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Selected Gene Variants in Type 2 Diabetes in Sri Lankan Tamils and associated Physiological and Biochemical Parameters: Focusing on Diet, Physical Activity, Body Composition and Insulin Resistance

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ABSTRACT

T2DM is a global public health risk in diabetic populations. Previous studies suggest South Asians appear to be at particularly high risk for developing T2DM compared with Caucasian and other ethnic group. Particularly, South Asian T2DM population's variation studies are still relatively limited. Especially, South Asians' diet has many dietary imbalances, such as low intake of monounsaturated fatty acids, polyunsaturated fatty acids, and fiber and high intake of saturated fats, carbohydrates and trans-fatty acids. These dietary imbalances (consumption of energy-rich foods) are associated with insulin resistance and developing T2DM. Physical activity is generally protective against T2DM. South Asian were found to be less (up to 50–75% less physical activity) physically active than Europeans and level of physical activity inversely correlated with blood glucose and insulin levels. The environmental factors and the fundamental molecular mechanisms involved in the advance of T2DM remain poorly understood in South Asians. From previous literature reviews we have learned, that the genetic variants may interact with environmental factors such as physical activity and nutrient and contribute significantly in` the development of T2DM in different ethnic populations. Therefore, more research studies needed to identify a pattern of gene-environment interactions to predict preventive strategies for T2DM.In the future, we planned to do a study on T2DM patients based on a previous study where genetic associations were found with diet and physical activity and contribution in the development of T2DM.

Keywords

Type 2 Diabetes, Biochemical Parameters, Diet, Insulin Resistance.

Introduction

World Health Organization (WHO) reports, about 422 million people diagnosed with diabetes in 2014 and it will be the 7th leading cause of death in 2030. A recent trend shows that more than 60% of the world's diabetic population will be in Asia [1]. Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (T1DM) is caused due to insulin insufficiency because of lack of functional beta cells. The basis of type 2 diabetes (T2DM) is not fully understood, but most scientists and physicians agree that the key independent risk factors for T2DM rising the disease are: dietary factors, obesity, genetic predispositions, family history, ethnicity (a few ethnic groups have higher prevalence of diabetes), hypertension, physical inactivity, history of gestational diabetes, low birth weight, polycystic ovarian syndrome leading to insulin resistance, and finally, decline in insulin secretion due to advancing age [2].

T2DM is the commonest form of diabetes constituting 90% of the diabetic population [3]. In Asia, South Asian people have a greater risk of T2DM among the general population. Over the last two decades, the significant epidemic of diabetes of South Asian region was rapidly increased [4]. Sri Lanka is a middle income developing country in the South Asian region with a population of nearly 21 million. It is estimated that over 2 million people are suffering from diabetes in Sri Lanka [5]. T2DM is a higher prevalence (>90 %) than autoimmune T1DM in Sri Lanka [6].

T2DM is of multifactorial origin where the multi-genetic variants interact with various environmental factors. Moreover, understanding of genetic predisposition of T2DM is a major challenging task with many limitations. T2DM genetic risk has few genes of major effect [7,8]. Estimates of heritability for T2DM range from 50% to 80% and are much higher than for T1DM [9]. In general, estimates have shown that 30-70% of T2DM risk can be described by genetic factors [10]. Strong family heritability of T2DM and the result of shared environmental factors between close relatives help to elevate clinical awareness of individual patient's T2DM risk. It is also apparent, for instance from a current study in family's heritability, that T2DM-related intermediate and quantitative traits show significant heritability [11]. Family studies have predicted that the risk of T2DM among offspring is 3.5-fold and 6-fold higher for those with a single diabetic parent and two diabetic parents, respectively, compared with offspring without parental diabetes when compared to a population risk of 5-10% [12]. In addition, the high prevalence of type 2 diabetes in specific ethnic groups such as Pima Indians and Mexican Americans and the higher rate of T2DM incidence in monozygotic (~70%) versus dizygotic twins (20-30%), all these outcome support to the importance of genetic determinants for T2DM [13].

There are many possible methods to identify susceptibility genes contributing significantly to T2DM. Candidate gene studies and the free genome-wide studies are suitable methods to study genetic susceptibility to T2DM. The genome-wide studies include genome-wide linkage mapping (GWL) and genome-wide association (GWA) studies. Researchers predicted the application of GWL technique for genetic analysis of the common form of T2DM is unsatisfactory [14]. Since 2007, genome-wide association studies (GWAS) have identified [15]. In order to that over last few years, researchers start to use the technique of GWA study for variant analysis on T2DM. Prediction of T2DM genes through genome-wide association (GWA) studies using high-density Single nucleotide polymorphisms (SNPs). Most of the genetic T2DM variants are noncoding variants, and therefore their functional regions are challenging to investigate. Many of the variants identified to date regulate insulin secretion and not insulin action in insulin-sensitive tissues [16]. From the identified T2DM variants, more than 40 loci have been associated with T2DM-related traits, such as fasting proinsulin, insulin, glucose, HOMA index and pancreatic β cell function [15,17-19]. The beginning of most recent SNP variation studies has predicted over 75 susceptibility genes that contribute to T2DM risk on different T2DM ethnic's populations [20].

Most of the GWA studies have been performed in European populations, and then recent T2DM genetic variation studies are relevant to all ethnic T2DM populations, South Asian, East Asian and African origin [21-27]. Relatively limited GWA studies carried out in T2DM South Asian population. Recently GWS studies targeting on compare of T2DM variation relationship between European populations and South Asian populations. For instance, compared to European populations, South Asians be likely to be diagnosed with diabetes earlier, with a lower BMI and has a more rapid decline in glycaemic control over time [4]. Sri Lankan ethnics specific diabetes studies indicate that the Sri Lankan Tamil ethnicity has the highest occurrence of diabetes-related with Sri Lankan Moor and Indian Tamil ethnic group [28].

Interestingly, similar SNP variation studies at 37 T2DM-risk loci was carried out for comparing European and South Asian, Sri Lankan T2DM ethnicity variation [29]. However, no SNP variation studies have been carried out in the Sri Lankan Tamils.

T2DM is a complex disease that results from the contribution of many genes, environmental factors and the interactions among these genes and environmental factors. The interactions between multiple genes and environmental factors such as diet and physical activity may play an important role of T2DM. There is evidence behind the role of gene-diet interactions (nutrigenomics) and gene-physical activity on T2DM [30-33]. Nutrigenomics is a study of the importance of gene variants, nutrients, nutrient interactions and dietary patterns on gene expression. In other words, nutrients affect the expression of genetic information and genetic composition affects how nutrients are metabolized. Epidemiological studies have shown that diets high in fat (especially saturated fat), low in fiber, and rich in carbohydrates with a high glycemic index may increase the risk of T2DM, and that diets rich in whole grain foods reduce the risk of T2DM. A study demonstrates that both amount of fat and quality influence insulin sensitivity. Furthermore, the basic mechanisms by which different nutrients may be involved in the pathogenesis of T2DM are poorly understood. Our understanding of Nutrigenomics is commonly targeted on dietary patterns according to genetic variations, the role of gene-nutrient interactions, gene-diet-phenotype interactions (homeostasis model assessment (HOMA) index or plasma insulin level), epigenetic alterations, RNA and miRNA alteration, protein expression and metabolic changes caused by nutrients. Moreover, potential epidemiological studies strongly suggest an association between elevated levels of physical activity and a decreased risk of T2DM [30]. Furthermore, the greater understanding of potential nutrigenomics and gene-physical activity interactions may be relevant for T2DM prevention and treatment.

Studies on Nutrigenomics and gene-physical activity associated variants on T2DM studies in Sri Lankan Tamils in the Northern Province have not been attempted so far. Therefore, we planned to conduct a case-control study to investigate the role of the most important gene-diet and gene-physical activity associated selected SNP variants (PPARG, TCF7L2, IRS1, FTO, ADIPOQ, GCKR, SLC2A2 and HNF4A), which were reported in other ethnic groups on T2DM risk in the Sri Lankan Tamils from Northern Province using selected SNP scan.

Our selected T2DM risk variants and role of gene-environment interaction on T2DM are described below.

Peroxisome Proliferator-Activated Receptor Gamma (PPARG)

It is the main gene that is implicated in adipogenesis, insulin resistance, and T2DM. PPARG is a transcription factor activated

by fatty acids in adipose tissue and it is involved in adipogenesis and in the regulation of adipocyte gene expression and glucose metabolism. Interestingly, it is ligand –independent activation, a proline to alanine substitution (Pro12Ala, rs1801282) has been identified [34]. PPARG Ala12 polymorphism reduces the risk of T2DM and is positively associated with insulin sensitivity [35]. This polymorphism has been revealed to be associated with obesity [34]. Some studies indicate this particular Ala12 polymorphism may be more sensitive to unsaturated fat and less sensitive to total and saturated fat on glucose homeostasis compared to Pro12 polymorphism. Pro 12 Ala polymorphism which affords a defense against insulin resistance and diabetes to Caucasians, do not appear to protect Indians [34]. Many studies propose that physical activity altered the association of the Pro12Ala polymorphism with glucose homeostasis and the risk of T2DM [30,36,37].

Transcription factor 7-like 2 gene (TCF7L2)

It is a transcription factor, involved in the wnt-signaling pathway expressed in many tissues (including fat, liver and pancreatic islets of Langerhans). The wnt-signaling pathway is a type of signal transduction pathway, which has the role of regulation of gene transcription involving metabolic homeostasis (glucose homeostasis) and signal transduction influencing on insulin secretion [2]. Transcription factor of TCF7L2 is a member of the wnt-signaling pathway. TCF7L2 is one of the most important polygene predicted for T2DM [38]. The T2DM association of this gene has been simulated in a variety of studies in different ethnicities [39]. TCF7L2 is increased expression in the islets of the pancreas in T2DM, which in turn results in impaired glucose-stimulated insulin secretion [40]. The previous study demonstrated the of variant TCF7L2 rs12255372 identified G>T polymorphism has associated carbohydrate quality and quantity of the diet altered risk of T2DM and increased the level of insulin [41]. Moreover, other TCF7L2 variant rs12573128 (A>G polymorphism) has interaction with dietary fat intake to control body fat (abdominal fat) and glucose homeostasis-related traits in T2DM [32]. Previously studied TCF7L2 is common T2DM risk variant in South Asians different populations [24,26].

Fat Mass- and Obesity-associated Gene (FTO)

FTO is also known as alpha-ketoglutarate-dependent dioxygenase enzyme and encoded by FTO gene. It is involved in alkylated DNA and RNA repair. FTO gene is associated with Body Mass Index and obesity risk [42]. Studies on the effect of FTO rs9939609 variant modulates dietary patterns of T2DM which are Mediterranean Diet (MedDiet). Med-Diet is rich in folate intakes. Although the same study found, the statistically significant interaction between the FTO polymorphism and the aggregate score and folate intake in determining fasting plasma glucose concentrations [43]. FTO-rs9939609 variant indicates Mediterranean diet and when adherence to the Mediterranean diet was low, A>T polymorphism of rs9939609 showed a higher T2DM risk. In contrast, when adherence to the Mediterranean diet was high, these associations disappeared [43]. Moreover, FTO rs9939609 (AA genotype) variant is associated with increased fat, decreased fiber consumption, several measures of adiposity (weight, BMI-SD, mid-upper arm circumference, tricipital skinfold thicknesses), total cholesterol, triglyceride, and LDL cholesterol levels in T2DM patients [44,45]. A study indicates, physical activity has decreased the effect of FTO variant rs1421085 (increased physical activity has decreased body mass index (BMI) and the body adiposity index (BAI)) on adiposity by 36–75% in 6 ethnic populations (South Asian, East Asian, European, African, Latin American, Native North American) [33].

Glucokinase Regulatory Protein (GCKR)

GCKR is needed to regulate Glucokinase (GCK) activity. GCK is a glucose sensor, has a key role in controlling blood glucose homeostasis in the liver and in pancreatic beta-cells. It is involved in signal transduction, glucose transport, sensing and associated with fasting glucose, fasting insulin and HOMA-IR [2]. GCKR gene polymorphism was firstly recognized to be associated with triglycerides levels by GWAS and the alleles which increasing triglycerides levels were found to lower the glucose, insulin levels and insulin resistance by different association studies [46,47]. Most studies show, higher intake of whole-grain foods were associated with increases in insulin sensitivity and reduce the risk of diabetes [48]. A study indicates, that dietary whole grain intake has interaction with GCKR variant rs780094 C > T polymorphism [49]. The subjects with the C polymorphism of rs780094, larger whole grain intake was associated with the smaller reduction of fasting insulin concentrations when compared to the presence of the no risk allele (T polymorphism) [49].

Insulin Receptor Substrate 1 (IRS1)

IRS1 plays an important role in the insulin-stimulated signal transduction pathway [50] and it has associated with insulin resistance, hyperinsulinemia and the risk of T2DM [51]. There is one study indicates IRS1 has reduced adiposity and impaired metabolic profile (e.g. visceral to subcutaneous fat ratio, IR, dyslipidemia, CVD (Cardiovascular disease), adiponectin levels) [2]. Interestingly, there is nutrigenomics relationship on T2DM that is IRS1 rs2943641 T polymorphism associate with higher circulating 25-hydroxtvitamin-D (25 (OH) D showed a lower risk of IR and T2DM compared to carriers of the major allele rs2943641 C polymorphism in women [52]. Particularly, the variant IRS1 rs2943641 has significant interaction with physical activity on T2DM (lower the risk of T2DM) [30].

Adiponectin (ADIPOQ)

Adiponectin is a protein hormone which is secreted from adipose tissue into the blood. It is encoded by the ADIPOQ gene and involving in glucose regulation and fatty acid oxidation. Adiponectin is a strong candidate for insulin sensitivity, obesity, and risk of T2DM. T allele is in present in normal adiponectin. The previous study indicates polymorphism of adiponectin SNP276 G > T and SNP45 G > T has been associated with T2DM in Japanese individuals [53] and SNP276 G > T has been reported to be associated with T2DM in Taiwanese patients [54] and the G allele of both SNPs has been not associated with obese diabetic in Korean men [55]. Therefore, the difference in variants of this polymorphism may be the result of different environmental

factors, such as diet. SNP276 G>T polymorphism of adiponectin in Korean T2DM patients indicating the level of plasma fasting blood glucose, HbA1C (Hemoglobin A1c), and HDL (High-density lipoprotein) cholesterol concentrations depends on dietary carbohydrate intake [56]. Furthermore, high dietary intake of polyunsaturated fatty acids (PUFAs) indicated they have adiponectin SNP45 G > T polymorphism in order to reduce the risk of T2DM [57].

Hepatocyte Nuclear Factor 4 α (HNF4)

HNF4 is a transcription factor. It is important for expression of pancreatic β-Cell genes and implicated in glucose metabolism and nutrient-induced insulin secretion. A variant of HNF4 rs4812829 showed a strong association to an increased susceptibility to T2DM in South Asia [22]. Another study indicates HNF4 rs4812829 variant has been associated with elevated hepatic glucose production, defective pancreatic β-cell function and impaired insulin secretion [2]. Interaction of T2DM variant HNF4 has interaction with physical activity [30]. The associations of variants HNF4A rs1885088 (G>A) with glucose tolerance and HNF4A rs745975 (C>T) with insulin secretion are modulated by physical activity.

Solute Carrier Family 2 (facilitated glucose transporter-GLUT2), member 2 (SLC2A2)

SLC2A2 is a glucose carrier protein and facilitative glucose transporter that affects insulin secretion by regulating the entry of glucose into the pancreatic β–cell. All four SNPs of SLC2A2 (promoter SNPs rs5393 and rs5394 and exon SNPs rs5400 and rs5404) are associated with T2DM [58]. Increased physical activity removed the effect of the risk variants such as SLC2A2 rs5393 (G/A), SLC2A2 rs5394 (C/T), and SLC2A2 rs5400 (G/A) on the risk of T2DM and has the ability to improve insulin sensitivity in the T2DM [31].

In this background of our proposed study of selected T2DM risk variants' (9 SNPs) gene-interaction evaluation finding will be supported to unravel the gene-environment interaction of T2DM susceptibility risk in Sri Lankan Tamils in Northern province. In addition, unraveling these genetic-environmental variation study will help to understand the pathophysiology of T2DM possibly leading to the identification of functional targets for diabetes and to develop a new pharmacological treatments in Sri Lankan ethnicity.

Table 1 shows T2DM risk variants which are associated with dietary factors from previous studied.

The main goal of our future project is to identify genes and knowing the biological pathways that respond to dietary change and physical activity to alter glucose and lipid metabolism and to develop dietary and physical strategies for prevention of T2DM.

Discussion

In our future study, T2DM-diagnosed Sri Lankan Northern Tamil patients will be recruited at the diabetic clinic teaching hospitals, Sri Lanka. T2DM patients will be diagnosed and confirmed according to the documented clinical American diabetes association diagnosis criteria of T2DM from hospital clinical records. Inclusion and Exclusion criteria and ethics will be considered when choosing the patients.

Considering study methods, the amount of physical activity will be assessed by International Physical Activity Questionnaires (IPAQ) [62], Dietary intake will be measured with a Diet history questionnaire, Basic anthropometric measurements such as height, weight and waist circumference of all T2DM subjects will be taken according to the standard procedures using standard equipments, Fasting insulin level and Fasting glucose level will be analyzed using automated biochemical analyzer, Insulin resistance will be measured using HOMA-IR calculator, HbA1c will be measured using Bio-Rad HbA1c analyzer, Measurement of lipid profile

Table 1: Gene-dietary pattern interactions in the cause of T2DM.

Gene	Region	SNP	Allele Change	T2DM-Related Traits	Dietary Factors	References
PPARG	3p25.2	rs1801282	C > G	HOMA-IR index	PUFA intake	[35]
TCF7L2	10q25.3	rs12573128	A > G	HOMA-IR index Oral glucose tolerance test	Fat intake	[32]
		rs12255372	G > T	T2DM risk	Carbohydrate intake	[40]
FTO	16q12.2	rs9939609	A > T	T2DM risk	Adherence to Mediterranean Diet	[43]
IRS1	2q36.3	rs2943641	C > T	HOMA-IR index	Vitamin D	[52]
GCKR	2p23	rs780094	C > T	Fasting insulin levels	Whole-grain intake	[49]
ADIPOQ	3q27	SNP276 G > T	G > T	Fasting glucose levels	Carbohydrate intake	
		SNP45 G > T	G > T	T2DM lower risk	PUFA intake	[57]
FABP2	4q28.31	A l a 5 4 T h r polymorphism	G > A	HOMA-IR index	SFA intake	[59]
CAV2	7q31.1	rs2270188	C > T	T2DM risk	SFA intake	[60]
PLIN	15q26.1	11482 G > A	G > A	HOMA-IR index	SFA fat and carbohydrates intake	[61]
		14995 A > T	A > T	HOMA-IR index	SFA fat and carbohydrates intake	[61]

will be analyzed by automated biochemical analyzer, SNPs will be genotyped using Applied Biosystems TaqMan SNP genotyping assay and Statistical analysis will be followed as key methods in future.

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