VDR Gene Polymorphisms and the Risk of Type 1 Diabetes Mellitus: Plots from Meta-Analysis Studies

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disease, caused by autoimmune destruction of the insulin secreting β-cells of the islets of Langerhans, in which the immune system plays a key role. The effect of active vitamin D on the pathogenesis of T1DMis directly via the nuclear vitamin D receptor (VDR), which is involved in triggering the immune system against the islet cells of the pancreas. The VDR big-four-inventory polymorphisms (SNPs), FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236), were extensively investigated among T1DM patients from different populations, with inconsistent outcomes. In this review, studies from meta-analysis were merely considered to figure out the role of these SNPs on the risk of T1DM in- and between- populations, taking in consideration their advantages over the individual studies, in terms of accuracy and less bias. Notwithstanding, the results from different continents and between populations was inconclusive, and warrant further studies encompass large sample sizes, equal geographic distributions, tackling haplotypes structure and LD between polymorphisms, and using advanced techniques other than the RFLP for determining individual polymorphisms. Taking these approaches could likely help to emphasize the link between the reviewed SNPs with different functional alleles that may be found in the VDR gene or in genes nearby VDR, and to construct haplotype maps for the candidate genes.

Keywords: Type 1 diabetes, Vitamin D, VDR Polymorphisms

INTRODUCTION

Type 1 Diabetes Worldwide

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disease characterized by reduction or ineffective production of insulin. T1DM is caused by autoimmune destruction of the insulin secreting β-cells of the islets of Langerhans, and is potentially triggered by the immune system, the environmental factors, and many genetics [1-3].

Worldwide, the annual incidence rate of T1DM is approximately 3%, with a proportion of 1 in every 300 persons, and is steadily rising in frequency [4]. Geographically, the incidence of T1DM varies widely, with European (EUR) region having the highest incidence rate (>25 % of the global total prevalence) [2,5,6], followed by the North America and Caribbean (NAC) region (20%), and Western Pacific (WP) region (9%). China and Africa regions reported the lowest incidence rates (1% and 2%, respectively) [5-7]. In the childhood, T1DM is considered the most common chronic disease that constitutes about 5% to 10% of all diabetes cases, with an incidence rate higher in the age between 0-14 years [2,8], and particularly among children less than 5 years of age [9]. It has been estimated that, around 600,900 children were living with diabetes, and almost 98,200 new cases were under the 15 years' age [5].

Pathogenesis of T1DM

The pathogenesis of T1DM is precisely unknown, despite the supporting evidence linked the damaged β-cells with the releases of β-cells autoantigens [10]. These autoantigens are proposed to be taken up and presented by antigen presenting cells (APCs) to the naïve CD4^{+} T-helper (Th0) cells in the pancreatic lymph nodes [11]. The IL-12 secreted by the APCs triggers the differentiation of naïve Th0 to active CD4^{+} T-helper (Th1) cells(pro-inflammatory) that are sequentially release the pro-inflammatory cytokines, IFN-γ and IL-2 [10]. The Th1-released cytokines trigger the

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classical activation of macrophages (CAMs) to release toxic cytokines (TNF-α and IL-1) and free radicals (NO), and in differentiation of CD8^{+} cytotoxic T cells, collectively to produce inflammatory substances and mediators to execute theβ-cells destruction [12-14]. The destruction of the β-cells can be prevented via the setting up of the Th2 cytokines, IL-4 and IL-10. Since, the secretion of IL-4 by natural killer cells (NKs) stimulate the Th0 to differentiate favorably into Th2cells (anti-inflammatory). Further secretion of IL-4 from Th2 cells, in addition to IL-10, prevent Th1 proliferation and macrophage (MΦ) activation [11,13,15]. The counterbalance of Th1 and Th2 cytokines are the key factors in controlling the pathogenesis in the pancreatic milieu, as well as, in other organ-specific autoimmunity diseases [16]. The role of vitamin D and its counterpart receptor (VDR) were found to be under the path of these settings.

Vitamin D Metabolism and Modulation in T1DM

Vitamin D is a fat-soluble steroid hormone, mainly taken from exposure to sunlight and adsorption through the skin. The biologically active form of vitamin D, the 1,25-dihydroxyvitamin D_3 [1,25($OH)_2D_3$] known as calcitriol, is generated from a cascade of reactions, starting from the formation of pre-vitamin D_3andvitamin D_3(cholecalciferol) from 7-dehydrocholesterol in the skin. Vitamin D_3undergoes hydroxylation in the liver by the enzyme vitamin D 25α-hydroxylase (25α-OHase; encoded by CYP2R1) forming25-hydroxyvitamin D_3 [25($OH)D_3$], which is the biologically inactive form of vitamin D3 known as calcidiol. The inactive calcidiol subsequently converted to the active calcitriol in the kidney by 1-alpha hydroxylase (1α-OHase; encoded by CYP27B1) [17-19].

Calcitriol is crucially carried in plasma by vitamin D binding protein (VDBP), which is further facilitate calcitriol cellular endocytosis [20]. Once calcitriol enters the cell, it binds vitamin D receptor (VDR), and subsequent conformation change take place allows the formation of heterodimerization complex with retinoid X receptor (RXR), 1,25($OH)_2D_3$-RXR-VDR. The 1,25($OH)_2D_3$-RXR-VDR complex then cross the nuclear envelop and enter the nucleus, where it can bind to specific DNA sequence elements such as vitamin D response elements (VDRE) located in vitamin D responsive genes [19].

In T1DM, calcitriol has the ability to affect the immune cells directly through binding to the intracellular vitamin D receptor (VDR), which is expressed in a variety of immune cells, including MΦ, dendritic cells (DCs), and activated T cells [21]. It has been stated that supplementation of calcitriol can significantly inhibit the maturation of DCs to present surface major histocompatibility complex (MHC) class II that can affect Th1 and Th17 differentiation [22]. Furthermore, calcitriol can reduce the ability of MΦ to present antigens to T cells by decreasing its surface expression to MHC class II [23,24]. It also inhibits the CD8^{+}

T cells to secrete less IFN-γ, IL-17, TNF-α, and IL-21, and more TGF-β and IL-5 [21]. Further, calcitriol promotes CD4^{+} T cells to produce pro-inflammatory cytokines such as IFN-γ, IL-17 and IL-21 [25,26]. Vitamin D deficiency and/or a defect in VDR could unlikely increase the Th1/Th2 ratio. The imbalance in the immune response as a risk factor for developing T1DM is not only depend on vitamin D insufficiency, resulted from the sunlight exposure, dietary behaviors, and supplementation intake, but also on polymorphisms in genes involved in the metabolic pathway of vitamin D, including VDR. Collectively, the immunomodulatory effect of calcitriol against autoimmune diseases, particularly T1DM, depends on its ability to induces immunological tolerance and dampen all mechanisms connected with the adaptive immunity that directed the anti-inflammatory effects.

VDR Polymorphisms and the Risk of T1DM

The VDR is the member of the nuclear/steroid receptor superfamily of transcriptional regulations [27], and is found in many tissues in the human body including the islet cells of the pancreas and immune cells, including T lymphocytes and APCs [28]. The human VDR composed of three domains, a C-terminal ligand-binding domain, an N-terminal dual zinc finger DNA-binding domain, and an unstructured region that links the two functional domains [29-31]. This gene spans over 60 kilobases (kb) of genomic DNA and located on the short arm of chromosome 12 (12q12–q14) [29]. The VDR gene contains 14 exons (8 protein-coding exons 2-9, and 6 untranslated exons1a–1f) directed by two distinct promoters [29,30-32]. The 6 untranslated exons were alternatively spliced generating VDR transcripts varied in their 5′ UTRs, and subsequent structural differences in the VDR N-terminal, which may vary between tissues and responsiveness to active vitamin D [29]. The structural VDR gene translated into two functional domains, N-terminal DNA-binding domain (encoded by exon 2 and exon 3) and C-terminal ligand-binding domain (encoded by exon 5-9), linked by unstructured region [31].

The human VDR gene harbors more than 200 SNPs, among them is the big-four-inventory and extensively investigated polymorphisms, FokI F>f alleles (T>C; rs2228570), BsmI B>b (G>A; rs1544410), ApaI A>a (T>G; rs7975232), and TaqI T>t (T>C; rs731236), which were identified with restriction fragment length polymorphism (RFLPs) **(Figure 1)**. The uppercase alleles (F, B, A, or T) represent the absence of the restriction site, while the lowercase alleles (f, b, a, or t) represent the presence of the restriction site.
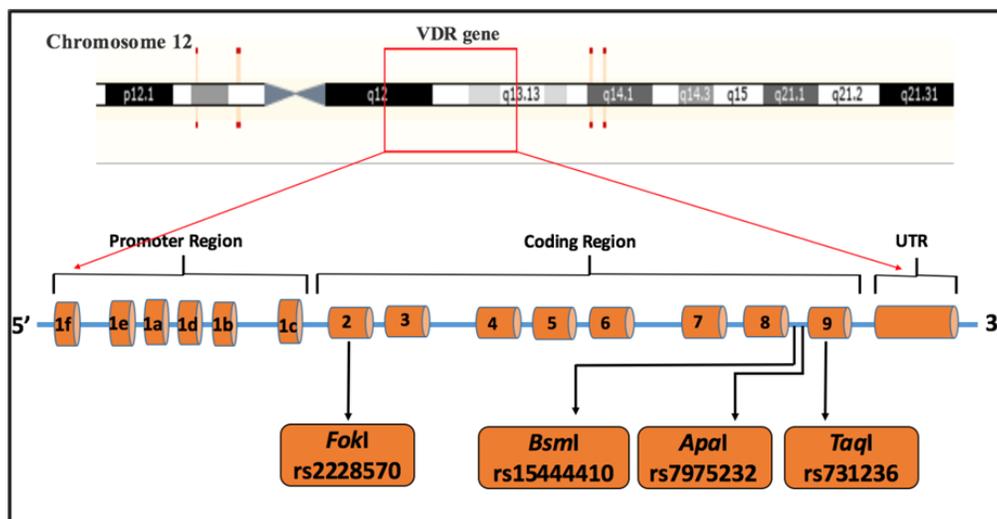
Figure 1. The VDR gene located in the short arm of chromosome 12 (12q12–q14), span over 60 Kb, and contains 8 protein-coding exons [2-9]and 6 untranslated exons (1a-1f). The gene encompasses various SNPs, the FokI, BsmI, ApaI, and TaqI are the common.

FokI Polymorphism

FokI polymorphism refers to starting codon polymorphism (ATG) due to thymine (T) to cytosine (C) substitution in the first translational initiation region located in exon 2. The presence of this polymorphism eliminates the original first starting codon (ATG to ACG), and create an alternative start codon six nucleotides downstream of the original. The new start codon leads to translation of mutant protein with an N-terminal three amino acids shorter (C allele or "F" allele; methionine at the fourth position; 424 amino acids) than the wild type protein (T allele or the "f" allele; methionine at the first position; 427 amino acids) [27,33,34]. The polymorphism FokI consequently generates higher transcription rate for the VDR gene and mutant protein 1.5- to 2.5-fold more active than the wild type [35,36]. Pooled and subgroup results from meta-analysis studies showed positive association between FokI polymorphism and the risk of T1DM in Africans [37] and in West Asians [38]. No association has been observed in children [36] or adults in populations from East Asia, Europe, America, Latin America, Australia, and Caucasia [38-44]. Even in the same continent, the results of this polymorphism varied between populations from the same country. For instance, studies in Egyptian children showed significant association of genotypes "ff" with the risk of T1DM [45,46], while others did not report this kind of association [47,48]. High frequency in "Ff" genotype and low of "ff" have been reported in Saudi children with T1DM [49], while other study from the same population doesn't found this association [50]. Moreover, Iranian studies in adults with T1DM showed discrepancy in results regarding this polymorphism [51,52].

BsmI Polymorphism

BsmI is non-functional polymorphism, located in intron 8, near the 3' end of VDR gene, and correspond to a G to T substitution. This polymorphism has nothing to do with the structure, function, and amount of VDR protein. Nevertheless, and together with ApaI and TagI, the most likely BsmI polymorphic effect on the VDR gene notably arise due to its linkage disequilibrium (LD) with the poly (A) microsatellite repeat in the 3' untranslated region (UTR) [34]. Despite the fact that this latter repeat has inconsistent impact on the VDR mRNA stability and translational activity [53,54], earlier studies have reported strong linkage disequilibrium (LD) between the BsmI alleles and BsmI-ApaI-TaqI haplotypes with the length of the poly A variable number of microsatellites repeat in the 3'UTR [34,55,56].

The proof of association between the non-functional activity of the BsmI polymorphism and the risk of T1DM was controversial among different populations and between continents as well. For instance, pooled results from meta-analysis studies showed positive association of BsmI polymorphism with the risk of T1DM in European, Asian, and Latino populations [39], and with subgroups from East Asia [38,39,43]. In contrary, the polymorphism showed negative association with the risk of T1DM among Americans [37]. Other meta-analysis studies did not find any association in populations from different countries [41,42]. At the allele and genotype levels, "bb" genotype was found to be associated with the risk of T1DM among Asians, Caucasians, Africans, and Latinos, while the "BB" genotype and "B" allele were reported in Africans, Asians, and Latinos [40]. Other meta-analysis study found association between the "Bb" and "bb" genotypes and the risk of T1DM in children from different populations [36].

ApaI Polymorphism

ApaI SNP located in intron 8 at the 3' untranslated region of the gene, and correspond to a T to G transition, which has no functional effect on the VDR protein. Similar to BsmI, ApaI has strong LD with the poly (A) microsatellite repeat in the 3' untranslated region (UTR), particularly it's allele [27]. Meta-analysis studies among different populations showed no association with this polymorphism and the risk of T1DM [36-44]. However, this SNP showed positive association with the development of T1DM in population from Greece and Pakistan [52,57,58]. On the other hand, SNP low frequency was found in T1DM patients from Saudi Arabia and Egypt [49,59]. This data indicates that this polymorphism alone has little or merely no effect on the risk of T1DM.

TaqI Polymorphism

TagI is a silent SNP (T > C) in axon 9 near the exon-intron boundary (gCTg/ATTg), likely to influence splicing [60]. Like ApaI and BsmI, TagIis strongly linked to a poly(A) microsatellite repeat in the 3' untranslated region, hence and might affect mRNA stability and the translation of VDR [27,34]. The association of this SNP and the risk of T1DM has be observed in children from different populations, particularly for the normal "TT" and mutant "tt" genotypes [36]. Other meta-analysis studies did not proof an association among adults with T1DM from different continents [41-44]. The lack of association of this SNP with risk of T1DM is attributed to its anonymous effect on the VDR protein, rather than the effect on haplotype and genotype analysis [55,66].

CONCLUSION

The VDR polymorphisms have been extensively studied in relation to different diseases. Of these, the big-four-inventory polymorphisms, FokI, BsmI, ApaI, and TaqI, were broadly investigated between different populations. FokI is only the functional polymorphism, and therefore it has an apparent association with the risk of T1DM, but this association differs in- and between- ethnic groups. The BsmI, ApaI, and TaqI, are nonfunctional polymorphisms, located between intron 8 and exon 9, near the 3' end of VDR gene, and they had strong LD with the poly (A) microsatellite repeat in the 3' untranslated region (UTR) of the VDR gene. Thus far, their plausible association with the risk of T1DM is meant to be hindered, because their anonymous functions still stand against their factual role.

The big-four-inventory polymorphisms and their association with the risk of T1DM have been gathered via consecutive meta-analysis studies. These kinds of studies are conclusive and more reliable as it includes large data sets to evaluate the genotype frequencies in certain diseases, hence reduce the effect of biased sampling that occur in individual study populations. Our review study indicated discrepancies in the association between the aforementioned polymorphisms and the risk of T1DM between continents and ethnics from same populations, when we examined such data from meta-analysis studies. Nevertheless, the hitherto inconclusive data so far is recalling for doing further studies with large sample size and equal geographic distribution of data collections between continents. Performing studies encompassing haplotype's structure and LD between polymorphisms, together with using advanced techniques other than the RFLP for determining individual polymorphisms, could likely help to emphasize the association of the reviewed SNPs and their linkage with totally different functional alleles that may found in the VDR gene or in genes nearby VDR, and to construct haplotype maps for candidate genes.

CONFLICT OF INTEREST

The author declares no conflicts of interest in this work.

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