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Analysis on type 2 diabetes genetic polymorphism of different races/ethnicity

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Abstract. Whether from the perspective of impact scope or patient number, type 2 diabetes is one of the most influential diseases around the world today. However, in regards to type 2 diabetes's pathology, scientists still could not provide an accurate explanation. In the long period of research, our understanding of the disease has already become deep enough to realize that type 2 diabetes is closely associated with genetics. This passage is based on this point of view and aims to take a glance at the polymorphism between genetic information of different racial/ethnic groups of people. From the analysis, it could be concluded that genetic polymorphism can provide useful information for the difference of pathology of patients, which could then inspire further drug development and more proper treatment scheme decision.

Keywords: type 2 diabetes, genetic, pathology

1. Introduction

As WHO predicted, the number of diabetes patients will exceed 100 million in 2025. Worse still, according to statistical results, the disease is affecting a wider range of people, specifically young people because of the prevalent unhealthy sedentary lifestyle and Western diet [1]. From previous research, it has been elucidated that the pathology of diabetes, especially type 2 diabetes, relates closely to genetics. With genome-wide association studies becoming available, a large number of susceptible loci have been found and brought us newer insight into the essence of the metabolic disorder. Analysis of data shows that people from different ethnicities tend to have different genetic pattern, and the understanding of this patterns may promote progress toward providing tailored treatment for diabetes patients.

This passage studies the genetic polymorphism between some of the global population groups with different races and ethnicities by reviewing literature and learning from the previous data of genome-wide association studies. The passage is with no discrimination of any specific race/ethnicity of people. With the analysis, the passage aims to find the correlation between racial identities and pathological mechanisms, which might help in future T2DM treatment and alternative more precise therapeutic agents research.

2. Overview on the pathology of type 2 diabetes(T2DM)

2.1. Epidemiology and pathophysiology of T2DM

Type 2 diabetes is a metabolic disorder that is characterized by the symptoms of hyperglycemia and related weight loss, fatigue, polyuria, and frequent hunger. Currently, there are about 415 million

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diabetes patients across the world and type 2 diabetes patients take most of the part [2]. Worse still, the disease is predicted to affect a larger number and age range of people [1]. The heavy global burden can be attributed to a fast rate of economic development, a Western diet, and a sedentary lifestyle [2]. Considering the various complications the disease might bring about, the medical costs involved in the treatment of this disease are pretty large. Therefore, finding effective ways to test, prevent, and treat the disease is a crucial task today.

Research on the risk factors of type 2 diabetes has already been conducted. From the research, it has been identified that both social factors and biological factors contribute to type 2 diabetes incidence. Common social factors include lifestyle and socioeconomic development as mentioned before. From research on biological factors of type 2 diabetes, genetic factors have been proven to play an important role.

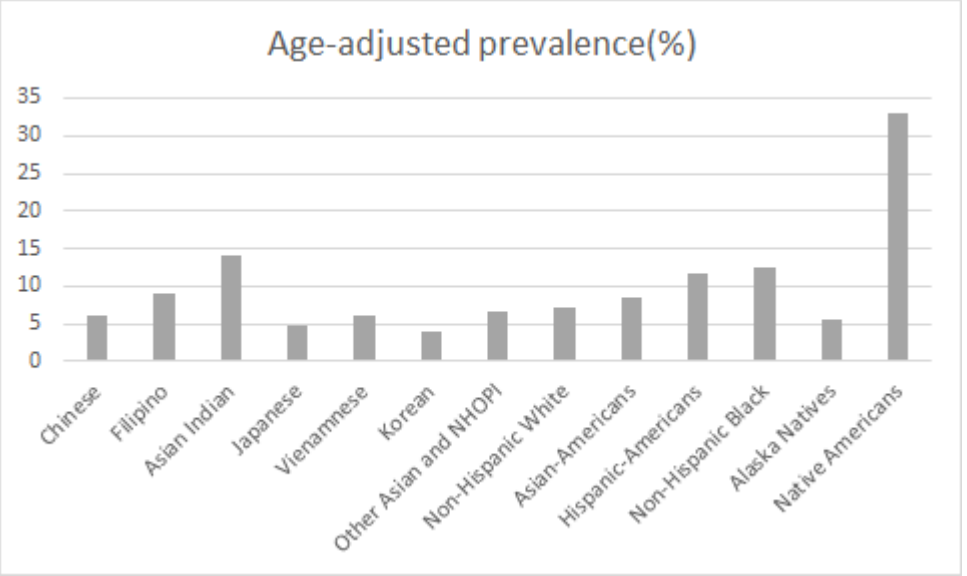

Figure 1. The age-adjusted prevalence of type 2 diabetes across different races/ethnicity of people

In previous statistical analysis, scientists found that both inheritance and environment correlate to T2DM [3]. As the methodology of genetic studies developed and genome-wide association study (GWAS) has been made possible, the genetics of different groups of people can be clearly researched to the detail of susceptible loci. Due to the limitations of sample diversity in each study, researchers in the past could only reach conclusions that apply to a certain region of people rather than get a panoramic view.

The pathophysiology mechanism of type 2 diabetes was the β-cell dysfunction. In a normal scenario, β-cell is responsible for the secretion of pre-proinsulin. After the maturation of secretory vesicles, granules of the cell store insulin until the start of insulin release, which is normally began after receiving the signal that glucose concentration is high. Under such circumstances, glucose transporter 2 will take the glucose into β-cells and lead to catabolism of glucose. When type 2 diabetes happens, β-cells do not function as they normally do. Conventionally scientists thought that the dysfunction is related to the death of β-cells, while recent evidence supports that the dysfunction is the result of complicated interactions between molecular pathways and environmental influence [4].

2.2. Current Treatment of type 2 diabetes

Due to the metabolic nature of type 2 diabetes, non-pharmacological treatment including nutritional control and physical exercises is one of the major options in treatment. By adjusting nutrition taken in and exercises, the goal of activating cellular mechanisms can be achieved, which might help relieve the pressure of metabolic disorder. The treatment of type 2 diabetes mainly includes weight control by

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setting a certain diet and keeping a certain amount of physical exercises and nutrition control by setting the proper part each nutritional molecule takes [5].

Currently, there are some new approaches to the pharmacological treatment of type-2 diabetes besides the conventional ones. The conventional anti-diabetic agents mainly include insulin secretagogues, Biguanides, and insulin sensitizers. Different kinds of pharmacological agents have different targets. Insulin secretagogues including Sulfonylureas exert a more direct stimulation on islet β-cells by binding to sulfonylurea receptors of potassium channels that are dependent on ATP on the membrane of the cell; while Biguanides are effective in controlling blood glucose levels and increasing insulin sensitivity by reducing hepatic glucose output, increasing glucose uptake that is promoted by glucose, and stimulating the glucose conversion to glycogen in skeleton muscle. Besides, insulin sensitizers, also known as Peroxisome Proliferator-Activated Receptor agonists(PPARs) are another agent targeting the regulation of protein and carbohydrate metabolism. The three types of PPAR receptors follow the nomenclature as PPARα, PPARδ, and PPARγ, of which PPARγ is much more common in diabetes treatment as the drug glitazone. As the name suggests, insulin sensitizers work by increasing the sensitivity of the cells to insulin. Its other functions such as to decrease systemic fatty acid production and uptake benefit in suppression of type 2 diabetes as well [6].

As drug development research is further conducted, new therapeutic agents were proposed for application. The four well-known novel agents are alpha-glucosidase inhibitor (AGI inhibitors), amylin agonists, incretin mimics, and SGLT2 antagonists or inhibitors [6]. Targeting glucosidase, molecules inhibiting the process of the polysaccharides converting to monosaccharides and thus carbohydrate absorption, the AGI inhibitors are quite effective for tackling postprandial hyperglycemia [7]. Apart from that, Amylin analogs help the treatment by delaying the emptying process in the stomach and suppressing glucagon secretion. The necessity of using chemical analogs of amylin is due to the nature of amylin as an insoluble protein [6]. The third novel agent is incretin mimics, specifically Glucagon-like peptide-1 agonists (GLP-1 agonists) and Dipeptidyl peptidase-IV (DPP-IV). This direction of treatment is based on the effectiveness of GLP-1 and glucose-independent polypeptide (GIP) to protect β-cells. Last but not least, researchers have also proved that sodium-glucose co-transporter could be harnessed as a drug target. The approach on targeting on the transporter molecule focuses on preventing the reabsorption of glucose and promoting the excretion of glucose in urine [6].

Besides, there are other treatments as part of the systemic type 2 diabetes treatment with roles that cannot be ignored. One of them is anti-inflammatory treatment, which is necessary as the immune system of a type 2 diabetes patient could undergo various changes. Thus, anti-inflammatory drugs like Salicylates and interleukin-1 antagonists are also commonly used [7].

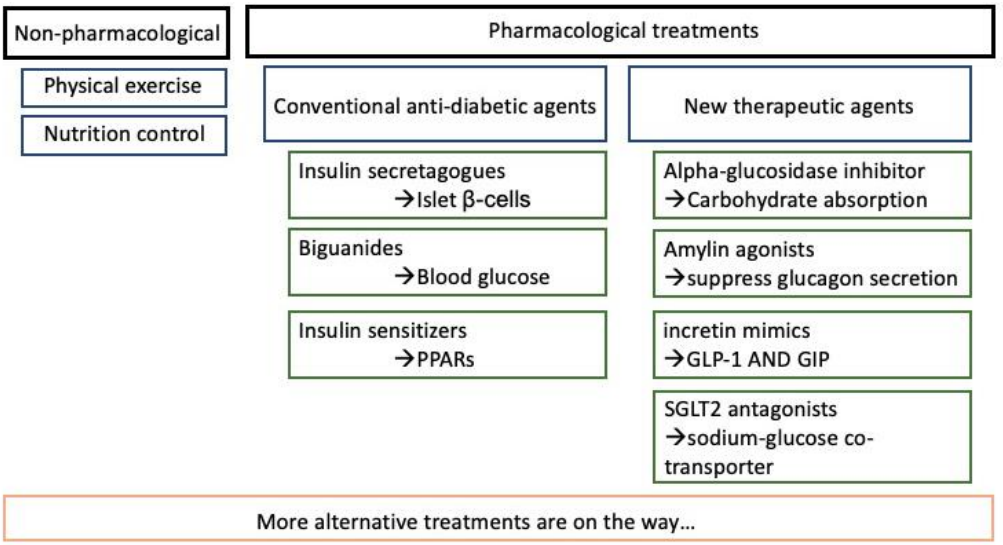

Figure 2. Current treatments for type 2 diabetes

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3. Genetic differences of different races/ethnicity

3.1. Genetic patterns in East-Asian group

Thanks to the genome-wide association study, it is now possible to view the differences in pathology between different racial groups of patients from a genetic perspective. With data obtained from previous literature, differences in susceptible loci of the disease across different groups were identified. The differences in the loci indicate a difference in susceptible pathological mechanisms, which has the potential to benefit the development of future type 2 diabetes treatment.

The susceptible loci in the East Asian population are mainly related to the dysfunction of certain agents in the insulin secretion mechanism. For example, the PAX 4 gene encodes a transcription factor, without which the development of human pancreatic endocrine cells would be altered thus leading to a higher risk of getting type 2 diabetes [8]. Other genetic loci related the the secretion process are CDKL1, KCNQ1, and GLIS3. CDKL1 protein inhibits CDK5 function, leading to defects in proinsulin conversion and glucose-stimulated insulin response [9]; The KCNQ1 gene encodes the voltage-gated potassium channel, which is involved in insulin secretion process with the role of activating Ca2+ channels [10]; and GLIS3 functions as a transcription factor in β-cell development [11]. It should be noted that CDKL1 and KCNQ1 are found in a study among the Han Chinese group of people, and therefore the susceptible loci should be considered specific to a subgroup in the East Asian population.

Among other identified loci there are also genes that encode proteins involved in other related mechanisms like inflammatory response and cell signal transduction. The genes correlated with inflammatory response are GPSM1 and RasGRP1. GPSM1 protein controls the pro-inflammatory pathway of macrophages [12], and RasGRP1 is associated with the promotion of the acute inflammatory response [13]. Chronic inflammation has been identified to be involved in the pathogenesis of insulin resistance and type 2 diabetes [14].

There are also several susceptible loci in the East Asian group that are in association with signal transduction. DUSP9 is the representative genetic locus. With the capacity to regulate insulin signaling, it can have a central role in many cases of type 2 diabetes pathogenesis [15]. Other identified susceptible loci are involved with nutritional intake. For instance, the leptin gene regulates food intake and body mass. In addition, SLC16A13 encodes for the lactate transporter protein, therefore impacting carbohydrate absorption.

Other identified loci cannot show a close relationship with the pathology of type 2 diabetes and are likely to be a product of experimental error.

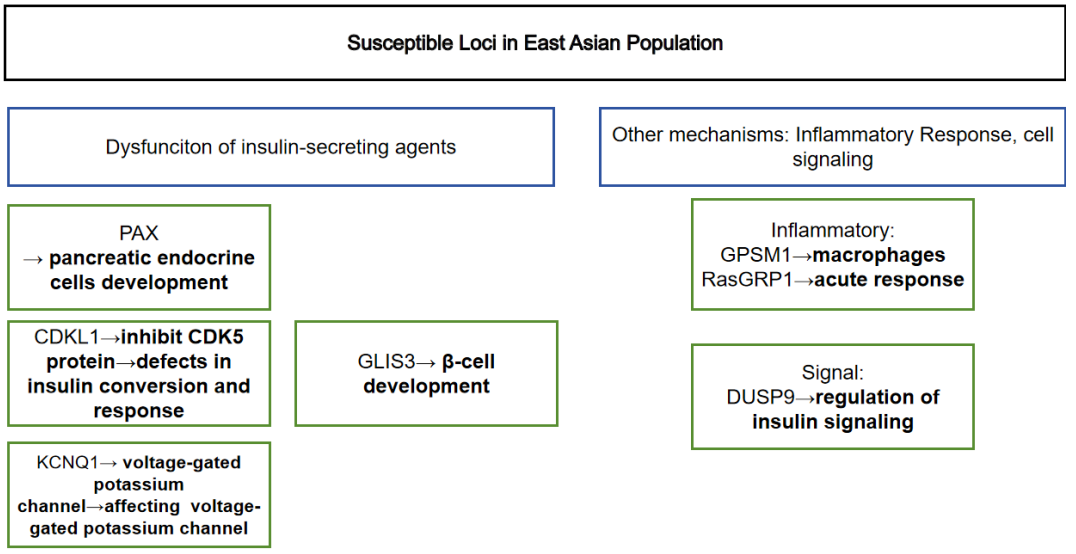

Figure 3. The categories of pathological mechanism and their corresponding discovered genetic loci in East Asian population

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3.2. Genetic Pattern in European Group

Based on analysis of the detected susceptible loci in European groups, there are mainly six directions of related pathological mechanism, which are cell progression correlated, gene expression correlated, insulin secretion connected, immune system connected, glucokinase correlated, insulin response and β -cell function correlated and those involved in signaling transduction. In terms of the proportion each category takes up, the most correlated mechanism is the disturbance of gene expression or signaling transduction.

The genes identified in the GWAS study engaged in cell development are RBMS1, ZFAND6, LAMA1, DUSP9, and ADAMTS9. Among the genes, some of them function diversely. For example, RBMS1 is responsible for various functions, including gene transcription, DNA replication, cell cycle progression, and cell apoptosis [16]; LAMA1 is implicated in cell adhesion, migration, and differentiation [17]. By contrast, other genes code for proteins that each have a single function related to the pathogenesis of type 2 diabetes. For instance, ZFAND6 plays the role of negative regulator in the progress of cell apoptosis [18]; DUSP9 impacts cell proliferation and cell differentiation by exerting negative regulation on mitogen-activated protein (MAP) kinase superfamily members [19].

Besides, there are also several genes found to be connected with the insulin secretion process. The representative gene is the CAMK1D gene, the gene coding for components of the calcium-regulated kinase cascade. It can be inferred from the close relationship between CAMK1D protein function and insulin secretion steps that the abnormalities with expression of this gene can affect the release of insulin by blocking the transportation of Ca2+ ions, and thus ATP required to initiate exocytosis of insulin-containing vesicles [20].

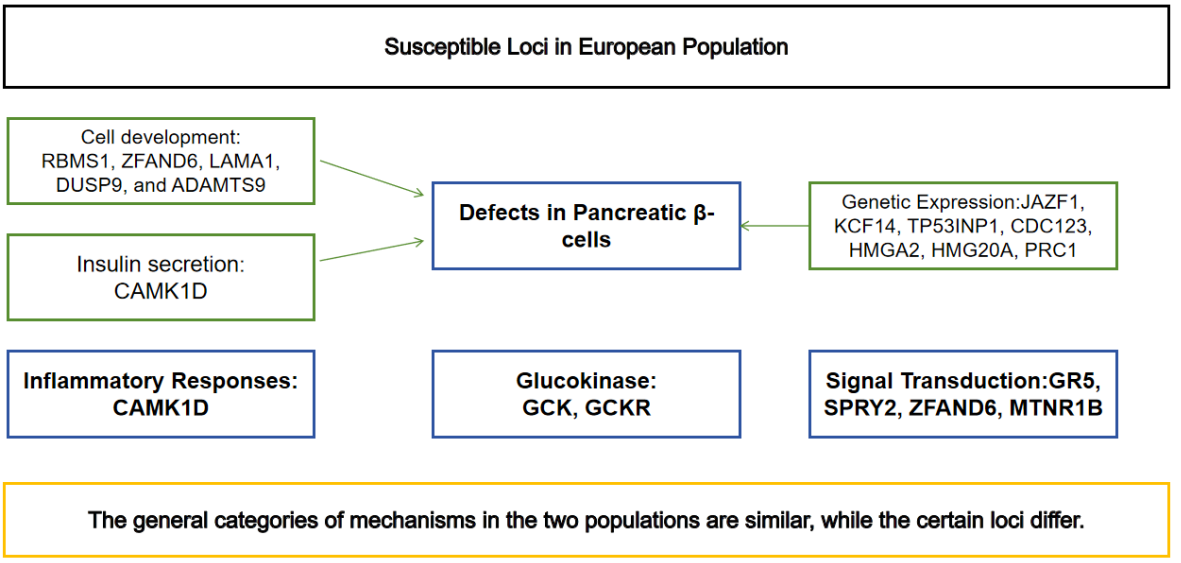

Figure 4. The categories of pathological mechanism and their corresponding discovered genetic loci in European population

CAMK1D is also capable of having an impact on neutrophil cell differentiation and activating neutrophil cell functions, which could be responsible for inflammatory responses in the human body. As an increasingly attractive topic in recent years, the association between inflammatory responses and type 2 diabetes has been researched. The conclusion suggested that the activation of immunity is highly correlated to the incidence of type 2 diabetes [21].

As generally expected, there have been genes discovered in the study related to Glucokinase, the enzyme catalyzing the conversion of glucose. Representative loci are GCKR and GCK: the former codes for Glucokinase regulator, and the latter codes for Glucokinase secretion. Because of Glucokinase's nature as an enzyme, its effect is likely to be more moderate than other glucose level controlling

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mechanisms. Therefore, it has been one scheme of novel diabetes drug development to agonize the function of this type of molecule [22, 23].

Last but not least, the passage will discuss the two wide categories: cellular signal transduction and genetic expression. Due to the intrigues and ubiquitousness of the two processes, a mutation in genes related will cause disturbance in normal metabolism. The susceptible loci for cell signaling are LGR5, SPRY2, ZFAND6, MTNR1B; and for genetic expression are JAZF1, KCF14, TP53INP1, CDC123, HMGA2, HMG20A, PRC1.

4. Discussion

For reasons of data availability, the scope of analysis in the passage is still relatively limited with the focus on East Asian and European groups. From comparing the results of GWAS studies it can be concluded that from the perspective of categories the two groups exhibit similar patterns: loci on pancreatic cell function, Glucokinase function, cellular signaling, immune system, genetic and epigenetic expression, and insulin secretion process. By taking a glance at South Asian and African American groups, we can identify that the general pattern works as well.

However, sharing a general pattern does not necessarily mean that the different groups are identical from a genetic perspective. In each direction the four studied groups show different susceptible loci, indicating a difference in the exact mechanism of diabetes incidence. For example, the proportion of cellular transduction genes in the European group is much larger than that in East Asians; while when it comes to immunity, the proportion is greater in East Asians. The differences between specific susceptible loci suggest the nuance between the pathology of the disease, offering inspiration on the focus of the treatment scheme and the target of drug development.

In recent years there has been some research conducted on pharmacogenetics, and the association between genetic information and treatment decision has aroused the interest of scientists. Nonetheless, the advance in pharmacogenetics mainly regards the prediction of physiological effects of medicine takers rather than optimizing therapies. To achieve the goal of a tailored medical scheme, the understanding about further information of the patients, especially genetics, will be necessary.

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