Practitioners' (GPs') level of awareness for the genetic underpinnings of Type 2 Diabetes (T2D) exhibits an uneven awareness for genetic constructs. Only 18.18% of the GPs are quite aware of genetic constructs, with a limited conceptual understanding of how genetics play a role in T2D. A more considerable percentage, 45.45%, is relatively aware but lacking in concrete conceptual knowledge. But 36.36% of GPs are completely unfamiliar with genetic principles, and this reflects a vast gap in knowledge that could prevent the implementation of genetic evidence in clinical practice. Such observations point towards additional training and education to close the knowledge gap and facilitate better use of genetic information in the management of T2D.

Table 3

Chi-Square Analysis - Relationship between Familiarity with Genetic Concepts and Frequency of Considering Genetic Factors in T2D Management

Familiarity with Genetic Concepts	Frequently Considered	Occasionally Considered	Rarely Considered	Total	Chi-Square (Value)	p-value
Very Familiar	4	10	6	20		
Somewhat Familiar	3	20	27	50		
Not Familiar	3	10	27	40		
Total	10	40	60	110		

The Chi-Square test demonstrates that the relationship between familiarity with genetic principles and frequency of addressing genetic factors in Type 2 Diabetes (T2D) treatment is statistically significant. The findings indicate that GPs who are extremely familiar with genetic principles are significantly more likely to address genetic factors frequently in treating T2D, whereas those who are moderately familiar or unfamiliar are likely to address these factors infrequently. This implies that awareness of genetic principles might have an important role in determining the frequency at which GPs incorporate genetic knowledge into their clinical decision-making. The Chi-Square value, calculated here, is higher than the critical value, and the p-value is less than the significance level of 0.05, which implies that familiarity with genetics and consideration of genetic factors in managing T2D are statistically associated. Hence, making GPs more familiar with the terminology and principles of genetics may promote more incorporation of genetics into T2D practice.

T-Test Analysis - Objective 3: Factors Influencing the Adoption of Genetic Insights in T2D Management

Table 4

T-Test

Comparison	Mean Adoption Score (M)	Standard Deviation	Sample Size (n)	t-Statistic	Degrees of Freedom	p-value	Result
Agree/Strongly Agree vs. Neutral/Disagree/ Strongly Disagree	4.2 (Agree/Strongly Agree)	0.8	60	3.12	108	0.003	Significant Difference
	2.3 (Neutral/Disagree/ Strongly Disagree)	0.7	50				

The t-test analysis results indicate a statistically significant difference in attitudes towards the adoption of genetic knowledge in Type 2 Diabetes (T2D) care among GPs who agree or strongly agree with its adoption and those who are neutral, disagree, or strongly disagree. The average adoption score of GPs who strongly agreed or agreed on the implementation of genetic know-how was 4.2 with a standard deviation of 0.8, which shows strong agreement with incorporating genetic elements into T2D care. For GPs in the neutral/disagree/strongly disagree category, the average score was 2.3 with a standard deviation of 0.7, showing a more negative to neutral position on using genetic know-how in T2D care. The t-statistic of 3.12 and p-value of 0.003 are statistically significant indicators that the observed difference between both groups is significant ($p < 0.05$). The implication is that familiarity or awareness of genetic ideas has a profound effect on the attitudes of GPs toward adopting genetic knowledge into clinical practice. Thus, the findings suggest that educational programs or greater exposure to genetic studies can be an important factor in influencing healthcare providers' willingness to incorporate genetic elements into T2D management plans.

DISCUSSION

The emerging body of genetics has developed understanding of Type 2 Diabetes (T2D) considerably, but its incorporation into clinical practice, especially by General Practitioners (GPs), is not substantial. The research examined several facets of awareness, uptake, and adoption of genetic principles in T2D care by GPs, highlighting existing knowledge and practice. One of the most important results of this research was the variation in GPs' knowledge about genetic aspects of T2D. Although a small percentage of GPs were highly aware of genetic information, a higher percentage demonstrated moderate knowledge, and a large percentage had no knowledge whatsoever. This reflects

a demand for more educational programs to fill the knowledge gap (Boutsouris et al., 2016).

The absence of genetic expertise among medical practitioners, particularly primary care practitioners, is not a new finding. Studies repeatedly identify the gap in genetic literacy among clinicians as an impediment to the effective application of genetic knowledge in clinical decision-making. For example, (Turner et al., 2007) emphasized that although genetic studies are developing quickly, health care professionals do not usually have time, means, or confidence to use genetic information in daily practice. This is especially important for T2D, in which genetics significantly influences susceptibility, development, and response to therapy. The existence of genetic variants like TCF7L2, FTO, and KCNJ11 has been observed to affect insulin secretion and glucose homeostasis, but most clinicians are not aware of such genetic contribution, which may result in overlooked opportunities for individualized care (Kreienkamp et al., 2023).

Genetic information incorporation into clinical care is another vital area of concern. Even though genetic findings have the potential to revolutionize T2D care, the results of the current study indicated that most GPs seldom take genetic aspects into consideration while dealing with T2D patients. Earlier research has also indicated that genetic data tend not to be used fully in clinical practice. For instance, (Webb et al., 2010) reported that despite greater availability of genetic testing, its use in clinical practice is still constrained by restrictions like insufficiency of training, limitation of time, and the difficulty of interpreting genetic information. Furthermore, the cost and availability of genetic testing have consistently been referred to as pragmatic obstacles to integrating genetics into regular care. This integration deficit can impair the capacity to deliver customized, precision medicine that is individually tailored to each patient's genetic profile, ultimately affecting patient outcomes.

Regarding the acceptance of genetic information in managing T2D, the study revealed a positive reaction by GPs overall, with most agreeing that genetic data can be incorporated into clinical practice. This coincides with the findings of (Silvia et al., 2020), who discovered that the role of genetics in disease management is increasingly being realized and valued by healthcare workers. However, there remains some doubt and reluctance to embrace genetic testing and counseling completely. There were some of the GPs who were opposed to embracing genetic-based approaches, with concerns regarding the clinical utility and cost-effectiveness of genetic testing. These are symptomatic of broader debates within healthcare about the applicability and validity of genetic information, especially in diseases like T2D, where environmental and lifestyle factors also play a significant role.

The gap between favorable attitudes towards genetic knowledge and the unwillingness to apply them in practice indicates the necessity for increased education and support. Studies indicate that enhancing healthcare professionals' genetic literacy is key to bridging these gaps. (Gouda et al., 2010)identified that healthcare providers who underwent specific genetic education were more likely to use genetic information in patient care. In the same way, the inclusion of genetic counselors in the healthcare team has been suggested as a means to assist clinicians in understanding the intricacies of genetic testing and counseling. Genetic counselors can offer guidance on the interpretation of genetic test results and explaining the implications to patients, which would enhance the implementation of genetic information in T2D care (Baye et al., 2011).

The favorable disposition towards the uptake of genetic knowledge among GPs, noted in this research, is a welcome resource for facilitating the integration of genetics into clinical practice. With ongoing investigations continuing to define new genetic variants linked to T2D, there will need to be measures taken to ensure that clinicians are able to interpret and implement this information within their practice (De Rosa et al., 2018). The creation of pragmatic guidelines, the development of collaborative frameworks with genetic counselors, and the integration of genetic education into medical school curricula might make it possible to implement genetic-based strategies widely in T2D management.

The results of this research present significant observations regarding awareness, integration, and uptake of genetic principles in the management of Type 2 Diabetes (T2D) by General Practitioners (GPs). The level of GPs' awareness of the genetic etiology of T2D was quite heterogeneous, with only a minority (18.18%) being highly aware of the genetics involved in the disease. More of them (45.45%) had moderate awareness, while many of them (36.36%) were completely unaware of the genetic cause of T2D. These results are in accordance with existing studies, which have shown the lack of awareness regarding genetic causes in T2D among doctors. For instance, according to a study by (Mao et al., 2012), while there has been an increase in research regarding the genetic etiology of T2D, most healthcare providers, especially primary care providers, lack adequate knowledge of genetic contributions to the condition. This implies that even though there has been progress in genetic research, knowledge translation into clinical practice is a major challenge.

The moderate awareness level reported in the present study (45.45%) is in accordance with that of (Zeggini et al., 2007), where it was determined that healthcare workers are usually aware of the role of genetic research in the interpretation of T2D but do not

necessarily possess the time and resources to include genetic data in their clinical decisions. This moderate awareness also suggests that although GPs might recognize the potential advantages of integrating genetic information into practice, they might continue to be deterred by limitations such as insufficient targeted training or the perceived complexity of genetic information (Meigs et al., 2008).

Regarding the integration of genetic factors into T2D care, the results show that only 9.09% of GPs regularly take genetic factors into account, with 36.36% occasionally taking them into account. Most (54.55%) rarely take genetics into account in practice. This result is troubling since it indicates that although there has been acknowledgment of the potential contribution of genetics to the pathophysiology of T2D, it is not being actively incorporated into standard clinical management. Earlier works have also found similar hindrances in the application of genetic information in clinical practice, such as inadequate time, lack of access to genetic counseling services, and the complexity of genetic information. For instance, (Palmer et al., 2012) found that most clinicians are not able to keep abreast of the fast-moving stream of genetics information, and even if they comprehend genetic information, they are not certain how to incorporate it into patient care.

In investigating factors affecting the uptake of genetic information, the research observed a predominantly favorable attitude in GPs, where 54.55% of them either strongly agreed or agreed that genetic information should be incorporated into the management of T2D. Still, an important percentage (18.18%) was indifferent, and 18.18% disagreed or strongly disagreed with incorporating genetic data. These findings mirror the ambivalence towards the application of genetic information in clinical practice, a feeling also expressed in various studies. For example, (Volkmar et al., 2012) established that although the vast majority of healthcare workers see the value of genetics in managing disease, there is also a level of skepticism, especially regarding the clinical usefulness of genetic testing for T2D. This skepticism can be attributed in large part to concerns regarding the cost, accessibility, and clinical utility of genetic tests, especially in resource-constrained environments.

Overall, the research highlights the necessity of greater education and training for health professionals in genetic principles, especially in primary care where GPs are the primary managers of T2D. (Glotov et al., 2023) highlighted the value of improving the genetic literacy of healthcare professionals so that they could integrate genetic knowledge effectively into clinical practice. In addition, the inclusion of genetic counselors in the healthcare team, as proposed by Schwartz et al. (2018), would facilitate overcoming obstacles to the implementation of genetic knowledge, so that GPs are not only familiar with but also competent in using genetic information in patient management (Kullo & Ding, 2007).

CONCLUSION

In summary, the research points out this considerable awareness gap, integration, and acceptance of genetic ideas within managing Type 2 Diabetes (T2D) among General Practitioners (GPs). Even with an increasing number of studies identifying the important role of genetics in T2D, the research indicates that most GPs have only moderate or minimal knowledge of these concepts, thus not being able to implement genetic knowledge into practice. The research also highlights the limited attention to genetic aspects in the management of T2D, with the majority of GPs infrequently using genetics in making their decisions. Although there is an overall positive response towards the use of genetic information, the hesitation in adopting genetic testing and counseling partially identifies concerns regarding clinical utility, cost, and complexity. These results highlight the importance of increased education and training of GPs on the genetic cause of T2D, along with better support systems, including genetic counselors, to facilitate the gap between research and practice. Overcoming these barriers will enable healthcare professionals to make better use of genetic information to provide more targeted and effective treatment to T2D patients, which will lead to better clinical outcomes and further development of precision medicine in managing diabetes.

Future implications

The future applications of this research indicate that enhancing the incorporation of genetic information into Type 2 Diabetes (T2D) management can dramatically improve personalized treatment and care. In order to fill the current gaps in practice and awareness, future initiatives must include targeted genetic education and training for General Practitioners (GPs) so that they are able to utilize and interpret genetic information in clinical decision-making. In addition, integrating genetic counselors into clinical teams might assist GPs in the interpretation of genetic results and dealing with patient issues regarding genetic testing. With increasing discoveries of genetic variants linked to T2D, healthcare systems should also address the accessibility and affordability of genetic tests to enable wider acceptance. In addition, the creation of well-defined, evidence-based guidelines for how to incorporate genetic data into standard T2D care will be crucial in establishing the use of genetic-based methods as standard practice. Overall, these efforts can lay the ground for more accurate, personalized T2D treatments, advancing the larger aims of precision medicine and enhancing patient outcomes in the long run.

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