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Review Article

Diabetes: Candidate Genes and Its Variants

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Abstract

Diabetes being one the fastest occurring disease globally and leading to the increase in death rates. In this review we identified the prevalence, epidemiology, types, diagnosis, management and mainly focusing on all the genes and their variants responsible for diabetes mellitus and diabetes insipidus studied and found till date. It was found that there are 18 regions/60 genes are involved in Type 1 diabetes mellitus (T1D) by use of genome-wide association study (GWAS) studies combined with new technologies such as Single nucleotide polymorphisms (SNPs) array genotyping, meta-analysis, taq sequencing etc. The gene that have higher risk in developing T1D is found to be in the region of Insulin dependent diabetes mellitus 1 (IDDM1) containing Human leukocyte antigens (HLA) gene and it's haplotypes HLA-DQ, HLA-DR, and HLA-DP while several other genes has been also discussed but the mechanisms of pathogenesis still unclear. In Type 2 diabetes mellitus (T2D) many genes have been put forward as candidate genes through (GWAS) and large meta-analysis, but only few susceptibility genes have shown convincing association in several studies, includes Peroxisome Proliferator-Activated Receptor-γ (PPARG γ), Potassium Inwardly Rectifying Channel Subfamily J Member 11(KCNJ11), Transcription Factor7-Like 2 (TCF7L2) and WFS1.In contrast gene responsible for hereditary, central and nephrogenic diabetes insipidus are mutated Arginine Vasopressin-Neurophysin II (AVP-NPII) gene and either The Arginine Vasopressin Receptor 2 (AVPR2) or Aquaporin 2 (AQP2) gene respectively and studied through sequence analysis.

Keywords: Diabetes Mellitus; Diabetes Insipidus; Mellitus; Central Diabetes Insipidus; Nephrogenic Diabetes Insipidus; HLA

Introduction

Diabetes is an incurable and very old disease, metabolic and non-communicable disease (NCD) [1], diagnosis of high blood sugar levels, causing severe damage to the heart, blood vessels, eyes, kidneys and nerves. Disorders of insulin secretion, insulin function, or both [2,5]. Insulin is a peptide hormone produced by beta cells in the pancreatic islets, a basic anabolic hormone of the body that helps keep glucose in your blood in control. It does this by releasing glucose into your bloodstream and transporting it to cells throughout your body. Cells then utilize glucose for energy and the excess store in liver, muscles, and fatty tissue [6,7].

There are different types of Diabetes, but the most common Diabetes is Diabetes Mellitus and its subcategories are Type-1 Diabetes (T1D) and Type-2 Diabetes (T2D). Type-1 i.e., insulin-dependent diabetes (T1DM) and Type-2 insulin-dependent diabetes (T2DM). Type-1 diabetes is an autoimmune disease that is characterized by local inflammation of the insulin cells and Type-2 diabetes mellitus is characterized by insulin resistance in the skin and inhibited insulin production [8]. People with DM are at greater risk of developing another serious or chronic disease such as cardiovascular disease, stroke, neuropathy, kidney failure, retinopathy, blindness, amputation etc [9].

The second is, Diabetes insipidus (DI) is a rare but treatable condition that is usually accompanied with high thirst (polydipsia) and excessive urine (polyuria) [10]. Distinguishing these symptoms from those of primary polydipsia, diabetes, and the causes of urinary incontinence without polyuria can be challenging. Diabetes insipidus is caused by formation of vasopressin in the pituitary gland Central Diabetes Insipidus (CDI), or the action of vasopressin in the kidneys, Nephrogenic Diabetes Insipidus (NDI) [10,11]. DI is a rare disease, usually found in 1:25,000. Diabetes DI can occur in anyone at any age, and the prevalence is equal for both men and women [8].

Diabetes mellitus, a major and rapidly growing problem of public health care. It grows frequently, and brings long-term problems with it, placing a heavy global burden on public health and socio-economic development [12,13]. The International Diabetes Federation (IDF) estimates that 451 million adults are living with diabetes worldwide in 2017, with an estimated increase of 693 million by 2045 if no effective control measures are opted [14]. Diabetes under 20 years of age is now over one million [15].

In 2012, 67% of deaths worldwide (i.e., 38 million out of 56 million deaths worldwide) were caused by NCDs, mainly cardiovascular diseases (CVDs), diabetes, cancer, and incurable respiratory diseases. About 73% (28 million) of these deaths occur in low and middle income countries [16]. People with diabetes are 2-3 times more likely to be at risk than healthy people. Diabetes mellitus is associated with an increase in mortality from heart disease, stroke, chronic kidney and liver disease, and cancer [17,18]. India is one of the historic sites for diabetes mellitus epidemic and has the second highest number of people with the disease in the world (~69 million people since 2015). Other countries in southern Asia, such as Bangladesh, Pakistan, Sri Lanka, and Nepal, also have high rates of diabetes mellitus [19].

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Epidemiology

India has the second largest population in the world and could surpass China as the world's most populous country by 2024. About 32% of Indians live in urban areas (2011 census) [20], an increase from 27% in 2001. Diabetes is caused by aging, urbanization, population growth, obesity and physical inactivity. The main cause of the epidemic is rapid genetic mutations, dietary patterns, and slower body movements [21,22]. Similar to the major metropolitan areas around the world, Indian cities are showing a higher rate of T1D than rural areas [23]. People living a sedentary lifestyle combined with a high-carbohydrate and high-fat diet, are contributing to an increase in the number of people with diabetes and related diseases throughout India [24].

Types of Diabetes

- Diabetes Mellitus
- Diabetes Insipidus

The most common type of diabetes found in India is diabetes mellitus (DM) which has two subtypes- Type 1 and Type 2. Among them type 2 is the most common in Indian people. Another type of diabetes is insipidus (DI) is a rare disorder that causes fluid imbalance. There are two types of diabetes insipidus, central and nephrogenic, and each has inherited and inherited causes. There is an excess of the amount of soluble urine (less than 300m Osm/kg) in all cases [25].

Diabetes mellitus

Type-1 Diabetes Mellitus: T1D can occur at any age (usually 10 -16), however it occurs most often in children and adolescents. In T1D, the body does not produce enough insulin to control glucose levels. More recently it has been called insulin-dependent diabetes mellitus or childhood diabetes [26]. In T1D, the immune system depletes the cells that produce insulin (beta cells) in the pancreas [27]. Some people are genetically predisposed to the disease. Patients with T1D are likely to have low insulin levels ranging from zero to low. Without insulin, sugar builds up in the circulatory system instead of entering cells. Therefore, the body cannot use this glucose. Likewise, high blood glucose levels cause blockages and damage to body tissues [27].

Symptoms & treatment: Excessive craving, excessive thirst, accidental weight reduction, frequent wetting, hazy vision, sluggishness, mood swing etc.

Insulin is the basic treatment for T1D, replacing a hormone that the body cannot carry. There are four kinds of insulin that are widely used. They are divided into how fast they start working, and how long the effect lasts. Immediate insulin starts to work within 15 minutes and lasts for 3 to 4 hours. Fast-acting insulin starts to work within 30 minutes and lasts 6 to 8 hours. Some insulin starts to work within 1 to 2 hours and lasts 12 to 18 hours [28].

Diagnosis & diet: The main T1D test is a randomized blood sugar test, which tells the amount of glucose circulating in a person's blood over a period of time. A blood sugar level of 200mg/dl confirms diabetes.

The second diabetes screening test was a glycated haemoglobin test (HbA1C; a test showing the concentration of glucose in the blood at 3 months). The average A1C level is between 5 and 5.5%, while anything higher than 5.7% indicates diabetes. If diabetes is controlled, a person's A1C levels will be lower [29].

Glucose levels depend on the type of food a person is taking. Delicious food causes glucose levels to rise rapidly [30]. A dietician may suggest limiting the daily intake of starch and the use of carbohydrate intake. Consulting a dietician and eating according to a diet chart to find the right balance of protein, fat, and carbohydrates can help control glucose levels [31].

Type-2 Diabetes Mellitus: T2D is more common in adults and accounts for about 90 percent of all diabetes cases. T2D is characterized by insulin resistance due to insulin resistance, decreased insulin production, and ultimately pancreatic beta-cell failure, resulting in reduced glucose transport to liver, muscle cells and fat cells. T2D occurs when a patient's body cells suppress the effect of insulin. This condition is called insulin obstruction in which glucose begins to rise in the blood. In people with insulin disorders, pancreas alters blood glucose levels. In response, the pancreas produces more insulin to maintain normal glucose [32].

Symptoms & treatment: Excessive cravings, excessive thirst, frequent physical activity, blurred vision, drowsiness, abrasions delayed healing time, recurrent contamination etc.

Diet and exercise can help people with T2D; they should take drugs as these drugs lower glucose in many ways:

Alpha-glucosidase inhibitors: Drugs that treat type 2 diabetes. There are two types of drugs in this class of drugs: acarbose (Precose) and miglitol (Glyset). They help keep your blood glucose level up immediately after a meal. Slight loss of sugar and starchy foods.

Biguanides: They work by reducing the amount of liver glucose produced during digestion. Metformin is the only biguanide currently available in most countries to treat diabetes. Meglitinides-secretagogues similar to sulfonylurea, although not related to structure. They stimulate the production of insulin in the pancreas, with a different mechanism of action and then sulfonylureas. This type of drug is given before the main meal.

SGLT2 inhibitors: Drugs used in diet and exercise to lower blood sugar in adults with T2D. Work by blocking the kidneys from restoring glucose in the blood and releasing excess glucose into the bloodstream.

Thiazolidinediones- (TZDs) are insulin sensors that improve insulin activity and increase insulin sensitivity [32].

Diagnosis and Diet: According to the ADA (American Diabetes Association), fasting glucose concentrations should be used for routine tests; but post-prandial blood sugar, random blood sugar and sugar tolerance tests are also used to determine blood sugar.

To diagnose diabetes, at least one condition must be used:

- Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc.) and normal glucose concentration in plasma = 11.1nmol/L (200mg/dL).
- Dietary plasma glucose = Its normal range is 70-110 mg/dl without caloric intake for at least 8 hours [33].

A dietician can help maintain the amount of sugar and grams consumed in all foods [34]. To control your glucose level, try to eat smaller portions of the day. Emphasize solid foods, for example, organic products, vegetables, whole grains, lean protein, poultry and fish, olive oil and nuts [35].

Diabetes insipidus (DI)

Diabetes insipidus (DI) is characterized by the inability of the kidneys to digest urine leading to chronic hypotonic polyuria more than 3 liters in 24 hours in adults and persist even when dehydrated. The two main types of DI can be described as follows [36].

Diabetes insipidus central (CDI): Diabetes insipidus Central DI (CDI) or Neurogenic DI is the most common type of DI, which occurs in both sexes equally and at any age. Diabetes insipidus is a type of DI that occurs when the body has a lower than normal amount of anti-diuretic hormone (ADH). ADH is also called vasopressin and produced by hypothalamus. ADH is then stored and excreted in the pituitary gland. This happens due to surgery or brain injury, resulting in traumatic injury to the hypothalamus or pituitary gland [11,37] and the destruction of neurons from the supraoptic nuclei and paraventricular hypothalamus [38].

Symptoms: DI first appears after 80-90% of damage to the magnocellular neurons in the hypothalamus [10]. Injury in the vicinity of the hypothalamic-neurohypophyseal area destroys more neurons than damage in the distant region. However, intimate injury accounts for 30-40% of post-traumatic and postoperative CDI, while distal trauma accounts for 50-60% of cases [11]. Acquired CDI is more common than congenital CDI, and approximately 25% of adult CDI cases are idiopathic [10,38]. CDI occurs in 12.5% of patients with mild head injuries and 40.9% of patients with head injuries [39].

Diabetes nephrogenic insipidus (NDI): NDI occurs when the kidneys are unable to respond to AVP. Urine production in patients with NDI is usually 12L/day. Children are more likely to have a inherited form while adults are more likely to have a diagnosed form of NDI [40]. In most cases (90%), inherited NDI is an X-linked condition caused by loss of function or mutation of V2R genes. It is rarely due to genetic mutations in AQP2 (10%). V2R is most commonly expressed in distal convoluted tubule and kidney-collecting tubes, and responds to AVP thus concentrating urine [41].

Diagnosis and symptoms: Proper diagnosis can provide important information about a possible primary diagnosis. The age at which symptoms begin to develop and intake of fluids, may affect after the diagnosis of diabetes insipidus. The main symptoms - polyuria and persistent polydipsia, and young children may be severely dehydrated, vomiting, constipation, fever, irritability, sleep disturbances, and developmental disabilities. Nocturia in children leading to bed-wetting.

Other symptoms are fever, dry skin and mucous membranes, weight loss, weak skin turgor. Hypotension and tachycardia with decreased right atrial pressure and pulmonary artery occlusion and altered levels of awareness may occur [37,38]. CNS ability to perform AVP and kidney ability to respond to it is measured by Hare-Hickey (dehydration test) and Desmopressin challenge tests. A 24-hour urine volume is used to confirm polyuria. During dehydration, hourly measurements of body weight and urine osmolality are performed, until 2-3 samples vary by 5% of body weight and/or plasma Na+ exceeds 143mEq/L or urine rises to normal. Desmopressin administration distinguishes between CDI and NDI [38].

New diagnostic markers Endogenous vasopressin equilibrium is an important diagnostic test between CDI and NDI. Copeptin (C terminal glycoprotein AVP prohormone) can be considered as a stable surrogate of plasma endogenous AVP. AVP is unstable, heavily attached to platelets and quickly erased. The small size of AVP makes the measurement difficult [10,42]. In one study, copeptin levels were found to be <2.5pmol/L in all patients with CDI, suggesting that it could be used to distinguish CDI from PP and NDI [43].

Genes Responsible for Diabetes

For Type-1 diabetes mellitus

Prior to genome-wide association (GWAS) studies, six loci in the genome were fully established to be associated with T1D. With the development of high-throughput single nucleotide polymorphism (SNP) genotyping array technologies, which allow researchers to develop more compact GWAS, more T1D-risk genes have been identified. Indeed, recent meta-analyzes of numerous databases from independent investigators have yielded nearly 60 proven T1D genetic predisposition. Currently, there is evidence that more than 20 genome regions may be involved in genetic predisposition to T1D. Among the all identified candidates genes, that had the most impact on T1D risk genetically in the HLA gene on chromosome 6p21. The regional human leukocyte antigen (HLA) was the first known candidate to be strongly associated with T1D in the 1970s. This region contains several hundred genes that are known to be involved in the immune response. Those most closely associated with the disease are HLA class II genes (i.e., HLA-DR, DQ, DP) (genetics and diabetes) and the second region is the insulin gene (INS) in chromosome 11p15. In 1984, the insulin gene (INS) embedded in chromosome 11p15 was identified as a second loci linked to T1D [44]. In 1996, a gene associated with the cytotoxic T-lymphocyte protein 4 (CTLA4) embedded in chromosome 2q33 was recognized as a third loop [45]. Another case-control study in 2004 reported protein tyrosine phosphatase, a type of non-receptor 22 (PTPN22), a gene enclosed in chromosome 1p13 to be associated with T1D risk [46]. Vella et al., 2005 reported the gene for interleukin 2 receptor alpha (IL2RA) as the fifth T1D loop in chromosome 10p15 [14]. In 2006, Smyth et al. identified the interferon-induced gene with gene 1 of helicase C (IFIH1) on chromosome 2q24.3 as the sixth T1D-closely associated candidate using the genotyping of 6,500 non-synonymous SNPs across genome [47]. This study was a precursor to the first GWAS approach. Table 1 contains all the genes identified before GWAS.

IDDM1 (Insulin dependent diabetes mellitus 1)

HLA class II genes, also known as IDDM1, contribute to about 40-50% of the potential risk of T1D (Hirschhorn et al., 2003) and diabetes in which haplotypes DRB1 * 0401-DQB1 * 0302 and DRB1 * 0301-DQB1 * 0201 provides a very high trend, and DRB1 * 1501 and DQA1 * 0102-DQB1 * 0602 provide disease resistance [48]. MHC Class I also appears to influence type 1 diabetes, independent of class II molecules [49].

Insulin (INS)

The INS gene, found on chromosome 11p15.5, has been identified

Table 1: Genes Known Before Genome Wide Association Studies (1970s-2006) [55].

Genes	Position	Year
HLA	6p21	1970s
INS	11p15	1984
CTLA-4	2q33	1996
PTPN22	1p33	2004
IL2RA	10p15	2005
IFIH1	2q24.3	2006

HLA: Human Leukocyte Antigen; INS: Insulin Gene; CTLA-4: Cytotoxic T-Lymphocyte Associated Protein -
4; PTPN22: Protein Tyrosine Phosphatase Non-Receptor Type 22; IL2RA: Interleukin2 Receptor Alpha; IFIH1: Interferon-Induced With Helicase C Domain 1.

as IDDM2. A positive correlation has been observed with a randomized number of tandem multipliers (VNTR) in 5' side position [50],[51]. There are two common types - short phase I variant is associated with T1D (approximate increase of: 1-2), whereas the long phase III variant appears to be more protective. Class III strains appear to produce higher levels of insulin mRNA than class I variants. Such differences may contribute to better immune tolerance in people with a stage III condition by increasing the risk of improper selection of auto-reactive T-cell clones. The effect of the INS appears to be racially different, with minimal effects on non-Caucasian people [52].

CTLA-4 (cytotoxic T lymphocyte-associated 4)

The CTLA-4 gene is found in chromosome 2q31-35 [53], where most T1D genes may be found. CTLA-4 strains have been linked to T1D, as well as other autoimmune diseases. CTLA-4 poorly regulates T-cell 5 activity 6. However, impaired function, associated with Thr17Ala variation, may increase the risk of T1D. Overall, the related increase in the risk of CTLA-4Ala17 variance is estimated at ~ 1.5. genetics and diabetes [53]. Some of the genes and risk factors identified so far are listed in the Table 2.

For Type-2 Diabetes Mellitus

T2D is thought to be influenced by a number of genes with minimal effects and environmental factors. Until recently, the T2D gene was relatively limited with only a few proven genes. Until 2007, genetic mutation in T2D was performed by linking microsatellites and applicant gene association studies [54]. With GWAS and a large meta-analysis of a few T2D novel genes that have finally been identified and validated, their function remains to be determined [55]. Many genes have been proposed as T2D candidate genes but only a few genes have been positively associated with several studies, including PPARG, KCNJ11, TCF7L2 and WFS1. It has also been shown that concordance levels of monozygotic twins, ranging from 60-90%, are significantly higher than those of dizygotic twins. Thus, it is clear that T2D has a strong genetic trait. One method used to identify endangered genes is based on gene identification [56,57]. Those genes are chosen because of their involvement in pancreatic β cell function, insulin action / glucose metabolism, or other metabolic conditions that increase the risk of T2D (e.g., energy intake/cost, lipid metabolism). To date, more than fifty T2D candidate genes have been tested on a variety of people worldwide. However, the effects of all candidate genes have always been conflicting. Possible explanations for the different findings include small sample sizes, differences in

Table 2: Genes Known after Genome Wide Association Studies (2007-2013) [55].

Region/ Locus	Genes	SNPs
16p13	CLEC16A	rs2903692, rs725613, and rs17673553
13q22	LM07	rs539514
2q23	EFR3B	rs478222
2q23	NCOA1, C2orf79 , CENPO, ADCY3, DNAJC27) POMC DNMT3A	Fine gene mapping and functional studies are needed for these genes to determine causal variants for 2q23 region
6q27	PHD, DLL1, PSMB1, TNFRSF11B, FOSL2, WDR27, C6orf120, PHF10, TCTE3, C6orf208, LOC154449, DLL1, FAM120B, TBP, PCD2	rs924043
12q24	CUX2	rs1265564
5p13-q13	HTR1A	
6q15	BACH2	
10p15	PRKCQ	
15q24	CTSH	
22q13	C1QTNF6, SSTR3	
12q13	ERBB3, RAB5B, SUOX, RPS26, CDK2	
1q32.1	IL10, IL19 and IL20	
9p24.2	GLIS3	
12p13.31	CD69	
16p11.2	IL27	

CLEC16A: C-Type Lectin Domain Family 16, Member A; LM07: Lim Domain Only 7; EFR3B: Protein EFR3 Homolog B; NCOA1: Nuclear Receptor Co-Activator 1 Protein; C2orf79peptidyl: tRNA Hydrolase Domain Containing 1; CENPO: Centromere Protein O Gene; ADCY3: Adenylate Cyclase 3 Gene; DNAJC27: DnaJ/Hsp40 Homolog; Subfamily C, Member 27 Gene; POMC: Pro-Opiomelanocortin Gene; DNMT3A: DNA (cytosine-5)-Methyltransferase 3 Alpha Gene; PHD: Plant Homeo Domain; DLL1: Delta-Like 1-Drosophila Gene; FAM120: Family with Sequence Similarity 120B Gene; PSMB1: Proteasome (prosome, macropain) Subunit, Beta Type, 1 Gene; PDCD2: Programmed Cell Death 2 Gene; TNFRSF11B: Tumor Necrosis Factor Receptor Superfamily, Member 11B; FOSL2: FOS-Like Antigen 2; WDR27: WD Repeat Domain 27; PHF10: PHD Finger Protein 10; TCTE3: T-Complex Testis-Specific Protein 3; C6orf208: Human Putative Uncharacterized Protein; DLL1: Delta Like Canonical Notch Ligand 1; FAM120B: Family With Sequence Similarity 120B; PSMB1: Proteasome 20S Subunit Beta 1; TBP: TATA Box Binding Protein; and PCD2: Programmed Cell Death Protein 2; CUX2: Cut-Like Homeobox 2; HTR1A-5: Hydroxytryptamine Receptor 1A; RFN180: The Ring Finger Protein 180; BACH2: BTB Domain And CNC Homolog 2; PRKCQ: Protein Kinase C Theta Gene; CTSH: Cathepsin H; C1QTNF6: C1q and Tumor Necrosis Factor-Related Protein 6; SSTR3: Somatostatin Receptor 3; ERBB3: Human Epidermal Growth Factor Receptor 3; RAB5B: Ras-Related Protein Rab-5B Gene; SUOX: Sulfite Oxidase; RPS26: Ribosomal Protein S26; and CDK2: Cyclin Dependent Kinase 2; IL10, IL19 and IL20: Interleukin Genes; GLIS3: Glis Family Zinc Finger Protein 3; CD69: Cluster of Differentiation 69.

T2D inclination across all ethnic groups, environmental exposure variations, and genetic interactions. Given the current controversy, this review will focus only on the genes of a few promising candidates. These include PPARγ, ABCC8, KCNJ11, and CALPN10. Many other genes have been found associated with T2D in some studies, including IRS1, CAPN10, ADBR3, PPARGC1A, ENPP1 and others [58]. Many of these genes have been investigated as candidate genes because of their biological function.

PPARγ (Peroxisome Proliferator-Activated Receptor-γ)

This gene has been studied extensively because it is important

for adipocyte and lipid metabolism. In addition, the purpose of hypoglycemic drugs is known as Thiazolidinediones. Another gene for PPARγ (Pro) reduces insulin sensitivity and doubles T2D risk. Perhaps most importantly this difference is very common in most people [59].

ABCC8 (ATP binding cassette, small family C, member 8)

This gene includes a high-affinity sulfonylurea receptor (SUR1) subunit composed of the Kir6.2 subunit (coded by UKCNJ11U, also known as the potassium channel, which repairs within the small family J, member 11) [60]. Both genes are part of the ATP-sensitive potassium channel, which plays a key role in regulating the release of hormones, such as insulin and glucagon, into the beta-cell. Modification of any type of gene may affect the activity of potassium channel and insulin production, ultimately leading to the development of T2D [59].

KCNJ11 (Potassium Inwardly Rectifying Channel Subfamily J Member 11)

Interestingly, ABCC8 and KCNJ11 are only 4.5 kb apart, and they are not far from the INS gene. Different genes KCNJ11 (Lys) and ABCC8 (Ala) are associated with T2D, as well as other diabetes-related factors. Because of the proximity of these genes, current studies examine whether they work in isolation, or rather have an independent effect on T2D inclination. Since PPARγ, ABCC8, and KCNJ11 are targeted drugs commonly used in the treatment of T2D, there are pharmacogenetic effects in maintaining good glycemic control. The reaction to hypoglycemic therapy may be related to the human genotype. Thus, genetic testing may not only help determine who is at high risk of developing T2D but may also help direct T2D treatments [59].

CAPN10 (calpain 10)

CAPN10 incorporates calcium-dependent cysteine protease into the cell that is ubiquitous [61]. The haplotype originally linked to T2D included the conversion of intronic A to G at 43, which appears to be involved in the recording of CAPN10. Two amino acid polymorphisms (Thr504Ala and Phe200Thr) are also associated with the risk of T2D. However, it has been suggested that coding and polymorphisms that are not deceptive do not independently affect the risk of T2D, but instead contribute to premature years in diagnosis. Physiological studies suggest that variability in calpain 10 activity affects insulin retention and, therefore, T2D uptake. Studies from different ethnic groups indicate that the local contribution to the increased risk of T2D may be much larger in Mexican-American than in the Caucasus [59].

IRS1 (Insulin receptor substrate 1)

It is one of the proteins involved in the transmission of insulin receptor signaling by its phosphorylation residues tyrosine [62]. Normal polymorphism G972R (rs1801278), close to tyrosine phosphorylation motifs, has been associated with T2D in some but not all studies [63]. The meta-analysis of 27 studies showed a modest correlation with T2D, but this correlation would not be confirmed by the current major study or T2D GWAS. The same polymorphism is also associated with insulin resistance in obese people but not in obese people [64]. And the expression of IRS1 mRNA has been reported to be low bone tissue from non-diabetic individuals. Mice lacking IRS1 showed low insulin resistance and hyperinsulinemia but did not develop diabetes. Special tissue tests show the role of IRS1 in showing insulin in skeletal muscle, adipose tissue and pancreatic cells [65].

Table 3: The other genes found to be in associated with T2D.

Genes	Position
SLC30A8	8
CDKN2A/B	9p21
IGF2BP2	3
HNF1B	17
FTO	16
JAZF1	7
CDC123, CAMK1D	10
TSPAN8/LGR5	12
THADA	2
ADAMTS9	3
NOTCH2	1

SLC30A8: Solute Carrier Family 30 (Zinc Transporter), Member 8; CDKN2A/B: Cyclin-Dependent Kinase Inhibitor 2A/B; IGF2BP2: Insulin-Like Growth Factor 2 mRNA Binding Protein 2; HNF1B: Hepatocyte Nuclear Factor 1 Homeobox B; FTO: Fat Mass and Obesity-Associated; JAZFI: JAZF Zinc Finger 1; CDC123: Cell Division Cycle Protein 123; CAMK1D: Calcium/Calmodulin-Dependent Protein Kinase ID; TSPAN8: Tetraspanin 8; LGR5: Leucine-Rich Repeat Containing G Protein-Coupled Receptor; THADA: THADA Armadillo Repeat Containing; ADAMTS9: ADAM Metallopeptidase with Thrombospondin Type 1 Motif 9; NOTCH2: Notch Receptor 2.

TCF7L2 (transcription factor7-like 2)

The association between polymorphisms in TCF7L2 and T2D was first discovered in 2006 by Grant and colleagues when investigating a T2D-connected region on chromosome 10q2531. However, the organization did not comment on communications with the region. The organization was subsequently validated for a number of studies, including all GWAS and TCF7L2 and is therefore considered to be the most potent gene for T2D32. TCF7L2 encrypts a transcription factor involved in the Wnt signalling pathway but how it contributes to the pathogenesis of T2D is not well understood [66]. Several studies have shown that intronic SNP in TCF7L2 is associated with inactive insulin production and β-cell function but not insulin action. It has been suggested that the release of dysfunctional insulin may be linked to a parasitic incretin effect [67].

WSF1

WFS1 has been identified as a T2D candidate gene in a study of 83 genes for β-cell and T2D activity. Meta-analysis of 11 studies confirmed rs10010131 as a variant of T2D [68]. WFS1 contains wolframin, a glycoprotein membrane that regulates calcium homeostasis in the endoplasmic reticulum. Mutations in WSF1 cause Wolfram syndrome, which is characterized by diabetes insipidus, DM, optic atrophy and augmentation [69].

Table 3 represents the other genes and region found responsible for type-2 diabetes.

Genes Responsible for Diabetes Insipidus

The genetic form of nephrogenic diabetes insipidus is associated with mutations in AVPR2 or AQP2 genes. Genetic AVPR2 mutation

is the source of 90% of nephrogenic diabetes insipidus nephrogenic diabetes insipidus most common and approximately the remaining 10% of cases are caused by AQP2 genetic mutations [36]. Molecular genetic testing such as serial single-gene testing or a multi-gene panel, can be used to check mutation/deletion/insertion or splice site variants etc in AVPR2

Congenital CDI has a small contribution to the etiology of CDI, with more than 60 genetic mutations in the AVP-NPII gene identified, most of which are in the NPII gene [26]. In a family CDI study, mutations in exon 2 of AVP were found studies through sequencing AVP gene [40].

Conclusion

To prevent the rapid increase in diabetes in the world it is necessary to work on the genetic level apart taking other measurements like managing weight, diet etc. Due to advances in the technologies several genes, genetic loci and it's variants show association in causing diabetes but still there several other region and genes found in the close relation with candidate genes show some visible association in the development of diabetes as we have complete human genome sequence and a other latest techniques like CRISPR, it is now easy to carried out studies. Identifying the function of particular genes in the pathogenesis of diabetes will be a most important element in future studies in this field. The review comprises of all studies of diabetes mellitus and insipidus in one place with all recent findings.

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