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Diabetes and Renin-Angiotensin-Aldosterone System: Pathophysiology and Genetics

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Abstract

Diabetes mellitus (DM) is a metabolic disorder and characterized by hyperglycemia. Being a concern of both the developed and developing world, diabetes is a global health burden and is a major cause of mortality world-wide. The most common is the type 2 diabetes mellitus (T2DM), which is mainly caused by resistance to insulin. Long-term complications of diabetes cause microvascular related problems (eg. nephropathy, neuropathy and retinopathy) along with macrovascular complications (eg. cardiovascular diseases, ischemic heart disease, peripheral vascular disease). Renin-angiotensin-aldosterone system (RAAS) regulates homeostasis of body fluid that in turn, maintains blood pressure. Thus, RAAS plays pivotal role in the pathogenesis of long-term DM complications like cardiovascular diseases and chronic kidney diseases. T2DM is a polygenic disease, and the roles of RAAS components in insulin signaling pathway and insulin resistance have been well documented. Hyperglycemia has been found to be associated with the increased plasma renin activity, arterial pressure and renal vascular resistance. Several studies have reported involvement of single variants within particular genes in initiation and development of T2D using different approaches. This chapter aims to investigate and discuss potential genetic polymorphisms underlying T2D identified through candidate gene studies, genetic linkage studies, genome wide association studies.

Keywords: diabetes, type 2 diabetes, renin-angiotensin-aldosterone system, hypertension, gene polymorphism, genome wide association study, genetics, COVID-19

1. Introduction

Diabetes is a global health burden and one of the leading causes of morbidity world-wide [1]. Diabetes mellitus (DM) is a metabolic disorder characterized by polydipsia, polyphagia, polyurea and weight loss due to hyperglycemia, which means persistent elevated levels of plasma glucose. The prolonged hyperglycemia results in long-term impediments of diabetes that cause macrovascular complications including cardiovascular diseases (CVDs) and other vascular complications including nephropathy (end-stage renal disease) or retinopathy (leading to blindness) [2]. On the other hand, renin-angiotensin-aldosterone system (RAAS) plays an important role in maintaining blood pressure and body fluid [3]. Inappropriate

activation of RAAS contributes to the hemodynamic abnormalities that lead to endothelial dysfunction, hypertension, and CVD [3, 4].

Diabetes, hypertension and CVDs, are important risk factors for severity and mortality in people infected with coronavirus infectious disease 2019 (COVID-19) [5, 6]. Both Type 2 diabetes (T2D), the commonest form of diabetes and hypertension are multifactorial and polygenic diseases caused by the association of both genetic and environmental factors. Understanding the underlying genetic causes of susceptibility to these diseases is important for people's health and health-related quality of life worldwide. In this chapter, we describe the pathophysiology of T2D and RAAS and their associated risks analyzed in term of genetic variants.

2. Diabetes

Diabetes is a global epidemic affecting people of both the developed and developing world. According to International Diabetes Federation, 9.3% of the world population had diabetes in 2019 and predicted that by 2045 about 10.9% of the world population may suffer from diabetes [7]. Prevalence of diabetes is increasing both in developing and developed countries. About 79% of the diabetic patients live in low-income or lower middle-income countries of which more than 60% belongs to Asian countries while rest of them are habitant of developed world [8]. Notably, diabetes is a health concern in adults compare to other age groups and it has been projected that between the years 2010 to 2030, developing countries will harbor 69% more adults with diabetes while 20% more adults with diabetes will be residing in developed countries [9]. Persistent elevated levels of plasma glucose result in long-term impediments of diabetes that cause macrovascular complications including CVDs, peripheral vascular disease, stroke and microvascular complications including nephropathy that leads to end-stage renal disease, retinopathy leading to blindness, neuropathy that causes damage to the nerves [2].

Diabetes can be classified into the following types [10]:

- i. Type 1 diabetes (T1DM; due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood).
- ii. Type 2 diabetes (T2DM; due to a progressive loss of adequate β -cell insulin secretion frequently on the background of insulin resistance).
- iii. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation).
- iv. Specific types of diabetes due to other causes, eg. monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the Human Immunodeficiency Virus treatment, or after organ transplantation).

Of the major types, T2DM is the commonest form. T2D was caused by developing insulin resistance due to lifestyle, obesity, reduced physical activity [3]. Individuals with T2DM will have seven to ten years shorter life span compare to non-diabetic individuals and 80% patients with T2DM develop cardiovascular disease [11]. CVD like coronary artery disease is responsible for the 2–4 fold

increased rate of death in adults [12, 13]. Diabetes being considered as the independent risk factor from other such factors as age, gender, smoking, weight for dying from liver disease, lung disease, cancer, mental disorders, cardiovascular complications [14]. Moreover, people are more prone to infections or infectious diseases who have already developed diabetes [15] due to high levels of glucose in blood that favors immune dysfunction by modulating both innate (alteration of neutrophil functions) and adaptive (reducing T cell response) immune response [16–20]. Most recent incidence of pandemic has revealed that the severity of COVID-19 exaggerates in individuals with hyperglycemia due to augmented production of pro-inflammatory cytokines as well as poor innate immunity [21]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection severely affects the survival rate of the infected individuals [21] with diabetes as it is a critical comorbidity [22].

T2D is a multifactorial and polygenic diseases caused by the association of different risk alleles located on multiple genes. Environmental factors modulating gene–gene interaction and/or expression are believed to be contributing factor for the development of T2D. Thus, genetic variants associated with T2DM are not only important for prediction and prevention of the disease along with its associated complications, but also will facilitate early treatment as well as need-based bona fide management of the disease.

3. Renin-angiotensin-aldosterone system

RAAS is one of the multifaced systems, which maintains homeostasis of body fluids, electrolyte balance and thus, regulates blood pressure [3, 23, 24]. Renin, initially known as pressor hormone, is an aspartic protease and it's only known substrate is angiotensinogen (AGT) [25]. Angiotensin converting enzyme (ACE) is a peptidase that is mainly found in the capillaries of lung followed by endothelial and kidney epithelial cells in human [26]. The classical RAAS involves cleavage of AGT for release of a small decapeptide, angiotensin-I (Ang-I). The peptidase ACE then converts Ang-I into an octapeptide, angiotensin-II (Ang-II). RAAS activity is intrinsically high in the lung where ACE level is very high and thus, a major site of systemic Ang-II synthesis.

The Ang-II is the most potent hormone peptide that utilizes G-protein coupled receptors (GPCRs) called angiotensin type 1 and type 2 receptors (AT1R and AT2R) to mediate physiological functions. Ang-II facilitates vasoconstriction, cell proliferation, cell hypertrophy, anti-natriuresis, fibrosis, and atherosclerosis using AT1R [27] while, via AT2R, the peptide elicits vasodilation, anti-proliferation, anti-hypertrophy, anti-fibrosis, anti-thrombosis, and anti-angiogenesis [28] (**Figure 1**). Ang-II also stimulates the production of the steroid hormone, aldosterone, which is the final product of the RAAS cascade. Aldosterone binds to the mineralocorticoid receptor and regulates the transcription of target genes, resulting in the upregulation of electrolyte flux pathways in the kidney. Dysregulation of RAAS can lead to adverse effects on fluid homeostasis, which in turn may lead to organ damage followed by CVDs.

Angiotensin converting enzyme 2 (ACE2) is a homolog of ACE. ACE2 is also highly expressed in the lung. The main activity of ACE2 is to degrade Ang-II into angiotensin 1–7 (Ang 1–7) by hydrolyzing of the C-terminal residue [29]. Thus, ACE2, in the lung, have a role in adjusting the balance of circulating Ang-II/Ang 1–7 levels. Also, product of ACE2 facilitates vasodilation and therefore opposing the role of ACE product (i.e. Ang-II). Ang 1–7 is expected to exert its action through the MAS-related (MAS1) GPCR [30]. It is evident that insulin exhibits adverse effects

Figure 1. Renin-angiotensin-aldosterone system (RAAS) and its linkage to type 2 diabetes mellitus (T2DM). The classical RAAS shows angiotensin-II (Ang-II) dependent pathway mediated different physiological effects via G-protein coupled receptors (GPCR) called angiotensin type 1 and type 2 receptors (AT1R and AT2R). Renin, secreted from kidney, regulates the rate limiting step of this pathway by converting its liver originated substrate angiotensinogen (AGT) into a decapeptide, angiotensin-I (Ang-I). Ang-I is converted into an octapeptide Ang-II by angiotensin converting enzyme (ACE). Ang-II binds to AT1R and AT2R to mediate the counterbalanced physiological functions. Angiotensin converting enzyme 2 (ACE2) is to cleave Ang-II into angiotensin 1-7 (Ang 1-7), which exerts the vasodilation effects.

on the structural and functional features of islet cells by inducing Ang-II mediated oxidative stress [31]. Through AT1R, Ang-II inhibits course of insulin action in vascular and skeletal muscle tissue, interferes insulin signaling via phosphatidylinositol 3-kinase and its downstream protein kinase B (Akt) signaling pathway [32].

Increased vasoconstriction and renal sodium reabsorption along with enhanced secretion of aldosterone results overactivation of RAAS followed by metabolic modulation leading to altered blood pressure and development of insulin resistance [33, 34]. Aldosterone has the ability to impair insulin signaling pathway by down-regulating insulin receptor substrate-1 (IRS-1) in vascular smooth muscle cells [35] and thus, contributes to the development of and/or deteriorating metabolic disorders including disruption of glucose homeostasis [36].

The (pro)renin receptor [(P)RR], cloned almost two decades before in 2002 [37], has now been considered as one of the pivotal members of RAAS. Modulation of renin/prorenin takes place after binding to their receptor. After binding to (P) RR, the enzymatic activity of renin increases while the proactive form of renin known as prorenin gets activated non-proteolytically and exhibits renin activity [38, 39]. Binding to (P)RR with prorenin causes a change in conformation within the prosegment region followed by opening of the active site and making it accessible to the substrate, AGT [39, 40]. Thus, receptor mediated activity of renin and prorenin possibly activate tissue specific renin-angiotensin system in an Ang-II dependent manner, which ultimately could contribute in modulating local RAAS. (P)RR has been found to be ubiquitously expressed in brain, heart, placenta, liver, pancreas and kidney [37]. The association between (P)RR gene polymorphism and high blood pressure has been demonstrated in Caucasian and Japanese male subjects [41, 42]. In another study with transgenic rats over expressing (P)RR in smooth muscles it was reported to elevate blood pressure and increase heart rate in their models [43]. A single mutation in exon 4 of (P)RR gene is associated with mental

retardation and epilepsy [44] while a silent mutation in exon 4 on human (P)RR facilitates enhanced expression of c321C > T that lacked exon 4 [44]. Though presence of this single nucleotide polymorphism (SNP) does not bring any change as far as the renin binding ability is concerned but it modulates ERK1/2 activation [44], which may in turn modifies gene expression pattern.

RAAS mediates diverse functions by the action of angiotensin receptors (**Figure 1**) and has the link to cancer through tissue remodeling, inflammation, angiogenesis and apoptosis [45, 46]. Genetic and epidemiological studies showed that polymorphism of the RAS components contribute to the risk of cancer. Either the insertion/deletion (I/D) polymorphisms of *ACE* or *AGT* M235T SNP confer the risks for developing breast cancer [45]. Two *AT1R* SNPs are associated with risk for renal cell cancer, and its associations are stronger in subjects with hypertension [47]. Although the identified SNPs could be a marker of disease linked to another disease-causing SNP, rather than the disease-causing SNP itself [47], further studies are warranted to clarify cancer etiology involving the RAS components.

4. Diabetes and RAAS

Development of insulin resistance at the cellular level is initiated by Ang-II and aldosterone via increasing oxidative stress and altering insulin signaling (**Figure 2**). Ang-II is also responsible for generating pancreatic β -cell oriented oxidative stress, inflammation, and apoptosis. Evidence also suggested involvement of aldosterone in diminished glucose induced insulin secretion from pancreas [33].

The therapeutic approaches for lowering glucose levels significantly reduces the chance of developing diabetes associated microvascular complications while modest improvement has been observed in case of improving diabetes associated macrovascular complications [48, 49]. A case-control study conducted in German population demonstrated increased prevalence of T2D among individuals with hypertension and higher concentration of aldosterone (but low Ang-II level and low plasma renin activity) compared to the control hypertensive individuals [50].

Figure 2. Involvement of RAAS components into pathogenesis of T2DM. Hyperglycemia causes oxidative stress through generation of reactive oxygen species (ROS) that along with the production of Ang-II through overactive RAAS, may contribute to the pathophysiology of T2DM. Thus, genetic polymorphisms present in the genes expressing the components of RAAS probably modulate gene expression followed by protein levels that ultimately involve in the disease pathogenesis. Also, variants within these genes may also involve in the initiation and development of diabetes.

Another study revealed association between higher levels of aldosterone and insulin resistance along with dose-dependent contribution of high aldosterone level to the risk of developing T2D [51]. **Figure 2** schematically represents components of RAAS involved in the regulation of physiology, and probable mechanism of their contribution to the pathophysiology of diabetes.

5. T2DM and RAAS: contribution of the RAAS components to the pathogenesis of T2D

The most important key features of the pathogenesis of diabetes are the resistance to insulin which in turn reduces the insulin ability to uptake peripheral glucose [52], and the failure of β -cells to produce adequate amount of insulin [53]. Obesity is one of the major risk factors for the development of insulin resistance along with sedentary lifestyle, lack of physical activities etc. that in turn increases the levels of glucose in blood [54]. Obesity is also involved in the activation of RAAS [55, 56]. On the other hand, RAAS has been found to be associated with multiple obesity-associated chronic diseases, especially for cardiovascular related disease [57, 58]. In addition, several lines of evidence revealed association between activation of RAAS and the onset of T2D [55, 59, 60]. The connection between renin angiotensin system and insulin signaling pathway along with insulin resistance has been established [61]. A meta-analysis demonstrated that use of AT1R blockers or ACE inhibitors reduces the chance of new onset of T2DM by 22% in a population who are vulnerable to diabetes [62]. Though association between ACE I/D polymorphisms and risk of T2D inconsistent even in the same population [63, 64], CAPP trial demonstrated that ACE inhibitor captopril-treated patient group had 11% reduced chance of developing diabetes compared to non-treated groups [65] while LIFE study showed 25% reduction in new onset of diabetes [66]. All together these studies strongly support linkage between RAS components and hyperglycemia. Moderate hyperglycemia at the early stage of diabetes results increased plasma renin activity, arterial pressure and renal vascular resistance with the activation of both local and circulating RAAS [67, 68]. Moreover, hyperglycemia causes glycosylation of p53 which leads to the AGT transcription followed by the production of Ang-II [69, 70]. This was further supported by Fiordaliso et al. who demonstrated a direct correlation among levels of glucose, p53 glycosylation and Ang-II production [71].

Genetic predisposition involving certain SNPs residing within the genes of RAAS has been anticipated as the risk factors for the development and progression of T2D and T2D associated complications hypertension [72], coronary heart disease [73], nephropathy [73–75] and retinopathy [76]. Human AGT, a member of serpin gene family, comprises of 5 exons accounting for a full-length of about 12 kb and is situated on chromosome 1 (1q42-q43). Most convincing evidence for the probable association of polymorphic sites within *AGT* gene with essential hypertension has been identified in the 5' flanking region, exons, and introns of the gene [77]. Strong association of rs11568020 (A-152G) and rs5050 (A-20C) in the promoter region as well as rs4762 and rs699 within exon 2 of *AGT* gene with hypertension was evident in Eastern Indian population [72]. Interestingly, incompatible findings with respect to the association of *AGT* variants with T2D have been observed [62, 72, 78, 79]. Variants rs699 and rs4762 within *AGT* gene found to be associated with the reduced risk of T2D in Eastern Indian and Malaysian Malays populations [72, 78] while no significant association was observed in the Chinese and the Japanese populations [63, 79]. However, rs699, rs4762 and rs5051 of *AGT* gene were reported to be associated with the increased risk of T2DM in the Pakistani [80], Korean [81] and Malaysian Malays [78] populations, respectively.

It has been documented that Ang-II is capable of stimulating the production of TGF- β [82] or inducing generation of reactive oxygen species (ROS) [83] that causes over-accumulation of extracellular matrix proteins or various cellular dysfunctions in patients with diabetes. Furthermore, variants present within the genes of RAAS components especially within *ACE*, *AGT* and *AT1R* genes have shown to be the most promising candidate genes susceptible to diabetic associated complications like nephropathy along with its progression towards renal failure as well as retinopathy [78, 84]. Haplotype TCG of *AGT* has been observed to be associated with increased risk of T2D [78]. According to Purkait et al. [72], three haplotypes (H4, H7 and H8) of *AGT* showed strong association with hypertension while H2 had protective role against this disease. It is reported that the *AT1R* A1166C is not likely a risk factor for chronic kidney disease in East Asians and Caucasians while it is shown to be a risk factor in South Asian population [85, 86]. Almost 30–50% of the diabetic individuals are prone to develop kidney disease [87, 88]. Previous studies reported association of *renin* gene polymorphisms with number of non-communicable diseases including diabetic nephropathy [89], increased risk of vascular complications [90], plasma renin activity [91], susceptibility to hypertension in a variety of ethnic groups [92–95], T2D [96] with inconsistent results [97–99]. Few studies did not find any significant association of *renin* rs16853055 with diabetes and diabetic nephropathy diseases [100, 101] while Purkait et al. [102] found an association of this variant with diabetic nephropathy in Indian population along with strong linkage disequilibrium with rs16853055. On the other hand, Deinum et al. reported weak association of *renin* gene polymorphism present in the first intron (involved in the regulation of transcription of renin) with diabetic nephropathy [89, 103]. Moreover, rs1799998 of the *CYP11B2* gene (aldosterone synthase) was associated with the levels of serum aldosterone and production [104, 105], blood pressure [106, 107], ischemic stroke [108], with the progression of renal function [109, 110] and end stage renal disease [111]. Meta-analysis performed by Xu et al. demonstrated association of allelic frequency as well as co-dominant homozygous and recessive models of inheritance with regard to –344 T/C polymorphism within promoter region of *CYP11B2* gene with the increased risk of diabetic nephropathy [112]. Similar association was observed by Purkait et al. [113] in Indian population. Promoter regions play important regulatory roles in gene transcription followed by formation of a functional protein through translation. Thus, presence of variants within the promoter region may be involved in the disease progression or pathogenicity which is definitely subject to further investigation and validation. Furthermore, methylation within the promoter region of a gene contributes to the expression of that particular gene [114]. Variant rs1799998 causes substitution of cytosine to thymidine within the promoter region of *CYP11B2* gene which is the binding site of a putative steroidogenic transcription factor-1 [115].

6. Pathophysiology and genetics of type 2 diabetes

Both environmental and genetic factors play pivotal role in the development of diabetes in human. However, some individuals develop diabetes while others do not although they use to live in the same environment. A substantial proportion of Pima Indians develop T2D even with a normal lifestyle in a normal environment that showed strong linkage of genetic make-up to T2D [116]. Thus, understanding genetics related to the pathogenesis of T2D is of utmost importance for the management of this global endemic disease. Familial studies orchestrated more robust data as proof that genes play important role as risk factor for the development of diabetes. First degree individuals with family history of T2D are at 3-fold increased

risk of developing T2D compared to those who do not have positive family history [117–119]. Studies with monozygotic twins demonstrated that 50% risk of developing type 1 diabetes is contributed by *HLA* genes while rest of the 50% is associated with environmental factors and epigenetic modifications [120, 121]. Several family, population and twin-based studies established that heritability of T2D ranges from 20–80% [122, 123]. Forty percent individuals possess risk of developing T2D who have one parent with T2D while 70% of the individuals have higher risk of developing T2D if both the parents are T2D [124]. Seventy percent of monozygotic twins are in concordance with the chance of developing T2D while the concordance rate in dizygotic twins has been found to be 20–30% [125, 126].

The primary method to identify genes susceptible to T2D was genome linkage analysis. This approach efficiently identified causal mutations specially for the monogenic forms of diabetes like maturity-onset diabetes in young (MODY), mitochondrial diabetes in neonates and insulin resistance [127–129]. This approach further recognized the short tandem repeats located on q arm of chromosomes 4, 5, 10, 12, 22 and p arm of chromosomes 2, 3, 6, 13 for their probable association with T2D in different ethnic populations [130–134] along with causative genetic variants within *calpain10* (*CAPN10*) [135], *ENPP1* [136], *HNF4A* [137, 138] and *ACDC* [139]. Calcium-activated neutral protease 10, one of the regulator of glucose homeostasis, gene (*CAPN10*) variants UCSNP-43 G/A in intron 3, UCSNP-19 2R (two 32-bp repeats)/3R (three 32-bp repeats) in intron 6 and UCSNP-63 C/T in intron 13 have been reported to be associated with T2D in Mexicans Americans, German and Finnish populations [135, 140]. The ectonucleotide pyrophosphatase phosphodiesterase (*ENPP1*) was supposed to be associated with insulin resistance [141]. The three-alleles risk haplotype (K121Q/IVS20 delT-11/A > G + 1044 TGA, QdelTG) within *ENPP1* was associated with childhood obesity, development of T2D and with adult obesity [136]. *HNF4A*, member of the steroid hormone receptor superfamily, plays major role in insulin expression and secretion followed by glucose metabolism in pancreatic β -cells along with gluconeogenesis in liver [142, 143]. Variants within *HNF4A* gene were identified as the risk factor for MODY and causative factor for β -cell dysfunctions [144]. Also, non-coding variants rs4812829 and rs6017317 as well as coding variant rs1800961 (T130I) within *HNF4A* were involved in the development of T2D [145–147]. Decreased level of adipose tissue-derived adiponectin in plasma is evident in individuals with obesity [148], insulin resistance [149] and T2D [148]. Adiponectin encoding *ACDC* gene variants 276G > T and 45 T > G were found to be associated with lower levels of plasma adiponectin in Japanese [150] and German obese people [151], respectively along with their predisposition to T2D. However, genome wide linkage analyses did not reveal any association of these variants of *ACDC* gene with obesity and T2D in Pima Indians [139]. Transcription factor *TCF7L2* showed strongest linkage to the risk of T2D before genome wide association study (GWAS) era [130]. *TCF7L2* involves in Wnt signaling pathway that regulates proliferation and survival of pancreatic islet cell functions [152] and its reduced expression is linked to impaired insulin secretion [153]. *TCF7L2* gene variants rs12255372 and rs7903146, showed strong linkage disequilibrium with composite at-risk alleles of the microsatellite marker (DG10S478).

Candidate gene association studies have also been proved to be effective to obtain substantial evidences of genetic predisposition to T2D. For example, insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*), an important candidate gene for T2D [154, 155], was involved with T2D development by reducing insulin secretion [156] may be through changing adipose tissue and β -cell function [157]. *IGF2BP2* was also associated with overweight and obesity [158]. Association of rs4402960 and rs1470579 within *IGF2BP2* with the risk of T2D demonstrated in French Caucasians while another study revealed that T2D patients carrying the

T allele of rs4402960 had higher levels of fasting plasma glucose, postprandial glucose, total cholesterol and postprandial serum insulin compared to individuals with the GG genotype [158]. Besides, *IGF2BP2* variants showed effect on treatment of diabetes. For example, lower efficacy of the repaglinide treatment for reducing fasting plasma glucose and postprandial glucose was observed in diabetic patients with rs1470579 AC + CC genotypes compared to AA genotypes. On the other hand, repaglinide treatment had higher effect on diabetic patients with GT + TT genotypes with regard to rs4402960 on postprandial insulin compared to GG genotype carrying patients [158]. The potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) has attracted attention due to its contribution to the pathogenesis of T2D by modulating insulin production and secretion [159] and thus, is a good candidate gene to elucidate its disease association. *KCNJ11* harboring four missense SNPs rs5219, rs1800467, rs5215, rs41282930 were recognized to influence risk of T2D by impairing insulin secretion [160]. Peroxisome proliferator activator receptor gamma (*PPARG*) was identified to harbor T2D disease susceptibility variants. Both *KCNJ11* and *PPARG* encode anti-diabetic drug targets and their respective missense SNPs rs5219 (E23K) and rs1801282 (P12A) are associated with the risk of T2D [161].

Although candidate gene and linkage analyses provided considerable evidences behind the genes for their probable association with the pathophysiology of T2D and/or with the risk of T2D, novel genes are yet demanding due to the inconsistent and discordant findings within the same population and also, in different ethnic groups. Screening of whole genome using GWAS helps to overcome the shortcomings of the above mentioned approaches to some extent by expediting regularly spaced variants without any prior knowledge of gene or their effects that has brought a significant breakthrough in understanding the genetic basis of T2D. This has become realistic after successful completion of the Human Genome Project and the International HapMap Project. This has given an opportunity to deposit millions of SNPs in the public databases [162] and presence of higher frequency of a particular SNP in cases compare to controls suggests association of that SNP with the case i.e., disease. Moreover, to satisfy association of SNPs statistically, stringent p value ($<10^{-8}$) is required in GWAS and it benefited researchers to eliminate false positive association out of the millions of reported SNPs [163]. Even with such strict threshold levels of statistics, several case-control studies in different ethnicities have generated replicative positive results through different independent datasets. T2D associated variants within genes uncovered by GWAS positioned at different chromosomal locations (**Figure 3A**) can be grouped into i) insulin secretion and processing related (*GIPR*, *CCND2*, *CDKAL1*, *GCK*, *TCF7L2*, *GLIS3*, *THADA*, *IGF2BP2*, *DGKB*), ii) impaired insulin function related (*PPARG*, *KLF14*, *IRS1*), iii) insulin resistance related (*ACDC*, *FTO*, *KLF14*, *DUSP9*), iv) β -cell mass and function related (*IGF2BP2*, *HCNQ1*, *CDKN2A*, *CDKN2B*) and iii) body mass index (BMI) and lipid level related (*NRXN3*, *CMIP*, *APOE*, and *MC4R*). Notably rs4731702 of intronless *KLF14* demonstrated an association with insulin resistance [164] while rs972283 contributed to elevated blood pressure [165], which may ultimately increase risk of cardiovascular disease; C allele of the rs2283228 within *HCNQ1* showed association with increased fasting glucose levels and impaired β -cell function in Asians [166], while C allele of rs2237895 in *KCNQ1* was found to be related to decreased risk of abdominal obesity in patients with T2DM [167, 168]; rs5945326 of *DUSP9* on X chromosome was related to the increased risk of T2D in Japanese [169], Pakistanis [170] and in European [171] populations; rs1558902 within *FTO* showed correlation with the incidence T2D in humans even after adjusting the data with confounding factors such as age and BMI [172] and rs9939609 may modulate the risk of T2D by regulating other genes, an incidence

Figure 3. Chromosomal locations of genes carrying variants (A) associated with β -cell function followed by insulin production and secretion (B), glucose utilization and homeostasis (C) along with glycemic traits and abnormal adipose tissue function (D) which all together may lead to T2D and of genes of major RAAS components. Several approaches specially GWASs identified several variants associated with pancreatic islet cell function followed by β -cell dysfunction, insulin secretion and processing (red), with development of insulin resistance followed by imbalanced glucose homeostasis (blue). Other variants are also associated with abnormal adipose tissue function which may also be caused by oxidative stress, a consequence of Ang-II (Figure 2). Variants within SLC30A8 and (P)RR (green) showed both protection against T2D and risk association with T2D as well as hypertension, respectively. Also, mostly non-coding and few coding variants within the genes (black) showed association with the risk of T2D. Variants within the major gene of RAAS have been found to be associated with the risk of T2D and T2D-associated hypertension other than their established risk association with essential hypertension and cardiovascular diseases. REN, renin; AGT, angiotensinogen; AT1R and AT2R, angiotensin type 1 and type 2 receptors, ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; CYP11B2, aldosterone synthase; (P)RR, (pro)renin receptor; In, insulin; Glc, glucose; IRS, insulin receptor substrate.

independent of BMI [173]; variants present within the tumor suppressor cyclin dependent kinase inhibitors, CDKN2A and CDKN2B, reported to be associated with T2D in Asians and Europeans [174–177]. rs10811661 of CDKN2A/2B is also, according to GWAS, linked to diabetes [178]; hematopoietically-expressed homeobox or HHEX gene variants rs11118745G/A, rs7923837A/G, and rs5015480C/T had been identified as risk factors for T2D in Japanese [179], German [180], Korean [181], Indian [182] populations. Association of a common variant, Trp325Arg within SLC30A8, with the risk of T2D [171, 183]

and, levels of glucose [184] and proinsulin [185] had been well documented. Interestingly, through genotyping of ~150,000 individuals from five ethnic groups, Flannick et al. (2014) revealed protective role against the development of T2D mediated by the loss of function variants harbored within *SLC30A8* [186]. AA genotype of rs11558471 of *SLC30A8* was found significantly more frequent in T2D patients than in controls in Han Chinese [187] and Indian [182] populations.

Non-coding variants within different genes [like variants of *PRC1*, *MADD*, *MTNR1B*, *FADS1*, *CRY2*, *GLIS3*, *LC2A2*, *ADCY5*, *GCKR*, *G6CP2* [184], *TP53INP1* [188], *GIPR* [189], *ADCY5* [189], *TSPAN8/LGR5*, *JAZF1*, *Notch1* [190], *HNF1B* [191], *FTO* [155], *ZEDB3* [188]], as presented in **Figure 3A**, were also recognized as major risk factors associated with the development of T2D and/or regulation of glucose/insulin homeostasis, and/or glycemic traits (**Figure 3B** and **C**) and abnormal adipose tissue function (**Figure 3D**) while few variants were discerned to have protective roles against the development of diabetes [184, 188–195]. Also, similar association was found with regard to intergenic variants rs972283 (G/A, 47 kb upstream) of *KLF14* [188], rs2943641 (C/T, 502 kb upstream) of *IRS-1* [155], rs1111875 (C/T, 7.7 kb downstream) of *HHEX* [183], rs10811661 (T/C, 125 kb upstream) of *CDKN2A/2B* [190], rs4607103 (C/T, 38 kb upstream) of *ADAMSTS9* [190], regulatory region variant rs5945326 (G/A, 8 kb upstream) of *DUSP9* [188], rs2191349 (T/G) of *DGKB/TMEM195* [196], promoter region rs2853669 of human telomerase reverse transcriptase (*TERT*) gene [197]. Non-coding variants positioned at essential regions like enhancer and promoter sequence may also modulate chromatin loops, alter sequence motifs and modulate histone marks that ultimately regulate gene expression, which could be one of the key reasons their disease association.

7. Pathogenesis and genetics of RAAS

RAAS is the enzymatic cascade to produce the effector molecule, Ang-II, by the multiple enzymes [23] (**Figure 1**). Various genotypes of the RAAS components [eg. AGT, renin, ACE, ACE2, AT1R, AT2R and (P)RR] have been investigated to find the link between genetic variation, blood pressure, and hypertension [198].

The two *AGT* genotypes (G-6A non-coding SNP and M235T coding SNP) are associated with higher plasma AGT levels and increased risks of essential hypertension [77]. The *AGT* SNPs occurring within the non-coding region could explain the association with plasma AGT concentration because of the alternation in *AGT* transcription [198]. It is plausible that the higher AGT concentration brings about the higher levels of Ang-II, which may lead to high blood pressure. In the study of 10,690 individuals, the associations of elevated blood pressure, ischemic heart disease and ischemic cerebrovascular disease were examined with four *AGT* variants (A-20C and G-6A non-coding SNPs and T174M and M235T coding SNPs) [199]. Both women and men with -6AA, 174TT, and 235TT (versus -6GG, 174TT, and 235TT) had higher mean levels of plasma AGT (861 ng/mL and 811 ng/mL, respectively). This finding suggests that the genotype has an effect on risk of elevated blood pressure in women, but not in men [199]. The association of the genotype with ischemic heart disease and ischemic cerebrovascular disease seems weak as a risk [199]. A meta-analysis of 45,267 individuals from different ethnic populations shows that M235T genotype is associated with an increase in plasma AGT levels [200]. An analysis of 424 individuals from 41 two-generation families from Utah indicates significant linkage between six *AGT* SNPs (rs5051, rs699, rs6687360, rs2478543, rs3789670 and rs943580) and plasma AGT levels whereas plasma AGT and blood pressure were not significantly correlated [201]. *AGT* SNPs have been

identified from various ethnic groups to show its association with hypertension [72, 202–205]. Of note, *AGT* genotypes (G-6A, T + 31C and M235T) with hypertension are not associated with plasma AGT level, while -1074 t|T235 haplotype is associated with an increase of AGT level but not with hypertension [202]. Sato et al. [202] suggested that the positive association between *AGT* polymorphism and hypertension is not simply explained by an increase of plasma AGT concentration.

Renin polymorphism was investigated by assessing the association of ten *renin* genotypes with hypertension risk in 570 hypertensive and 222 normotensive Caucasians [95]. Subjects with DM, secondary hypertension, significant medical illness or severe obesity were excluded, and their food intakes were also controlled. The A allele of rs6693954 SNP and the haplotype containing rs6693954A were significantly associated with higher risk of hypertension [95]. Compared to other haplotypes, the same haplotype showed the higher levels of plasma renin activity, suggesting that a direct renin inhibitor is effective to reduce blood pressure of rs6693954A carriers [95]. In addition, the haplotype displayed a blunted mean arterial pressure response to exogenously infused Ang-II [95], which infers the dysregulation of RAAS at the tissue level [206]. This study [95] confirms the association between *renin* genotypes and risk for hypertension.

As described above, genetic variations in individual RAAS components can contribute to the onset of physiological outcomes, which probably brings about the increase in blood pressure. But hypertension is a multifactorial disease involving both genetic and environmental factors [207] like T2D. The mechanism of susceptibility to hypertension and CVD is much more complex, since various genes work in an additive or interactive manner, together with environmental factors [198]. Ji et al. [205] provided the experimental evidence to support the idea. In a study of 905 hypertensive and 905 normotensive Han Chinese population, 41 SNPs of the five RAAS components (*AGT*, *renin*, *ACE*, *AT1R*, and *CYP11B2*) and the non-genetic factors were analyzed to investigate their associations with essential hypertension [205]. Subjects with CVD, DM, kidney diseases, secondary hypertension and other major chronic illnesses were excluded. Serum levels of total cholesterol and triglyceride, and BMI were significantly higher in the hypertensive group than in the normotensive group. Six SNPs (rs3789678 and rs2493132 within *AGT*, rs4305 within *ACE*, rs275645 within *AT1R*, rs3802230 and rs10086846 within *CYP11B2*) were shown to associate with hypertension. The interaction between BMI and rs4305 (*ACE* SNPs) increased the susceptibility to hypertension. Together with non-genetic factors, the genetic variations in the RAAS components may play an important role in determining an individual's susceptibility to hypertension [205].

GWAS analysis performed by Ji et al. [208] provided one important viewpoint on genetic polymorphism of RAAS. The authors searched GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) and identified all known RAAS genes and relevant diseases and traits. Remarkably, SNPs within *AGT*, *renin*, *ACE2*, *CYP11B2*, *ATP6AP2* [(P) RR] and *HSD11B2* were not associated with any disease and trait. There were SNPs being associated with other disease and trait: *ACE* (metabolic traits), *AT1R* (leads levels in blood), *AT2R* (fibrosis), *MAS1* (lipoprotein levels), *RENBP* (schizophrenia) and *NR3C2* (thyroid function). But these six SNPs showed no direct association with hypertension. The only SNP associated with a blood pressure trait was rs17367504, which is located in the intronic region of methylenetetrahydrofolate reductase (*MTHFR*) gene near many plausible candidate genes, including ion channel *CLCN6*, natriuretic peptides *NPPA* and *NPPB*, and RAAS component *AGTRAP*. The authored emphasized that the contribution of RAAS variants needs to be reconsidered when evaluating one's susceptibility of hypertension [208]. GWAS analysis is providing a new dimension for understanding genetic architecture of blood pressure and Page's "mosaic theory" of hypertension [209].

SARS-CoV-2 has emerged in December 2019, which caused COVID-19. The SARS-CoV-2 spike protein directly binds to ACE2, which is present on lung epithelial cells and other tissues [210]. ACE2 converts Ang-II to Ang 1–7 leading to tissue repair signal (**Figure 1**). When SARS-CoV-2 is attached to ACE2, it likely reduces the ACE2 activity associated with reduced inflammation, thereby increasing lung injury due to the decrease in Ang 1–7 generation [210]. It was observed that the severe COVID-19 patients are likely to have a history of diabetes, hypertension or CVD [5, 6]. For reducing the infection by COVID-19 and the other coronaviruses, deciphering the susceptibility to hypertension in term of genetic variations should be indispensable, which will be achieved by steady efforts to clarify the genetic background of each ethnic.

We recently reported probable association of five non-coding SNPs within *renin* and *(P)RR* genes with T2D, hypertension and T2D-associated hypertension in Bangladeshi population [211]. *Renin* SNP rs3730102 was associated with an increased risk of the three diseases. *Renin* SNP rs11571079 was associated with an increased risk for hypertension and T2D-associated hypertension, while the SNP showed a decreased risk for T2D, exerting a protective effect. *(P)RR* rs2968915|rs3112298 haplotypes were related to an increased risk of T2D and T2D-associated hypertension. These findings highlight important roles of non-coding variants of *renin* and *(P)RR* genes in the etiology of several polygenic diseases [211]. Although there is a limitation for genotyping the candidate SNPs for the disease risk prediction, finding the candidate gene in different ethnic group through “one-to-one” approach should be valuable to design a measure for ensuring health and quality of life at all ages in each population group.

8. Conclusion

Though several studies have revealed genetic approaches to identify the pathophysiology of diabetes, hypertension and/or diabetes associated complications, it is still very challenging to uncover a definite candidate for the genetic etiology of these diseases due to overlapping involvement of genes, loci or even SNPs. GWASs have come forward to get rid of this elusiveness through scanning of whole genome. However, it is still very challenging due to the ethnic variations and ethnicity-dependent gene expression patterns even harboring the same loci and/or variants to recognize genetic risk factors. Rather panels of variants (panels of variants for more closely related to T2D, panels for more closely related to hypertension and panels of overlapping variants in case of T2D and hypertension) could be a more meticulously related suggestive diagnostic, predictive and prognostic biomarker for these diseases. Known variants along with their gene expression pattern may play a pivotal role in determining disease pathogenesis.

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Conflict of interest

The authors declare no competing interests.

Abbreviations

Ang 1–7	angiotensin 1–7;
ACE	angiotensin converting enzyme;
ACE2	angiotensin converting enzyme 2;
AGT	angiotensinogen;
Ang-I	angiotensin-I;
Ang-II	angiotensin-II;
AT1R	angiotensin type 1 receptor;
AT2R	angiotensin type 2 receptor;
COVID-19	coronavirus infectious disease 2019;
CVD	cardiovascular disease;
DM	diabetes mellitus;
ENPP1	ectonucleotide pyrophosphatase phosphodiesterase;
GPCR	G-protein coupled receptor;
GWAS	genome wide association study;
I/D	insertion/deletion;
IGF2BP2	insulin-like growth factor 2 mRNA-binding protein 2;
IRS-1	insulin receptor substrate-1;
KCNJ11	potassium inwardly rectifying channel subfamily J member 11;
MAS1	MAS-related;
MODY	maturity-onset diabetes in young;
(P)RR	(pro)renin receptor;
RAAS	renin-angiotensin-aldosterone system;
ROS	reactive oxygen species;
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2;
SNP	single nucleotide polymorphism;
T2D	type 2 diabetes;
T1DM	type 1 diabetes mellitus;
T2DM	type 2 diabetes mellitus;
PPARG	peroxisome proliferator activator receptor gamma;
TERT	telomerase reverse transcriptase

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