Genes Associated With Free Fatty Acid Levels and Dyslipidemia in Type 2 Diabetes Patients

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Abstract

Type 2 diabetes mellitus (T2D) is a complex metabolic disorder associated with disturbances not only in carbohydrates and proteins but also with impairment of lipid metabolism. It is largely influenced by complex interactions of environmental and genetic factors, or both. High prevalence and increasing number of patients with T2D in the world, represent constant challenge for better elucidation of pathophysiological processes that lead to development of disease. In this paper, I have tried to summarize the results of my research and new findings from recent analyses of genome-wide association studies (GWAS) which helped us in the identification of common and rare genetic variants associated with insulin resistance (IR), dyslipidemia, Metabolic syndrome (MetS) and Type 2 diabetes. Many variants of certain genes are directly involved in glucose metabolism; however, functional and additional studies are suggested in order to be able to understand the contribution of other variants associated with impaired lipid and lipoprotein metabolism. New technologies such as metabolomics, proteomics, genomics, a more recently, lipidomics clearly point out directions in identification and detection of good/best biological gene candidates involved in fatty acid and lipoprotein metabolism. Mutational sequencing for these genes i.e. genetic regions associated with T2D, obesity, dyslipidemia and IR, could serve as a protective measure for not only insulin sensitivity but also, insulin secretion, obesity and other glycemic traits.

Keywords

Gene variation • Free fatty acid • Dyslipidemia • Type 2 diabetes

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A. Badnjevic et al. (eds.), *CMBEBIH 2019*, IFMBE Proceedings 73,
https://doi.org/10.1007/978-3-030-17971-7_89

1 Introduction

Type 2 *Diabetes mellitus* (T2D) is a complex and chronic metabolic disease characterized by defective production or action of insulin and high glucose and lipid levels in the blood. As a result of alterations in lipid metabolic pathways, circulating plasma free fatty acids (FFAs) and lipoproteins concentration rises. It is well known that the long chain fatty acids (polyunsaturated fatty acid, PUFA), very important biomolecules and main constituents of cell membrane play a key role in the cell function and therefore regulate the β-cells functionally, with effects on insulin sensitivity and secretion. Elevated concentration of FFAs (especially saturated fatty acids) in plasma is associated with impaired insulin sensitivity and secretion, as well as glucose intolerance. Chronic elevation of FFAs can lead to β-cell dysfunction, which in turn lead ultimately leads to hyperglycemia [1–3].

A disturbance in the regulation of free fatty acid metabolism is a key event responsible for insulin resistance (IR) and Type 2 diabetes. According to the glucose-fatty acid cycle of Randle et al., preferential oxidation of free fatty acids over glucose plays a major role in insulin sensitivity and leads to metabolic disturbances of diabetes [4]. However, other underlying mechanisms are now being described in order to explain the molecular basis of insulin resistance. Finally, modulation of transcription factors by free fatty acids through their binding to peroxisome proliferator-activated receptors and nuclear receptors could also contribute to impaired glucose and insulin metabolisms [5–10].

1.1 Genetics of Type 2 Diabetes

Type 2 diabetes is heterogeneous disorder and it is caused by more than 500 genes; but still, it is not known all genes that are responsible for T2D. This metabolic disease is caused not only by single gene, such as MODY type of diabetes, it the case of diabetes when mutations happen on hepatocyte

Table 1 Genes that is associated with risk of T2D

Gene/nearest gene	Traits	Ref.
TCF7L2	Impaired insulin secretion, FG, T2D, HOMA-B	[12, 37]
IRS1	Insulin production, IR, FG, dyslipidemia	[11, 16, 37]
IGF2	T2D	[12, 21, 32]
KNCJ11	Hyperinsulinemia, T2D, increased glucagon level	[13, 25]
HNF4A	Hyperinsulinemia, T2D	[23, 28]
GCKR	FG, T2D	[12, 17]
SLC2A2	T2D, decreased HOMA-B	[28, 37]
FADS1/2	FG, decreased HOMA-B	[14, 24, 28]
CETP	FG, HOMA-IR, T2D	[10, 30]

FG—fasting glucose, HOMA-B—homeostatic model assessment for B-cell, HOMA-IR—homeostatic model assessment for IR

nuclear factor (*HNF1A*) and/or on glucokinase (*GCK*). It is important to mention that MODY is sometimes misdiagnosed as type 2 diabetes. Nowadays, it is known that T2D represent strong heritable and polygenic disease which caused by interaction of many various gene and, also some environmental factors (lifestyle, diet, etc.). Mechanisms and processes which underlying and involved in these interactions is still poorly understood and completely elucidate [11–14]. Some of genes that are known that are T2D related genes are *CAPN10* (CAPN10 encodes a cysteine protease) and *TCF7L2*. It has a role in intracellular remodeling, post-receptor signaling and in some other intracellular functions. Also, there are more specific candidate gene studies which focus on genes that are involved in glucose metabolism, insulin secretion, post-receptor signaling and lipid metabolism. According to the recent studies in Table 1 presented some of new discovered genes that are linked with the T2D development [15–17].

1.2 Genetics of Fatty Acids

Fatty acids (FA) as a lipid represent biomolecules that are having very important roles in human physiology: (i) there are a source of energy and main structural components for cell membranes; (ii) and signal molecules, involved in gene expression of lipids, carbohydrates and proteins. Also, there are influenced on cell growth and differentiation. Specific fatty acid especially free non-esterified fatty acids (NEFA) affect on gene expression is influenced by their different structure and metabolism and interact with genome through several mechanisms. Various types of FFA regulate the activities of some transcription factors such as *PPAR, LXR, HNF4* and *SREBP*. They are having a direct impact on gene transcription by binding to some transcription factor, as well on some specific enzyme mediated pathways (such as cyclooxygenase, lipoxygenase, protein kinase C, or sphingomyelinase signal transduction pathways). Involving in changes of metabolic processes in membrane lipid composition, fatty acids affect to G-protein receptors or tyrosine kinase-linked receptors signaling. Genes that directly influence on fat storage are *GRB14, PPARG, HMGA1, FTO, LPIN1,* etc [18–21].

1.3 Fatty Acids and Type 2 Diabetes

Free fatty acids play important roles in skeletal muscles, liver, heart and pancreas. In diabetes, lipid and carbohydrate metabolism are regulated improperly by insulin. It is important to mention that free fatty acids provide energy and they also have role as signaling molecules in many processes including insulin secretion. This mechanism is not clear yet but they compete with glucose for energy source and oxidation [4]. In conditions with increased free fatty acids concentration in body it will be lead to insulin resistance. Also, the mechanisms by which free fatty acids make some changes in glucose transport or some phosphorylation activity are still not known [22–28]. Association of certain genes and fatty acids with glucose level and insulin sensitivity in T2D was presented in Table 2.

1.4 Type 2 Diabetes and Dyslipidemia

T2D patients usually have disturbance in lipid and lipoprotein concentrations and they are developing a dyslipidemia (high total cholesterol (TC), high triglycerides (TG), elevated low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL). The cause of dyslipidemia may be genetic, environmental, or both. Patients with diabetic dyslipidemia have increased expression of genes such

Table 2 Genes associated with FFA levels and T2D

Gene/nearest gene	Traits	Ref.
GRB14	T2D, decreased, IS, increased HOMA-B	[12, 28]
PPARγ	T2D	[12, 20, 30]
HMGA1	T2D	[13, 18, 32]
CAPN10	T2D	[16]
LXR	LDL, VLDL	[14, 22, 31]
HNF4	T2D, decreased β-cell function	[14, 23, 28]
SREBP	T2D, FG, FI	[14, 22, 31, 36]
FADS1/2	T2D, FG	[14, 24, 28, 39]
LPIN1	T2D	[39]
ALG14	T2D	[28]
LPGAT1	T2D	[28]
GCK	FG, glycemic control, T2D, HOMA-B	[16, 17, 24]
HNF1AN	T2D, reduced β-cell function	[21, 28]
THADA	T2D	[15, 20, 37]
FTO	BMI, T2D, dyslipidemia	[12, 23]

BMI—body mass index, LDL—low density lipoprotein, VLDL—very low density lipoprotein, FI—fasting insulin

Table 3 Genes associated with dyslipidemia in T2D

Gene/nearest gene	Traits	Ref.
LDLR	Total cholesterol	[14, 20]
PCSK9	FG, total cholesterol	[17, 29]
FADS1/2	TG, HDL, LDL	[14, 24, 36, 39]
MTHFR	FG, reduced β-cell function	[23, 28]
CETP	TG, FI	[12, 14, 36]
GCKR	TG, VLDL, HDL, LDL	[14, 24]
FABP2	T2D, HDL, LDL	[10, 23]
FTO	T2D, dyslipidemia	[12, 23]

TG—triglyceride, HDL—high density lipoprotein

as IL10 and IFNA genes. T2D is characterized with changes in metabolism in lipids as well as with insulin deficiency and dysfunction of β-cells. Dyslipidemia i.e. impaired lipid metabolism is involved in glycemic control and plasma lipid elevation. It is known that diabetic patients with dyslipidemia have higher risk for macro- and microvascular complications and atherosclerosis. Also, T2D patients with dyslipidemia have high mortality level of cardiovascular diseases which are caused by metabolic abnormality and by changes in serum lipids and lipoproteins [29–37]. Genes FADS1 and FADS2 linked with polygenic dyslipidemia which contributes cumulative effects of multiple common variants of certain gene or nearest gene (showed in Table 3).

2 Materials and Methods

In this paper, were presented the summarized results of my research as well as the results of other authors, obtained from previous and newly studies of GWAS analyses. These findings provide the most comprehensive view to data of the genetic contribution to type 2 diabetes with respect to free fatty acids and dyslipidemia association with common and rare variants of certain or nearest gene/s.

New technologies such as metabolomics, proteomics, genomics, a more recently, lipidomics bring a good opportunity to development of new trends and clear directions in

identification and detection of good biological gene candidates involved in fatty acid and lipoprotein metabolisms for their association with dyslipidemia in T2D. "*Omics*" technologies uses modern analytical methods and techniques in the analysis the large number of metabolites in different biological samples in order to understanding of cellular processes and pathophysiological mechanisms of T2D and, also, the development of new pharmacological target in therapy. Application techniques include: GC-MS, LC-MS/MS, flow injection analysis, NMR, MRS, ESR, etc.

3 Results

The results of recent genetic test and identification studies, as well data from three large scale of genome-wide association studies: DIAbetes Genetic Replication And Meta-analysis (DIAGRAM), the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), and Meta-analysis using canonical correlation analysis (Meta-CCA) for glycemic and other traits were presented. The characteristics of these studies are summarized in Tables 1, 2 and 3.

4 Discussion

The main objectives of the present work are summarize results of my research and new findings from recent analyses of genome-wide association studies (GWAS) which were helped to us to the identification of common are rare genetic variants of associated with insulin resistance (IR), dyslipidemia, Metabolic syndrome (MetS) and Type 2 diabetes. Many variants of certain genes e.g. PPARγ, LXR, HNF4, GRB, FTO, SLC27A4 and SREBP, are directly involved in glucose metabolism (Table 1).

However, functional and additional studies are suggested the contribution of the other variants influenced by impaired lipid and lipoproteins metabolism as consequence of elevated free fatty acids (FFA). Some specific gene such as *LPIN1, ALG14, FADS1/2, LPGAT1, GCKR, HNF1AN*, and *PDK2L1* variations were identified which affected de novo lipogenesis (synthesis and metabolism of fatty acid as well cellular signaling and metabolic pathways) and were significantly associated with concentrations of C16:0, C18:0, C16:1 and C18:1, as a major saturated and unsaturated fatty acids (Table 2). In addition, it is shown that *FADS1* variant is associated with T2D markers and other triats. Importantly, here was reported for the first-time our findings of association of *FADS1* polymorphism rs174550 with levels of selected (different chain length and degree of saturation) of free fatty acids: lower levels of C14:0 and C18:0, and positive association with C18:1 [39]. Also, in the same study, *FADS1* variant was correlated with markers of dyslipidemia (Table 3). Our previous study with *LPIN1* suggested the association of this gene with C14:0, C14:1, and C20:3 [38]. Finally, here was reported for the first time analysis of *FADS1* polymorphism rs174550 and their association with FFAs in the sample of BH population.

5 Conclusions

Metabolome and GWASs analysis has allowed identification and detection of numerous genetic variants that associate with T2D and dyslipidemia. Also, they was shown which polymorphism of certain genes associated with specific FFAs in T2D patients with dyslipidemia. Importantly, previous and future findings from GWAS analysis demonstrated of links between genetic variants associated with lipids and T2D in order to applied in further identification as well for precise diagnose and individual therapy treatment of diseases such as dyslipidemia, MetS and Type 2 diabetes.

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