American Journal of Clinical Medicine Research, 2018, Vol. 6, No. 2, 24-34
Available online at http://pubs.sciepub.com/ajcmr/6/2/2

DOI:10.12691/ajcmr-6-2-2

A Review of Signaling Pathways and the Genetics Involved in the Development of Type 2 Diabetes: Investigating the Possibility of a Vaccine and Therapeutic Interventions to Prevent Diabetes

Sabitha Vadakedath[1], Venkataramana Kandi[2,*], Venkata Bharat Kumar Pinnelli[3], Vikram Godishala[4]

[1]Department of Clinical Biochemistry, Chalmeda Anandrao Institute of Medical Sciences, Karimnagar, Telangana, India
[2]Department of Clinical Microbiology, Prathima Institute of Medical Sciences, Karimnagar, Telangana, India
[3]Department of Biochemistry, Vydehi Institute of Medical Sciences and Research Centre, #82, EPIP Area, Nallurhalli, Whitefield, Bangalore – 560066, Karnataka, India
[4]Department of Biotechnology, Vaagdevi Degree and PG College, Warangal, Telangana, India
*Corresponding author: ramana_20021@rediffmail.com

Abstract Diabetes mellitus is a chronic debilitating non-communicable disease prevalent throughout the world. There are two different types of diabetes; the type 1 diabetes usually presents in children and young adults, and the type 2 diabetes, a most frequent age-related condition usually noted among the adults aged over 40 years. The type 1 diabetes results due to an immunological reaction against insulin and the insulin secreting cells. The type 2 diabetes can occur due to various factors that include genetic predisposition, lifestyle disorders, insulin resistance, and lack of adequate insulin production. Since lifestyle management is an adjustable risk factor for diabetes, may people with genetic predisposition could delay the onset of clinical diabetes. Further there is an increasing need to understand the genetics behind the signaling pathways involved in the development of type 2 diabetes, which could pave the way for formulating, and implementing therapeutic, and preventive strategies.

Keywords: *diabetes mellitus, non-communicable disease, type 1 diabetes, type 2 diabetes, genetic predisposition, insulin resistance, signaling pathways*

Cite This Article: Sabitha Vadakedath, Venkataramana Kandi, Venkata Bharat Kumar Pinnelli, and Vikram Godishala, "A Review of Signaling Pathways and the Genetics Involved in the Development of Type 2 Diabetes: Investigating the Possibility of a Vaccine and Therapeutic Interventions to Prevent Diabetes." *American Journal of Clinical Medicine Research*, vol. 6, no. 2 (2018): 24-34. doi: 10.12691/ajcmr-6-2-2.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major public health problem worldwide. The incidence of this disease increases with age, physical inactivity, unhealthy diet, obesity, genetic predisposition, impaired glucose tolerance; and the prevalence rates of diabetes is increasing in children [1,2]. There are many genes contributing to this disease, out of which 36 genes account for 10% of overall genetic component of the disease [3]. Previous studies indicate that there could be a 3.5-fold risk of acquiring the disease if only one of the parent is diabetic, and a 6-fold increased risk if both parents are diabetic. Thus, genetic factors appear to contribute up to 30-70% cases of T2DM [4,5]. The inheritance pattern of T2DM is polygenic and heterogenous, hence multiple genes are involved, and different combination of genes play a role in development of T2DM.

2. The Signaling Pathways Involved in the Development of Diabetes

There are two approaches available for genetic factor analysis which include the candidate gene analysis and the linkage analysis. The candidate gene analysis examines a specific gene with a possible role of it in the disease progression. The major disadvantage of this approach is that it assumes a gene involvement in disease progression before testing. This approach helped in identification of numerous genes, but only fraction of them have been further confirmed in follow-up studies [7,8,9,10,11]. The linkage analysis identifies various genes through their genomic position, and hence this type of gene analysis helps in monogenic disorders (Maturity Onset Diabetes of Young (MODY), neonatal diabetes and rare forms of childhood obesity) [12,13,14]. The new approach based on single nucleotide polymorphism for genetic studies

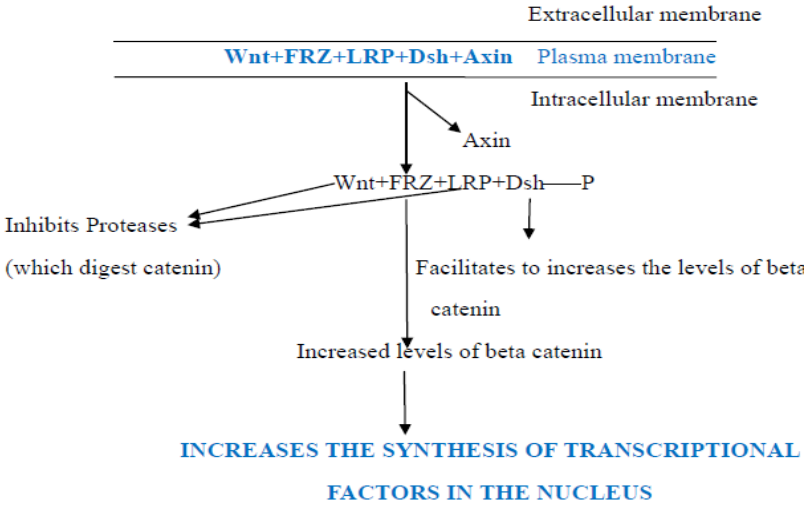
was found successful to detect genetic variations with modest phenotypic effects [15].

3. Wnt Signaling Pathways (Wingless-related Integration Site)

These are a group of signal transduction pathways made of proteins that pass signals from outside of a cell through cell surface receptors into the cell. These proteins attach to the receptors on plasma membrane and activate different Wnt pathways via paracrine (cell–cell communication) and autocrine (same–cell communication) mode of communications [16,17]. This pathway plays an important role in cell proliferation, migration, cell fate specifications, and body axis patterning [18].

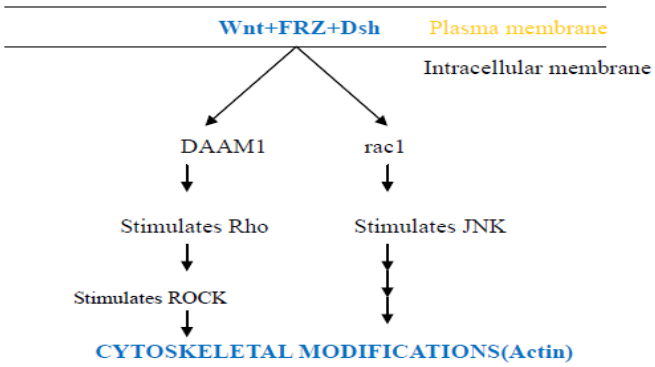
Wnt proteins are lipid modified glycoproteins which perform lipid modifications predominantly by palmitolyation (addition of palmitic acid) of cysteine residues [19]. There are three Wnt signaling pathways which include the Canonical Wnt pathway, Non-canonical planar cell polarity pathway, and the Non-canonical Wnt/Calcium pathway.

All the three Wnt pathways are activated by binding of Wnt protein ligand to a Frizzled family receptor, which passes the signal to Disheveled inside the cell. The clinical importance of this pathway lies in the fact that mutations may be responsible for a variety of diseases like breast and prostate cancer, glioblastoma (a type of brain cancer), and T2DM. The Wnt Canonical pathway acts via beta Catenin and regulates transcription of gene [20,21]. Non-canonical planar cell polarity pathway doesn't involve beta catenin, and LRP (Lipoprotein Receptor related protein) receptors. The Non-canonical Wnt/Calcium pathway also does not involve beta Catenin and helps in regulation of intra cellular calcium levels [22]. The flow charts depicting the canonical Wnt pathway, Non-canonical planar cell polarity pathway, and the Non-canonical Wnt/Calcium pathway are shown in Figure 1, Figure 2, and Figure 3 respectively.



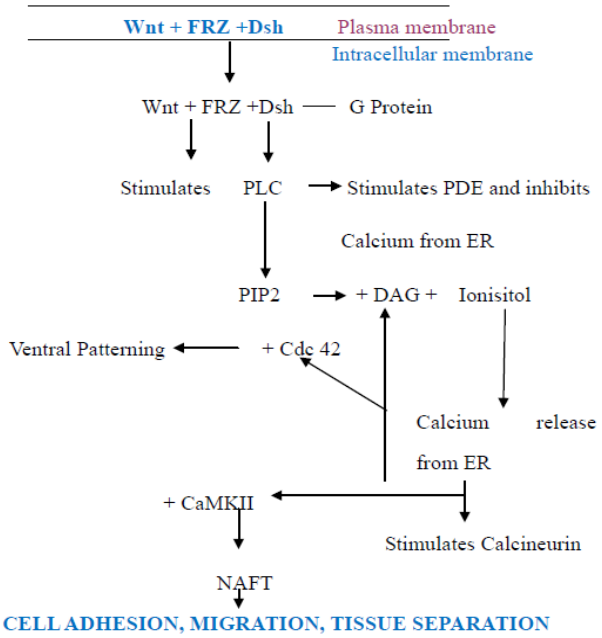
Wnt- Wingless-related integration site
LRP- Lipoprotein receptor related protein
FRZ- Frizzled related protein
Dsh- Dishevelled protein
P-Phosphorylation

Figure 1. Canonical Wnt pathway



Wnt- Wingless-related integration site
FRZ- Frizzled related protein
Dsh- Dishevelled protein
DAAM – Disheveled associated activator of morphogenesis
rac 1- Ras-related C3 botulinum toxin substrate 1
Rho- Small G-protein
JNK-Janus-N-Kinase
ROCK- Rho associated Kinase

Figure 2. Non-Canonical planar cell polarity pathway



LRP- Lipoprotein receptor related protein
FRZ- Frizzled related protein
Dsh- Dishevelled protein
PLC-Phospholipase C
PDE-Phosphodiesterase
PIP-Phosphoinositol phosphate
ER-Endoplasmic reticulum
DAG-Diacyl glycerol
Cdc-Cyclin-dependent kinase
CaMKII- calmodulin-dependent protein kinase
NAFT-Nuclear factor of activated T cells (transcription factor)

Figure 3. Non-Canonical Wnt/Calcium pathway

Canonical Wnt pathway increases the sensitivity of the cell to insulin, especially Wnt 10b protein increases the insulin sensitivity in skeletal muscle cells. This pathway increases the cells insulin sensitivity by increasing glucose uptake by the cells mediated by enhanced glucose transporters [23]. Over expression of Wnt 5b increases the susceptibility to type 2 diabetes because of its role in adipogenesis. Wnt signaling pathway also activates mitochondrial biogenesis, which increases the production of ROS (Reactive Oxygen Species), damages DNA, and leads to acute hepatic insulin resistance or injury-induced insulin resistance [24,25]. Mutation in LRP 5/6 leads to development of diabetes and obesity. Beta catenin / TCF, mutation in one of transcription factor regulated by Wnt signaling. TCF7L2 also increases the susceptibility to T2DM [26]. The canonical Wnt pathway is attenuated due to competition between Fork head box transcription factor subgroup O (FOXO) protein and T cell transcription factor (TCF) protein because of ageing together with T2DM [27].

This signaling is important in embryonic development including body axis patterning, cell fate specification, cell proliferation, and cell migration. The mutation of this pathway may lead to breast, prostate cancer, glioblastoma, and T2DM [28].

3.1. TCF7L2 (Transcription Factor 7-like 2)/TCF4

TCF7L2 is a gene which codes for a protein acting as a transcriptional factor [29]. It is a member of Wnt signaling pathway, and the stimulation of this pathway leads to association of beta catenin with B cell Lymphoma-9 (BCL9) gene. It was noted that translocation of this gene to nucleus could activate target gene and represses proglucagon synthesis in enteroendocrine cells (cells of GIT and pancreas with endocrine function) [30,31].

The single nucleotide polymorphism (SNP) within the TCF7L2 gene is most significant marker associated with T2DM risk. SNPs in this gene are linked to higher risk of T2DM and gestational diabetes as noted by previous studies [32,33]. Frameshift mutation in this gene may lead to colorectal cancer [34,35].

3.2. Peroxisome Proliferators-activated Receptor Gamma (PPAR-G)/Glitazone Receptor/NR1C3

It is a nuclear receptor of type II class encoded by PPARG gene. There are mainly two isoforms including the gama1(found in all tissues except muscle) and gamma 2 (present in adipose tissue and intestine) [36]. It regulates fatty acid storage and glucose metabolism [37]

PPARG is activated on binding with various natural agents like arachidonic acids and arachidonic acid metabolites like 5-hydroxyeicasotetraenoic acid (HETE) and 15-HETE, 5-Oxoeicosatetraenoic acid etc. [38,39]. The activation of PPARG inturn inhibits the growth of cultured human breast, gastric, lung, prostate and other cancer cell lines [40]. PPARG has a role in pathogenesis of obesity, diabetes, atherosclerosis, and cancer. Thiazolidinediones

used in the treatment of diabetes targets PPARG to lower serum glucose without increasing pancreatic insulin secretion.

Fat mass and obesity associated protein (FTO)/alpha-ketoglutarate-dependent dioxygenase (AlkB)

FTO is an enzyme coded by FTO gene and it oxidatively demethylates DNA (deoxy ribonucleic acid). FTO gene is expressed in both fetal and adult tissues [41]. It demethylates methyl adenosine of mRNA, tRNA, rRNA, small nuclear RNA(snRNA) in eukaryotes as well as prokaryotes [42,43,44]. Thus, FTO helps in processing of mRNA and other nuclear RNAs [45].

FTO is indirectly associated with T2DM as it increases the body fat distribution; may lead to metabolic syndrome, and increased fasting insulin [46,47]. FTO gene in a carrier state increases the risk of Alzheimer's disease [48].

Potassium channel, inwardly rectifying subfamily Jmember11(KCNJ11)/BIR/HHF2/PHHI/IKATP/TNDM3/KIR6.2

Potassium channels are present in all mammalian tissues and they carry out various physiological responses. The protein encoded by this gene is an integral membrane protein, which is inward-rectifier type and the function of this protein is to allow potassium to flow into the cell [49]. Its function is controlled by G-protein associated with sulphonylurea receptor(SUR) [50].

Mutation or alteration in this gene may lead to an autosomal recessive disorder with unregulated insulin secretion, persistent hyperinsulinemic hypoglycemia of infancy (PHHI), non-insulin dependent type II diabetes (NIDDM), transient neonatal diabetes, and permanent neonatal diabetes (PNDM) [51,52].

Neurogenic locus notch homolog protein2 (NOTCH2)

It belongs to type-1 transmembrane protein family [53]. The domains of this protein are extracellular and can help in binding to epidermal growth factors (EGF) [54]. It plays an important role in developmental processes by controlling cell fate decisions and conserves intercellular signaling pathways by regulating interactions between physically adjacent cells [55]. It functions as a receptor for membrane bound ligands and play a significant role in vascular, renal and hepatic development [56].

Mutation in this gene may lead to removal of PEST domain, escapes non-sense mRNA decay and leads to Hajdu-cheney syndrome, a progressive and severe bone disorder [57,58,59] and genetic variation in NOTCH2 among the people exposed to arsenic increases the susceptibility to T2DM [60].

Wolframin (WFS)

It is a transmembrane protein that act as a channel selective for cations [61], and it plays an important role during stress conditions and beta cell apoptosis [62]. Mutation in exon8, of this gene leads to Wolframan Syndrome, characterized by insulin dependent diabetes mellitus (IDDM) and bilateral progressive optic dystrophy, psychiatric illness, autosomal dominant deafness (DFNA6), and congenital cataract [63,64].

Insulin-like growth factor2 mRNA binding protein2 (IGF2BP2)

It is a growth factor binding protein [65] which binds to 5' UTR (Untranslated region) of insulin-like growth factor 2 (IGF2) mRNA and regulates its translation [66,67]. Thus, involved in pancreatic development and stimulates insulin production. Mutation/alteration in this gene could cause diabetes mellitus.

Solute Carrier family 30 (zinc transporter) member 8 (SLC30A8)

It is a zinc transporter involved in insulin storage and secretion [68]. Certain alleles of this gene (P.Trp325 Arg) increases the risk of T2DM and also elevates glucose and proinsulin levels [69,70,71]. Thus, the inhibitor of this zinc transporter serves as therapeutic strategy in preventing T2DM [72].

Juxtaposed with another zinc finger protein (JAZF1)/TAK1-interacting protein 27(TIP27)/Zinc finger protein 802 (ZNF 802)

This is a Zinc finger protein, which acts as a transcriptional repressor [73]. There are different isoforms for this protein. However, variation in any form of this protein increases the risk for prostate cancer and abnormal insulin response [74].

Haematopoietically expressed homeobox (HHEX)

This gene codes for a member of transcription factor involved in hematopoietic differentiation [75]. HHEX acts as transcription promoter or inhibitor [76,77]. It promotes developmental processes of organs like liver, thyroid, and forebrain [78]. It interacts with SCL (Stem Cell Leukemia) factor, a significant transcription factor for blood and endothelial cell differentiation [79]. It interacts with promyelocytic leukemia protein, represses VEGFA, inhibits endothelial cell differentiation [80]. Because of its role in pancreatic development it might influence the insulin release and insulin sensitivity. Mutation in this gene in experimental mice showed defects in forebrain development, heart, vasculature, liver, monocyte and thyroid abnormalities.

Prospero homeobox 1 protein (PROX1)

It is a transcriptional factor that plays a key role in cell fate determination, neurogenesis and embryonic development of liver, pancreas, heart and lymphatic system [81]. It specifically interacts with hepatocyte nuclear factor (HNG alpha), which activates CYP7A1 gene (involved in the bile acid synthesis (cholesterol homeostasis) and phosphoenol pyruvate carboxy kinase (PEPCK) gene (involved in gluconeogenesis) [82,83]. It represses the activity of acid related orphan receptors like ROR and regulates circardian rhythms [84]. Mutation in this gene or functional deletion of it leads to abnormal cellular proliferation via down regulation of cell cycle inhibitors like p27(kip1) and p57 (kip2) [85,86]. Such changes may lead to hematological carcinomas, biliary carcinomas, obesity and indirectly to T2DM.

Diacyl glycerol kinase beta (DGKB)

This gene encodes diacyl glycerol kinase, a beta enzyme found in neurons which regulates intracellular availability of second messenger, diacylglycerol (DAG) for various cellular activities [87]. The DAG stimulates protein kinase C (PKC) involved in insulin secretion. High levels of calcium in beta cells of pancreas activates release of DAG and insulin secretion via PKC [88]. Thus, mutation of this gene has a role to play in development of T2DM.

Potassium voltage gated channel subfamily Q member 1(KCNQ1)

This gene is involved in the regulation of potassium

channels. They are involved in the transport of potassium ions and produce membrane potential. These channel proteins are active in the inner ear, cardiac muscle, kidney, intestine and pancreas. Proper ion balance is maintained by these channels for hearing and to maintain regular cardiac rhythms. Mutation in this gene leads to atrial fibrillation, long Q wave syndrome, hearing loss, and may leads to improper insulin secretion from islet cells of pancreas [89,90].

Cyclin dependent kinase inhibitor 2A / 2B (CDKN2A / 2B)

These are adjacent genes located on chromosome 9, which encodes two protein $p16^{INK4a}$ and $p15^{INK4b}$. P16 inhibits cyclin dependent kinase 4 (cdc4), a regulator of pancreatic beta cell replication and its overexpression leads to pancreatic islet hypoplasia and diabetes [91,92].

Hepatocyte Nuclear Factor 1 homeobox A (HNF1A/ IDDM20/LFB1/MODY3/TCF1)

This gene encodes for a protein required for the transcription factor expressed in liver. It regulates expression of liver specific genes [93]. It helps in glucose homeostasis, renal glucose absorption, insulin secretion and transcription [94]. A mutation in this gene may lead to maturity onset diabetes of young type 3 (monogenic diabetes), hepatocellular adenoma and carcinoma of ovary [95,96,98,99].

Hepatocyte Nuclear Factor 1B (HNF1B / TCF2/ VHNF1 / MODY5)

This gene encodes for a protein which binds to DNA, and forms a homo or hetero dimer with HNF1A. It has role in nephron development as well as in regulating the development of embryonic pancreas, parathyroid gland, liver, and brain. Thus, mutation in this gene leads to maturity onset of Diabetes (MODY5) [99]. Cystic renal disease is the prominent features of HNF1B gene mutation. Mutation in this gene is initially associated with hypomagnesemia, early onset diabetes, gout, hyperparathyroidism, elevated liver enzymes, and congenital anomalies of urinary tract [100].

Gastric Inhibitory Polypeptide Receptor (GIPR/PGQTL2 / Insulinotropic polypeptide receptor)

This gene codes for a protein which is coupled with G protein and acts as a receptor for gastric inhibitory polypeptide (GIP). It was initially identified for its activity in gut for inhibiting gastric acid secretion and gastrin. Later it was known for its activity in insulin secretion in the presence of elevated glucose levels. The oral glucose causes intestinal cells to secrete insulin secretagogues, mainly glucagon-like peptide 1 (GLP1) and gastric inhibitory peptide leading to higher insulin response than intravenous glucose load. Thus, it could be concluded that GIPR gene mediates insulin secretion after oral glucose stimulation or after eating [101]. A defect in enteroinsular axis (the relationship between insulin secretion and the entrance of a glucose load into the intestine) may contribute to pathogenesis and progression of diabetes [102].

Hepatocyte nuclear factor 4 alpha (HNF4A / TCF14 / FRTS4/ MODY1)

It is a nuclear transcription factor which binds to DNA and forms a homodimer and regulates expression of several hepatic genes. HNF4A is also expressed on pancreatic beta cells. It regulates expression of genes required for glucose transport and metabolism, sex hormone binding globulin (has a role in decreasing insulin resistance) and interacts with TCF1 [103]. This gene also has a role in development of liver, kidney and intestine. Mutation in this gene leads to maturity onset diabetes (MODY1) and abnormal expression of islet cells of pancreas.

Melatonin receptor 1B (MTNR1B / FGQTL2 / MT2)

This gene codes for a membrane protein, and when it is coupled with G protein, forms a receptor for melatonin and is found primarily in the retina and the brain. It participates in light dependent functions of retina and is involved in neurobiological effects of melatonin [104]. It is expressed in human beta islets cells of pancreas [105,106]. Mutation in this gene is associated with increased average blood sugar levels and thus increases the risk for developing type 2 diabetes [107].

Zinc finger BED Domain containing protein3 (ZBED3/Axin interacting protein)

It is a member of zinc finger domain protein superfamily and this gene interacts with Axin, a core protein of Wnt/beta catenin signaling pathway [108]. It is a novel secretory protein found abundantly in muscle and adipose tissue. Its activity increases in parallel to glucose levels. The serum concentrations of this protein have been found to increase from pre-diabetic to diabetic stage indicating its role in insulin signaling pathway [109]. The mutation of this gene thus may lead to obesity and type 2 diabetes.

Cyclin dependent kinase 5 regulatory subunit associated protein -1like (CDKAL1)

It is a member of methyl thio transferase family and is found in human pancreatic cells, skeletal muscles, and brain. It is involved in methyl thio modification in t-RNA lysine residues of CDK5 protein [110]. CDK5 is a serine/threonine protein kinase that regulates insulin secretion from pancreatic cells at high glucose load, protect pancreatic cells from gluco toxicity [111]. This gene is involved in controlling first phase of insulin exocytosis (in response to meals the rapid secretion of insulin) of beta cells of pancreas by mechanisms other than CDK5 mediated regulation [112]. CDKAL1 gene mutation leads to loss of inhibitory effect of CDK5 and increases the risk for type 2 diabetes.

GLIS Family Zinc Finger Protein 3 (GLIS/ZNF515/NDH)

This gene belongs to zinc finger protein family and encodes for a nuclear protein. It functions both as repressor and activator of transcription and is involved in the development of pancreatic beta cells, thyroid, eye, liver, and kidneys [113]. Mutation in this gene showed dilated pancreatic tubules and could be responsible for neonatal diabetes due to insufficient pancreatic beta cells [114].

Glucokinase (hexokinase4) Regulator (GCKR/GKRP/FGQTL5)

It codes for a protein produced by hepatocytes, binds with Glucokinase enzyme (GK), thereby controls both activity and intracellular location of glucokinase enzyme involved in glucose metabolism [115]. This gene modulates GK activity according to the levels of glucose and then moves into nucleus in inactive form [116,117]. Thus, low glucose levels inactivate this gene. Mutation of this gene leads to diabetes (MODY2), hyper insulinemic

hypoglycemia [118].

Growth factor receptor bound protein 14 (GRB14 / GRB 14 adapter protein)

This gene encodes for a growth factor receptor binding protein, which is expressed in testis, ovary, heart, liver, skeletal muscles, kidney, and pancreas. It interacts with insulin receptors and insulin-like growth factor receptors and has an inhibitory effect on tyrosine kinase signaling and on insulin receptor signaling [119,120]. It is a potent inhibitor of insulin stimulated MAPK3 phosphorylation and regulates PDPK1(Phosphoinositol phosphate dependent phosphorylation of PDK1) membrane translocation in response to insulin stimulation. Recruits PDPK1 to activated insulin receptor and promotes PKB/AKT1 phosphorylation and transduction of insulin signal [121,122]. Overexpression of this gene results in decreased insulin stimulation, glycogen synthesis, and dysregulation of insulin mediated pathways. Mutation of this gene is associated with reduced insulin sensitivity.

B Cell CLL / Lymphoma 11A (BCL11A/ EV19 / HBFQTL5 / ZNF856)

This gene encodes a zinc finger protein and its action is like proto-oncogen Bcl-6. The hemopoietic cell differentiation down regulates the activity of this gene, and therefore has a role in suppression of fetal hemoglobin production and sickle cell anemia [124,125]. Recent studies indicate that this gene is a novel breast cancer gene and is expressed in luminal progenitor cells of mammary gland and its involvement in breast cancer progression could be via p21 transcription [126]. It has a role in both B and T lymphocyte development and beta cell function. This gene is associated with non-metabolic syndrome, and is not associated with abdominal obesity, but is a risk factor for type 2 diabetes [127].

RNA Binding Motif Single Stranded Interacting protein 1(RBMS1/MSSP/SCR2/ C2orf12)

This gene codes for a protein which binds with either single stranded DNA/RNA and are involved in DNA replication, gene transcription, cell cycle progression and apoptosis. It binds to single stranded DNA binding protein that interacts with upstream region of c-myc gene [128]. This gene together with ITGB6 gene (Integrin coding transmembrane protein) is expressed in heart, muscle, liver and adipose tissue. RBMS1 gene is involved in the development of type 2 diabetes through inflammatory response as well as intake high fat diet.

Insulin receptor substrate 1 (IRS1/HIRS-1)

It is an adapter protein involved in the transmission of signals from the insulin and insulin-like growth factor-1(IGF-1) receptors to intra cellular pathways like PI3K/Akt and Erk MAP kinase pathways. Tyrosine phosphorylation of the insulin receptors/ binding of ligand to IGF-1 stimulates IRS1, which in turn activates PI3K pathway and MAP kinase pathway [129,130]. Presence of fatty acids, TNF alpha, AMPK phosphorylates serine proteins which degrades IRS1 leads to insulin resistance and related changes leading to diabetes [131]. Abnormality of IRS1 is also associated with various types of cancers including the colorectal, prostrate, lung and breast cancers.

Thyroid Adenoma associated gene (THADA/KIAA1767)

It helps in maintaining thyroid epithelium/follicular epithelium of thyroid [132,133] and is involved in death receptor pathway of apoptosis. Any variations of this gene are associated with insulin sensitivity, reduced GLP1 induced insulin release, and decreased beta cell mass due to increased apoptosis [134]. Mutation of this gene may lead to thyroid cancers and type 2 diabetes.

Beta galactoside alpha -2,6-sialyltransferase 1(ST6GAL1 / SIAT1 / ST6N)

This gene encodes a member of glycosyltransferase, which transfers sialic acid from CAMP – sialic acid to galactose – containing substrates found in Golgi apparatus. It has a role in pancreatic beta cell function and in glycosylation of complex gangliosides [135]. The defective action of this gene was found to have impaired intra cellular lipid and lipoprotein transport [136]. Overexpression of sialyated proteins can be seen in various cancers including the pancreatic, gastric, colon, breast, bladder and brain cancers. The raised sialyated proteins further activates PI3K/AKT pathway and thus could lead to T2DM.

ADAMTS9

ADAMTS9 codes for matrix metalloproteins which help in the breakdown of structural matrix proteins like aggrecan, versican, and breavican [137], and transport of proteins from endoplasmic reticulum (ER) to golgi [138]. These proteins are essential for blood coagulation, ovulation, extracellular matrix turnover, and have an important role in angiogenesis and cancer. These proteins also activate proinflammatory cytokines like interleukin (IL-1β) and tumor necrosis factor (TNF-∞). The activated cytokines destroy beta cells, causes beta cell death and phosphorylates serine residues of insulin receptor substrate (IRS-1), and inhibit glucose induced insulin secretion [139]. Experimental evidence shows that IL-1β induces SOCS-3, an inhibitor of insulin signaling pathway [140]. Thus, ADAMTS9 gene potentially impairs islet cell functioning via induction of proinflammatory cytokines (IL-1β & TNF-∞) resulting in T2DM.

ADCY5 (Adenyl Cyclase 5)

It is a member of Adenyl cyclase enzymes, which are membrane bound enzymes. These enzymes are coded on ADCY5 gene and help in the formation of cyclic Adenosine monophosphate(cAMP) from Adenosine triphosphate (ATP) [141]. The activity of ADCY5 is stimulated by G-protein and inhibited by Protein Kinase A (PKA) and calcium. It also helps in regulating cytosolic calcium levels in response to raised blood sugar levels. Thus, it has a role in calcium dependent insulin secretion [142]. It also helps in protecting cardiac muscle against apoptosis and restoring function of beta cells of pancreas. Mutation of this gene effects the functions of neighboring genes like SEC22, and PDIA5 which are involved in vesicle trafficking and protein folding [143]. The misfolded proteins impair the conversion of proinsulin to Insulin, resulting in increased release of proinsulin from beta cells of pancreas, and beta cell dysfunction, leading to raised blood glucose levels [144].

TLE4 (Transducin – like – Enhancer of Split 4)/ ESG (Enhancer of split groucho)4/ Groucho related gene (GRG)4

This gene codes for TLE or Groucho protein, which plays an important role in sex determination, segmentation and neurogenesis. In humans groucho proteins interacts with histone deacetylase to form a multiprotein – DNA

complex which repress chromatin structure [145]. TLE4 gene suppresses the activation of a protein Pax2, which are DNA binding transcriptional factors that regulates kidney growth, and the development of special regions of nervous system like eye, ear and hind brain. The phosphorylation process of Pax2 is done by c-Jun N-terminal Kinase (JNK), which is inhibited by TLE4 gene [146]. The JNK activates insulin signaling pathway, and its activity positively influences insulin secretion [147]. Thus, TLE4 gene interaction with Pax2 not only stops JNK transcription, but also inhibits insulin secretion, and indirectly contributes to the development of T2DM.

PTPRD (Protein Tyrosine Phosphate Receptor type D)

This gene codes for a protein which belongs to the class of tyrosine phosphatases and is involved in the receptor signaling. It is expressed in skeletal muscles, pancreas and brain. PTPRD proteins are involved in signaling pathways that help in regulating various cellular processes like cell growth, differentiation, and oncogenic transformation. The deficiency of this gene in experimental studies reveal an impaired learning, memory, early growth retardation, neonatal mortality and posture as well as motor defects [148]. PTPRD, and its role in T2DM can be explained by the fact that it activates PPAR-G2, a gene which is a high-risk factor for the development of T2DM. PPAR-G2(Peroxisome Proliferator – Activated receptor Gamma) is a nuclear receptor protein coding gene that plays an important role in fatty acid storage and glucose metabolism [149]. PPAR-G2 activation increases the expression of PTPRD gene, which inhibits STAT3 (Signal Transducers and Activators of Transcription) oncoproteins. STAT proteins are involved in cell transformation and inhibit apoptosis. This helps us to know the role of this gene as tumor suppressor. Exact role of PTPRD gene can be understood by its epigenetic silencing which is found in the progression of T2DM from middle to late stages of the disease, but never in the early stages [150]. Thus, PTPRD role in T2DM is due to sequence of activation of other risk alleles of the gene which is indicated in the late stages of the disease.

Arf (ADP-ribosylation factor)-GAP (GTP associated protein) with Rho-GAP domain, ANK repeat and PH domain-containing protein 1(ARAP1)

ARAP1 activates ADP (Adenosine diphosphate) activity as well as Rho (a transcriptional Protein), and GTPase (Guanosine triphosphate) which regulates membrane trafficking and actin cytoskeletal reorganization [151]. It is located near Golgi and has a role in regulating the members of Arf, Rho, and GTPase family [152]. Experimental evidence shows that there is a decreased release of proinsulin from islet cells of pancreas in response to glucose stimulation after 1 hour due to overexpression of ARAP1 gene. This shows that normally proinsulin is secreted from islet cells of pancreas along with mature insulin in small amounts and when this gene is overexpressed it decreases or stops the release of proinsulin and thus, regulates proinsulin release via its ARF – GAP domain. It was also observed that ARAP1 has a role in insulin packing, trafficking, or exocytosis and an overexpression may stop release of all forms of insulin (preproinsilin, proinsulin, insulin) and contributes to defective functioning of beta cells of pancreas resulting in T2DM [153].

SPRY2 (Sprouty homologue 2)

This gene codes for sprouty protein 2, which are developmental proteins involved in cell signaling. It suppresses the insulin–receptor and epidermal growth factor (EGF) receptor transduced MAPK (Mitogen Activated Protein Kinase) pathway [154]. since insulin receptor and EGF receptor are both involved in tyrosine kinase signaling, it also inhibits tyrosine kinase signaling. SPRY2 interacts with WFS1 gene and indirectly has a role in the development of T2DM. The role of WFS 1 gene is to keep endoplasmic reticulum (ER) stress free and further helps in proper folding of proteins. Because WFS1 gene is expressed only in beta cells of pancreas and is required for proinsulin folding proteins and processing in the ER of beta cells of pancreas, the loss of function of WFS1 gene causes abnormal calcium homeostasis in ER, which leads to ER stress and loss of insulin secretion [155]. SPRY2 inhibits phospho ionositol kinase (PIK) activity (role in calcium signaling), decreases calcium efflux from ER, creates a stress to ER, and activates unfolded protein response (UPR). UPR tries to remove misfolded proteins, and if activated for a long time, it could cause insulin resistance as it decreases the phosphorylation of insulin receptors and subsequently delays insulin signaling pathway. If UPR is not able to clear accumulated misfolded protein it activates apoptotic enzymes leading to apoptosis (cell death) [156].

DUSP9 (Dual Specific Phosphatase 9)

This gene codes for dual specific phosphatase 9, an enzyme which belongs to the family of phosphatases and can remove phosphate (dephosphorylate) both from tyrosine as well as serine/threonine residues at their catalytic sites [157]. This dephosphorylates members of mitogen activated protein kinase superfamily MAPK, ERK (Extracellular signal Regulated Kinase), JNK (c-Jun N-terminal Kinase), SAP (Stress Activated Protein), P^{38} (a class of MAPK) which are involved in cell proliferation and differentiation. As it acts on MAPK it is also called as MAP Kinase Phosphatase -4(MKP-4). The structure of MKP-4 reveals a cAMP dependent protein kinase phosphorylation site near to the c-terminal end of this gene which helps in mediating PKA (Protein Kinase A) pathway, mitogen and stress–activated pathways [158]. It was observed that inhibitory role of MKP-4 on MAP Kinase family initially inhibits cell proliferation and glucose uptake of certain cells but do not completely block the action of insulin. Thus, overexpression of DUSP9 gene improves insulin resistance especially in a stressed environment and can be used as a site of therapeutic intervention in treating T2DM.

4. Conclusion

The genetic reasons for the development of T2DM involves a complex interlinked signaling cascade. There are certain genes which influence post translational modifications (ARAP1, ADCY5, SPRY2, FTO), some genes related to metabolism (RBMS, HNF4A, HNF1A, PROX1, PPARG, GCKR), some involved in the development of pancreas (GLIS, HNF1B, HHEX, IGF2BP2), and a few are related to insulin secretion

(GRB14, CDKAL1, ZBED3, GIPR). There are also some genes (SLC30A8) involved in insulin storage, glycosylation (ST6GAL1), apoptosis (THADA), cancer (BCL11A), metal related gene (NOTCH2), and drug related genes (KCNJ11). Understanding the pathways, and the genetics behind the pathways could help us in designing therapeutic interventions to reverse as well as prevent T2DM.

References

[1] Mokdad AH, Bowman BA, Ford ES, Vinicoor F, Marks JS et al.,. The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001; 286: 1195-1200.

[2] Venkataramana R, Nanda NC, Baweja G, Parikh N, Bhatia V. Prevalence of diabetes mellitus and related conditions in Asian Indians living in the United States. Am J Cardiol. 2004l; 94: 977-980.

[3] Herder C, Roden M. "Genetics of type2 diabetes: pathophysiologic and clinical relevance". European Journal of clinical investigation. 2011; 41(6): 679-92.

[4] Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring study. Diabetes. 2000; 49(12): 2201-7.

[5] Doria A, Patti ME, Kahn CR. The emerging genetic architechture of type 2 diabetes. Cell Metab. 2008; 8(3): 186-200.

[6] Hattersley AT, McCarthy MI. What makes a good genetic association study?. Lancet. 2005; 366(9493): 1315-23.

[7] Hopper JL, Bishop DT, Easton DF. Population-based family studies in genetic epidemiology. Lancet. 2005; 366(9494): 1397-406.

[8] McCarthy MI. Growing evidence for diabetes susceptibility genes from genome scan data. Curr Diab Rep 2003; 3(2): 159-67.

[9] Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Metanalysis of genetic association studies support a contribution of common variants to susceptibility to common disease. Nat Genet 2003; 33(2): 177-82.

[10] Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet 2001; 29(3): 306-9.

[11] Waterfield T, Gloyn AL. Monogenic beta cell dysfunction in children: clinical phenotypes, genetic etiology and mutational pathways. Pediatric Health.2008; 2(4): 517-32.

[12] O'Rahilly S. Human genetics illuminates the paths to metabolic disease. Nature.2009; 462(7271): 307-14.

[13] Vaxilliare M,Froguel P. Genetic basis of maturity-onset diabetes of the young. Endocrinol Metab Clin North Am 2006; 35(2): 371-84.

[14] Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996; 273(5281): 1516-7.

[15] Nusse ROel, Varmus, Harold E. Wnt genes. Cell. 1992; 69(7): 1073-87.

[16] Komya Y, Habas R. Wnt signal transduction pathways. Organogenensis. 2008; 4(2): 68-75.

[17] Kurayoshi M, H Yamamoto S Izumi, A Kikuchi. Post translational palmitoylation and glycosylation of Wnt-s are necessary for its signaling. Biochemical Journal. 2007; 402(3): 515-523.

[18] Logan C W, Nusse R. "The Wnt signaling pathway in development and disease". Cell Dev Bio. 2004; 20: 781-810.

[19] Mac Donald, Bryan T, Tamai, Keiko, He, Xi. Wnt / beta catenin signaling: components, mechanisms and diseases. Developmental cell. 2009; 17(1): 9-26.

[20] Stall FJ, Clevers H. TCF/Lef transcription factors during T cell development: unique and overlapping functions. The Hematology Journal. 2000; 3-6.

[21] Klaus A, Birchmeier W. Wnt signaling and its impact on development and cancer. Nature Reviews Cancer. 2008; 8(5): 387-398.

[22] Habas, Raymond, Dawid, Igor B. Dishevelled and Wnt signaling: is the nucleus the final frontier?. Journal of Biology. 2005; 4(1): 2.

[23] Sugimura, Ryohichi and Linheng Li. Noncanonical Wnt signaling in vertebrate development, stem cells, and diseases. Birth defects Research Part C: Embryo Today Reviews. 90.4. 2010; 243-256.

[24] Welters, HJ, RN Kulkarni. Wnt signaling: relevance to beta cell biology and diabetes. Trends in Endocrinology & metabolism. 2008; 19(10): 349-355.

[25] Yoon JC, Ng A, Kim BH, Bianco A, Xavier RJ et al.,. Wnt signaling regulates mitochondrial physiology and insulin sensitivity. Genes & Development. 2010; 24(14): 1507-18.

[26] Zhai L, SW Ballinger, JL Messina. Role of reactive oxygen species in injury-induced insulin resisitance. Molecular Endocrinology. 2011; 25(3): 492-502.

[27] Grant, Struan FA, Thorleifsson, Gudmar, Reynisdolttir, Inga et al.,. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature Genetics. 2006; 38(3): 320-323.

[28] Jin T. The Wnt signaling pathway and diabetes mellitus. Diabetologia. 2008; 51(10): 1771-80.

[29] Castrop J, Van Norren K, Clevers H. " A gene family of HMG-box transcription factors with homology to TCF-1". Nucleic Acids Res. 1992; 20(3): 611.

[30] Komiya Y, Habas R. "Wnt signal transduction pathways". Cell Dev Bio. 2004; 20: 781-810.

[31] SampietroJ, Dahlberg CL, Cho US, Hinds TR, Kimelman D, Xu W. "Crystal structure of a beta-catenin/BCL9?Tcf4 complex". Mol Cell. 2006; 24(2): 293-300.

[32] Jin T, Liu L. "The Wnt signaling pathway effector TCF7L2 and type2 diabetes mellitus". Mol Endocrinol.2008; 22(11): 2383-92.

[33] Zhang C, Bao W, Rong Y, Yang H, Bowers K et al.,. "Genetic variants and the risk of gestational diabetes melliteus: A systematic review. Human Reproduction Update. 2013; 19(4): 376.

[34] Slattery ML, Folsom AR, Wolff R, Herrick J, Caan BJ, et al.,. "Transcription factor 7-like 2 polymorphism and colon cancer". Cancer Epidemiol Biomarkers Prev. 2008; 17(4): 978-82.

[35] Hazra A, Fuchs CS, Chan AT, Giovannucci EL, Hunter DJ, et al.,. "Association of the TCF7L2polymorphism with colorectal cancer and adenoma risk". Cancer Causes Control. 2008; 19(9): 975-80.

[36] Dreyer C, Keller H, Mahfoudi A, Laudet V, Krey G et al.,. Positive regulation of the peroxisomal beta oxidation pathway by fattyacids through activation of peroxisome proliferators-activated receptors(PPAR). Biol cell. 2993; 77(1): 67-76.

[37] O'Flaherty JT, Rogers LC, Paumi CM, Hantgan RR, Thomas LR, at al.,. 5-Oxo-ETE analogs and the proliferation of cancer cells. Biochim Biophys. Acta. 2005; 1736(3): 228-36.

[38] Krishnan A, Nair SA, Pillai MR. Biology of PPAR gamma in cancer: a critical review on existing lacunae. Curr Mol Med. 2007; 7(6): 532-40.

[39] Atanasov AG, Wang JN, Gu SP, Bu J, Kramer MP, at al.,. Honokiol: a non-adipogenic PPAR gamma agonist from nature. Biochim Biophys Acta. 2013; 1830(10): 4813-9.

[40] Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, et. al.,. Natural product agonists of peroxisome proliferators-activated receptor gamma(PPARG): a review. Biochem Pharmacol. 2014; 92(1): 73-89.

[41] Jia G, Fy Y, Zhao X, Dai Q, Zheng G, et al.,. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol. 2011; 7(12): 885-7.

[42] Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, et al.,. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316(5826): 889-94.

[43] Nicholas JL, N6-methyladenosine in maize poly(A)-containing RNA. Plant Science Letters. 1979; 15(4): 357-61.

[44] Kennedy TD, Lane BG, Wheat embryo ribonucleates XIII. Methyl-substituted nucleoside constitutents and 5'-terminal dinucleotide sequences in bulk poly(AR)-rich RNA from imbibing wheat embryos. Can J Biochem. 1979; 57(6): 927-31.

[45] Aloni Y, Dhar R, Khoury G. Methylation of nuclear simian virus 40 RNAs. J Virol. 1979; 32(1): 52-60.

[46] Meyer KD, Saletore Y, Zumbo P, Elemento O, Mason CE, et al.,. Comprehensive Analysis of mRNA methylation reveals enrichment in 3'UTRs and near stop codons. Cell. 2012; 149(7): 1635-46.

[47] Sandholt CH, Hansen T, Pedersen O. Beyond the fourth wave of genome-wide obesity association studies. Nutr Diabetes. 2012; 2: e37.

[48] Keller L, Xu W, Wang HX, Winblad B, Fratiglioni L, Graff C. The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer's disease risk: a prospective cohort study. J Alzheimers Dis. 2011; 23(3): 461-9.

[49] "Entrez Gene: KCNJ11 potassium inwardly-rectifying channel, subfamily J, member 11".

[50] Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, et al.,. Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes. 2003; 52(2): 568-72.

[51] Pinney S E, MacMullen C, Becker S, Lin Y W, Hanna C, Thornton P, et al.,. Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. J Clin Invest. 2008; 118: 2877-2886.

[52] Smith AJ, Taneja TK, Mankouri J, Sivaprasadarao A (2007). Molecular cell biology of KATP channels: implications for neonatal diabetes. Expert Rev Mol Med. 9 (21): 1-17.

[53] Larsson C, Lardelli M, White I, Lendahl U. The human NOTCH1, 2 and 3 genes are located at chromosomes positions 9q34, $1p^{13}$-p^{11}, and $19p^{13.2}$-$p^{13.1}$ in regions of neoplasia associated translocation. Genomics. 1994; 24(2): 253-8.

[54] Sh Shimizu K, Chiba S, Kumano K, Hosoya N,Takahashi T et al.,. Mouse jagged 1 physically interacts with notch2 and other notch receptors. Assessment by quantitative methods. J Biol Chem. 1999; 274(46): 32961-9.

[55] Shimizu K, Chiba S, Hosoya N, Kumano K, Saioto T, Kurokawa M et al.,. Binding of delta 1, jagged 1, and jagged 2 to Notch1 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. Mol. Cell. Biol. 2000; 20(18): 6913-22.

[56] Espinosa L, Ingles – Esteve J, Aguilera C, Bigas A. Phosphorylation by glucogen synthase kinase-3 beta down-regulates Notch activity, a link for notch and Wnt pathways. J Biol Chem. 2003; 278(34): 32227-35.

[57] Shimizu K, Chiba S, Saito T, Kumano K, Takahashi T, et al.,. Manic fringe and lunatic fringe modify different sites of the Notch2 extracellular region, resulting in different signaling modulation. J Biol Chem. 2001; 276(28): 25753-8.

[58] Simpson MA, Irving MD, Asilmaz E, Gray MJ, Dafou D et al.,. Mutations in Notch2 cause Hajdu-cheney syndrome, a disorder of severe and progressive bone loss. Nature Genentics. 2011; 43(4): 303-5.

[59] Majewski J, Schwartzentruber JA, Caqueret A, Patry L, Marcadier J et al.,. Mutations in NOTCH 2 in families with Hajdu-chenoy syndrome. Hum Mutat. 2011; 32(10): 1114-7.

[60] Isidor B, Lindenbaum P, Pichan O, Bezieau S, Dina C et al.,. Truncating mutations in the last exon of NOTCH2 cause a rare skeletal disorder with osteoporosis. Nature Genetics. 2011; 43(4): 306-8.

[61] Osman AA, Saito M, Makepeace C, Permutt MA, Schlesinger P, et al.,. Wolframin exression induces novel ion channel activity in endoplasmic reticulum membranes and increases intracellular calcium. J Biol Chem. 2003; 278(52): 52755-62.

[62] Diria A, Patti ME, Kahn CR. The emerging genetic architecture of type2 diabetes. Cell Metab. 2008; 8(3): 186-200.

[63] Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, et al.,. A gene encoding a transmembrane protein is mutated in patients with dibetes melliteus and optic atrophy (Wolfram syndrome). Nat Genet. 1998; 20(2): 143-8.

[64] Berry V, Gregory-Evans C, Emmett W, Waseem N, Raby J et al.,. Wolfram gene (WFS1) mutation causes autosomal dominant congenital nuclear cataract in humns. Eur J Hum Genet. 2013; 21(12): 1356-60.

[65] Entrez gene: IGFBP2 insulin-like growth factor 2 mRNA binding protein2.

[66] Nielsen J, Christiansen J, Lykke-Andersen J, Johnsen AH, Wewer UM, et al.,. A family of insulin-like growth factor II mRNA-binding proteins represses translation in late development. Mol Cell Biol. 1999; 19(2): 1262-70.

[67] Rutter GA et al.,. Think zinc:new roles for zinc in the control of insulin secretion Islets 2010; 2(1): 49-50.

[68] Dupis J et al.,. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nature Genetics. 2010; 42(2): 105-16.

[69] Strawbridge R J et al.,. Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type2 diabetes. Diabetes. 2011; 60(10): 2624-34.

[70] Morris A P et al.,. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nature Genetics. 2012; 44(9): 981-90.

[71] Flannick, Jason et al.,. Loss-of-function mutations in SLC30A8 protect against type 2 diabetes. Nature Genetics. 2014.

[72] Adams MD,Soares MB, Kerlavage AR, Fields C, Venter JC. Rapid cDNA sequencing from a directionally cloned human infant brain cDNA library. Nat Genet. 1993; 4(4): 373-80.

[73] Manolio TA, Guttmacher, Alan E, Manolio, Teri A. Genome wide association studies and assessment of the risk of disease. N Engl J Med. 2010; 363(2): 166-176.

[74] Bedford FK, Ashworth A, Enver T, Wiedemann LM. HEX: a novel homeobox gene expressed during haemotopoiesis and conserved between mouse and human. Nucleic Acids Res. 1993; 21(5): 1245-9.

[75] Denson Lee; Karpen, Saul; Bogue, Clifford; Jacob,Harris. Divergent homeobox gene Hex regulates promoter of the Na+-dependent bileacid cotransporter. American Journal of physiology-Gastrointestinal and Liver physiology. 2000; 279(2): 347-355.

[76] Brickman, Joshua; Jones,C; Clements, Melanie; Smith, J; Beddington, Rosa. Hex is a transcriptional repressor that contributes to anterior identity and suppresses Spemann organizer function. Development. 2000; 127: 2303-315.

[77] Martinez Barbera, Juan; Clements, Melanie; thjoman, Paul; Rodriguez, Tristen; Meloy et al.,. The homeobox gene Hex is required in definitive endodermal tissues for normal forebrain, liver and thyroid formation. Development. 2000; 127: 2433-45.

[78] Topcu Z, Mack DL, Hromas RA, Borden KL. The promyelocutic leukemia protein PML interacts with the proline-rich homeodomain protein PRH: a RING may link hematopoiesis and growth control. Oncogene. 1999; 18(50): 7091-100.

[79] Liao, Wyne Ho, Chi-Yip;Yi, Lin Yan, Postlewait, John Stainier, Didier. Hhex and Scl function n parallel to regulate early endothelial and blood differentiation in zebrafish. Development. 2000; 127: 4303-4313.

[80] Hallaq, Hafia Pinter, Emese Enciso, Josephine McGrath James Zeiss, Caroline Brueckner Martina et al.,. A null mutation of Hhex results in abnormal cardiac development, defective vasculogenesis and elevated Vegfa levels. Development. 2004; 131: 5197-5209.

[81] Takeda Y, Jetten AM. Prospero-related homeobox 1 (Prox1) functions as a novel modulator of retinoic acid-related orphan receptors α- and γ-mediated transactivation. Nucleic Acids Res. 2013; 41: 6992-7008.

[82] Song K. H, Li T, Chiang J. Y. Prospero – related homeodomain protein is a novel co-regulator of hepatocyte nuclear factor 4 alpha that regulates the cholesterol 7 – alpha hydroxylase gene. Biol chem.. 2006.

[83] Steffensen, K.R., Holter, E., Båvner, A., Nilsson, M., Pelto-Huikko, M., Tomarev, S., Treuter, E. Functional conservation and interaction between a homeodomain cofactor and a mammalian FTZF -1 homologue. EMBO Rep. (2004)[Pubmed].

[84] Jetten AM, Kang HS, Takeda Y. Retinoic acid-related orphan receptors α and γ: key regulators of lipid/glucose metabolism, inflammation, and insulin sensitivity. Front Endocrinol. 2013; 4: 1-8.

[85] Harvey NL, Srinivasan S, Dillard ME, Johnson NC, Witte MH, Boyd K. Lymphatic vascular defects promoted by Prox1 haploinsufficiency cause adult-onset obesity. Nat Genet. 2005; 37: 1072-1081.

[86] Laerm, A., Helmbold, P., Goldberg, M., Dammann, R., Holzhausen, H.J., Ballhausen, W.G. Prospero-related homeobox 1 (PROX1) is frequently inactivated by genomic deletions and epigenetic silencing in carcinomas of the bilary system. J Hepatol. 2001.

[87] Goto K, Kondo H (Sep 1993). "Molecular cloning and expression of a 90-kDa diacylglycerol kinase that predominantly localizes in neurons". *Proc Natl Acad Sci U S A* 90 (16): 7598-602.

[88] Kaneko YK[1], Ishikawa T. Diacylglycerol Signaling Pathway in Pancreatic β-Cells: An Essential Role of Diacylglycerol Kinase in the Regulation of Insulin Secretion. Biol Pharm Bull. 2015; 38(5): 669-73.

[89] Jespersen T, Grunnet M, Olesen SP. The KCNQ1 potassium channel: from gene to physiological function. Physiology (Bethesda) 2005; 20 (6): 408-16.

[90] Anna Jonasson, Bo Isomaa, Tiinamaija Tuomi, Jalal Taneera, Albert Salehi, et al.,. A Variant in the KCNQ1 Gene Predicts Future Type 2 Diabetes and Mediates Impaired Insulin Secretion. American Diabetes Association. 2009; 58(10):2409-13.

[91] CDKN2A. Genetics Home Reference. National Library of Medicine. 2015.

[92] Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science. 2007: 316: 1336-1341.

[93] Szpirer C, Riviere M, Cortese R, Nakamura T, Islam MQ et al.,. Chromosomal localization in man and rat of the genes encoding liver-enriched transcription factors C/EBP, DBP,HNF1/LFB-1 and of the hepatocyte growth factor/scatter factor gene (HGF). Genomics. 1992; 13(2): 293-300.

[94] Ban N, Yamada Y, Someya Y, Miyawaki K, Ihara Y, Hosokawa M, et al.,. Hepatocyte nuclear factor-1alpha recfruits the transcriptional co-activator p300 on the GLUT2 gene promoter. Diabetes. 2002; 51(5): 1409-18.

[95] Vaxillaire M, Boccio V,Philippi A, Vigouroux C, et al.,. A gene for maturity onset diabetes of the young (MODY) maps to chromosome 12q. Nature Genetics. 1995; 9(4): 418-23.

[96] Bioulac-Sage P,BlancJF, Rebouissou S, Balabaud C et al.,. Genotype phenotype classification of hepatocellular adenoma. World Journal Of Gastroenterology. 2007; 13(19): 2649-54.

[97] Kobel M, Kalloger SE, Carrick J, Huntsman D, Asad H, Olivia E et al.,. A limited panel of immunomarkers can reliabily distinguish between clear cell and high grade serous carcinoma of the ovary. The American Journal of Surgical Pathology. 2009; 33(1): 14-21.

[98] Stefan S Fanjans, Graem I Bell, Kenneth S Polonsky. Molecular mechanisms and clinical pathophysiology of Maturity-Onset Diabetes of the Young. N Engl J Med. 2001; 345: 971-980.

[99] Hepatocyte nuclear factor 1beta associated kidney disease: more than renal cysts and diabetes. J Am Soc Nephrol. 2016; 27(2); 345-53.

[100] Richa Saxena, Marie-France, Hivert, Richard M Watanabe. Genetic variation in GIPR influences the glucose and insulin responses toan oral glucose challenge. Nature genetics. 2010; 42(2): 142-148.

[101] Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K et al.,. Glucose intolerance caused by a defect in the entero-insularaxis: astudyin gastric inhibitory polypeptide receptor knockout mice. Proc Nat Acad Sci. 1999; 96: 14843-14847.

[102] Entrez gene: HNF4A hepatocyte nuclear factor 4 alpha.

[103] Yamagata K. Roles of HNF1A and HNF4A in pancreatic beta cells: lessons from amonogenic forms of diabetes (MODY). Vitamins and Hormones. 2014. 95:407-23.

[104] Entrez Gene: MTNR1B melatonin receptor 1 B.

[105] Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, et al.,. Variants in MTNR1B influence fasting glucose levels. Nature Genetics. 2009; 41(1): 77-81.

[106] Gene that regulates glucose levels and increases risk for diabetes identified. ScienceDaily.2008-06-08. Retrieved 2009-01-18.

[107] Staiger H, Machicao F, Schafer SA, Kiirchhoff K, Kantartzis K, et al.,. Polymorphisms within the novel type 2 diabetes risk locus MYNR1B determine beta – cell function. PLOS ONE. 2008; 3(12): e3962.

[108] Zeng L, Fagotto F, Zhang T et al.,. The mouse fused locus encodes Axin, an inhibitor of the Wnt signaling pathway that regulates embryonic axisformation. Cell. 1997; 90: 181-92.

[109] Y Jia, L Yuan, W Hu, Y Luo, L Suo, Y Wang, et al.,. Zinc finger BED domain containing 3 (Zbed3)is a novel secreted protein associated with insulin resistance in humans. Journal of Internal Medicine. 2014; 275(5): 522-533.

[110] Zhou B, Wei F, Y Kanai, N Fujimura, A Kaitsuka, T Tomizawa . Identification of a splicing variant that regulates type 2 diabetes risk factor CDKAL1 level by acoding -independent mechanismin human. HumMolec. Genet. 2014; 23: 4639-4650.

[111] Wei F Y et al.,. Cdk5 – dependent regulation of glucose – stimulated insulin secretion. Nat Med. 2005; 11: 1104-8.

[112] Ohara – Imaizumi, M et al,.,. Deletion of CDKAL1 affects mitochondrial ATP generation and first – phase insulin exocytosis. PLOS One. 2010(5). E15553.

[113] Kim Y S, Nakanishi G, Lewandoski M, Jetten A M. GLIS3, a novel member of the GLIS subfamily of kruppel – like zinc fingerproteins with repressorand activation functions. Nucleic Acids Res. 2003; 31: 5513-25.

[114] Kang H S, BeakJ Y, KimY S, Herbert R, Jetten A M. Glis3 is associated with primary ciliaand Wwtr1/TAZand implicated in polycystickidney disease. 2009; 29: 2556-2569.

[115] Dela IglesiaN, Veiga-da-Cunha M,Van Schaftingen E,Guinovart JJ,FerrerJC,et al.,. Glucokinase regulatory protein is essential for the proper subcellular localization of liver glucokinase.FEBS Lett.1999; 456(2): 332-8.

[116] Shiota C, Coffey J,Grimsby J, Grippo JF, Magnuson MA, Coffey,Grimsby, Grippo et al.,. Substrate induced nuclear export and peripheral compartmentalization of hepaticglucokinase correlates with glycogen deposition. Int J Exp Diabetes Res. 2001; 2(3): 173-86.

[117] Gracia-Herrero CM,Galan M, Vincent O,et al.,. Functional analysis of human glucokinase gene mutations causing MODY2: exploring the regulatory mechanisms of glucokinase activity. Diabetologia .2007; 50(2): 325-33.

[118] Grimsby J, Coffey JW, Dvorozniak MT, et al.,. Characterization of glucokinase regulatory protein-deficient mice. J Biol Chem.2000;275(11):7826-31.

[119] Daly R J, Sanderson G M, JanesP W, Sutherland RL. Cloning and characterization of GRB14, a novel member of theGRB7 gene family.J BiolChem. 1996; 271(21): 12502-510.

[120] King C C, Newton A C, The adapter protein Grb14 regulates the localization of 3-phosphoinositide-dependentkinase-1. J BiolChem. 2004; 279: 37518-527.

[121] Depetris R S, Wu J, Hubbard S R. Structural and functional studies of the Ras-associating andpleckstrin-homology domains of Grb10and Grb 14. NatStruct. Mol. Biol. 2009; 16: 833-839.

[122] Hemming R, R Agatep, KBadiani, et al.,. Human growth factor receptor bound 14binds the activated insulin receptor and alterstheinsulin – stimulated tyrosine phosphorylationlevels of multiple proteins. Biochem Cell Biol.2001; 79: 21-32.

[123] Entrez Gene: BCL11A B cell CLL/Lymphoma 11 A (zincfingerprotein).

[124] Saiki Y, Yamazaki Y, YoshidaM, Katoh O, Nakamura T.Human EV19,a homologue of the mouse myeloidleukemia gene, is expressed in the hematopoietic progenitors and down regulated during myeloiddifferentiation of HL60 cells. Genomics. 2000; 70(3): 387-91.

[125] Walid T Khaled, Song Choon Lee, John Stingl,Xiondfeng Chen, et al.,. BCL11A is a triple negative breast cancer gene with critical functionsin stem and progenitor cells. Nature Communications. 2014; 6: 5987.

[126] Xiaomu Kong, Xuelian Zhang, Xiaoyan Xing, Bo Zhang, Jing Hong, Wenying Yang, et al.,. The association of type 2 diabetes loci identified in genome – wide association studies with metabolic syndrome and its components in a Chinesepopulation with type 2 diabetes. PLOS ONE. 2015; 10(11): e0143607.

[127] Takai T, Nishita Y, Iguchi – Ariga S M, and Ariga H. Molecular cloning of MSSP-2, a c- myc gene single-strand binding protein: characterization of binding specificity and DNA replication activity. Nucleic Acids Res. 1994; 22: 5576-5581.

[128] Shoelson S E, Lee J, and Goldfine A B. Inflammation and insulin resisitance. J Clin Invest. 2006; 116: 1793-1801.

[129] Sun XJ, Rothenberg P, Kahn CR, Backer JM, Araki E, Wilden PA, et al.,. structure of the insulin receptor substrate IRS1 defines a unique signal transduction protein. Nature.1991; 352(6330): 73-7.

[130] Aguirre V, Werner ED, Giraud J, Lee YH, Shoelson SE, White MF. Phosphorylation of Ser307 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action. The Journal of Biological Chemistry. 2002; 277(2): 1531-7.

[131] Dearth RK, Cui X, Kim HJ, Hadsell DL, Lee Av. Oncogenic transformation by the signaling adaptor proteins insulin receptor substrate (IRS)-1 and IRS-2. Cell Cycle. 2007; 6(6): 705-13.

[132] Kloth et al.,. Decrease in thyroid adenoma associated (THADA) expression is a marker of dedifferentiation of thyroid tissue.BMC ClinicalPathology. 2011; 11: 13.

[133] Annemarie M, Simonis-Bik, Giel Nijpels, Timon W Van Haeften, Jeanine J,et al.,. CDC123/CAMKID, THADA, ADAMTS9, BCL11A and MTNR1B affect different aspects of pancreaticbeta cell function. Diabetes. 2010; 59(1): 293-301.

[134] Grarup N, Andersen G, Krarup NT, et al. Association Testing of Novel Type 2 Diabetes Risk Alleles in the *JAZF1, CDC123/CAMK1D, TSPAN8, THADA, ADAMTS9*, and *NOTCH2* Loci With Insulin Release, Insulin Sensitivity, and Obesity in a Population-Based Sample of 4,516 Glucose-Tolerant Middle-Aged Danes. *Diabetes*. 2008;57(9):2534-2540.

[135] Gong M, Castillo L, Redman R S, Garige M, Hirsch K, et al.,. Down – regulation of liver Galbeta1, 4GlcNAc alpha2,6 – Sialyltransferase gene by ethanol significantly correlates with alcoholic steatosis in humans. Metabolism 2008; 57: 1663-1668.

[136] Hongye Ma, Lei Cheng, Keji Hao, Yanping Li, Xiaobo Song, Huimin Zhou, Li Jia Reversal Effect of ST6GAL 1 on Multidrug Resistance in Human Leukemia by Regulating the PI3K/Akt Pathway and the Expression of P-gp and MRP1. PLoS ONE. 2014; 9(1): e85113.

[137] .Clark ME, Kelner GS, Turbeville LA, et al.,. ADAMTS9, a novel member of ADAM-TS/metallospondin gene family. Genomics. 2000; 67: 343-350.

[138] Yoshina S et al.,. Identification of novel ADAMTS9 / GON-1 function for protein transport from ER to golgi. Mol. Biol. Cell.2012; 23(9): 1728-41.

[139] Demirican K, et al., ADAMTS9 is synergistically induced by interleukin – 1 β(IL-1β) and tumor necrosis factor - ∞ in OUMS - 27 chondrosarcoma cells and in human chondrocytes. Arthritis Rheum.2005; 52(5): 1451-60.

[140] B Emaneulli, M Glondu, C Filloux, et al.,. The potential role of SOCS-3 in the interleukin-1-β induced desensitization of Insulin signaling in pancreatic beta cells. Diabetes. 2004; 53(suppl 3): S97-S103.

[141] Prentiki M Matschinsky FM. Calcium and cAMP and phospholipid – derived messengers in coupling mechanisms of insulin secretion. Physiol Rev.1987; 67: 1185-1248.

[142] Ding Q, Gros R, Gray ID, Taussig R, et al.,. Raf activation of adenyl cyclase; isoform – selective regulation. Mol Pharmacol. 2004; 66: 921-928.

[143] Mancias JD, Goldberg J. The transport signal on Sec22 for packaging into COPII-coated vesicles is a conformational epitope. Mol. Cell. 2007; 26(3):403-414.

[144] Scheuner D, Kaufman RJ. The unfolded protein response: a pathway that links insulin demand with beta cell failure and diabetes. Endocr Rev.2008; 29: 317-333.

[145] Michele Milili, Laurent Gauthier. A new Groucho TLE4 protein may regulate the repressive activityof pax5 in human B lymphocytes. Immunology. 2002; 106(4): 447-455.

[146] Cai Y, Brophy PD, Levitan I, Stifani S, et al.,. Groucho suppresses Pax2 transactivation by inhibitiob of JNK-mediated phosphorylation. EMBO J, 2003; 15: 22(20): 5522-9.

[147] Yong Hee Lee, Jodel Giraud, Roger J Davis, et al.,. c-JUN N-terminal Kinase (JNK) mediates feed back inhibition of the insulin signaling cascade. J Biol. Chem. 2003; 278: 5(31): 2896-2902.

[148] T Sai F-J, Yang C-f, Chen C-C, Chuang L-M, Lu C-H, et al.,. A genome – wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese. PLOS Genet. 2010; 6(2): e1000847.

[149] Jones JR, Barrick C, Kim KA, Lindner J, et al.,. Deletion of PPAR-gamma in adipose tissues of mice protects against high fat diet – induced obesity and insulin resistance. Proc Natl Acad Sci. 2005; 102(17): 6207-12.

[150] Yng – Tay Chen, Wei – De Lin, Wen – Lin Liao, et al.,. PTPRD silencing by DNA hypermethylation decreases insulin receptor signaling and leads to type 2 diabetes. Oncotarget. 2015; 6(15): 12997-13005.

[151] Miura K, Jacques K M, Stauffer S, Kubosaki A, Zhu K, Hirsch D S, et al.,. ARAP1: a point of convergence for Arf and Rho signaling. Mol. Cell. 2002; 9: 109-119.

[152] Baschieri, F., & Farhan, H. (2012). Crosstalk of small GTPases at the Golgi apparatus. Small GTPases. 2012; *3*(2), 80-90.

[153] Jennifer R Kulzer, Michael L. Stitzel, Mario A Morken, Jeroen R Huyghe, Christian Fuschsberger. A common functional regulatory variant at a type 2 diabetes locus upregulates ARAP1 expression in the pancreatic beta cell. Am J Hum Genet. 2014; 94(2): 186-197.

[154] Lim J, Yusoff P, Wong ES, Chandramouli S, Lao DH, et al.,. The cysteine – rich sprouty translocation domain targets mitogen-activated protein kinase inhibitory proteins to phosphor ionositol 4,5 bisphosphate in plasma membranes. Mol. Cell. Biol. 2002; 22(22): 7953-66.

[155] Sonya G Fonseca, Mariko Fukuma, Kathryn L Lipson, Linh X, Nguyen, et al.,. WFS1 is a novel component of unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta cells. Journal of biological chemistry. 2005; 280(47): 39609-39615.

[156] Z Pappalardo. A whole genome RNA interference screen reveals a role for spry2 in insulin transcription and the unfolded protein response. Diabetes. 2017; 66(6): 1703-1712.

[157] Denu JM, Dixon JE. A catalytic mechanism for the dual – specific phosphatases. Proc. Natl Acad Sci. USA. 1995; 92(13): 5910-4.

[158] Dickinson RJ et al.,. Phosphorylation of the kinase interaction motif in mitogen – activated protein (MAP) kinase phosphatase - 4 mediates cross-talk between protein kinase A and MAP kinase signaling pathways. Journal of Biological Chemistry. 2011; 286: 44: 38018-38026.