



Invited critical review

Vitamin D receptor polymorphisms and diseases

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Abstract

The vitamin D endocrine system is central to the control of bone and calcium homeostasis. Thus, alterations in the vitamin D pathway lead to disturbances in mineral metabolism. Furthermore, a role for vitamin D has been suggested in other diseases, like cancer, diabetes and cardiovascular disease. Expression and nuclear activation of the vitamin D receptor (VDR) are necessary for the effects of vitamin D. Several genetic variations have been identified in the VDR. DNA sequence variations, which occur frequently in the population, are referred to as “polymorphisms” and can have biological effects. To test whether there is a linkage between VDR polymorphisms and diseases, epidemiological studies are performed. In these studies, the presence of a variation of the gene is studied in a population of patients, and then compared to a control group. Thus, association studies are performed, and a link among gene polymorphisms and diseases can be established. Since the discovery of VDR polymorphisms a number of papers have been published studying its role in bone biology, renal diseases, diabetes, etc. The purpose of this review is to summarize the vast amount of information regarding vitamin D receptor polymorphisms and human diseases, and discuss its possible role as diagnostic tools.

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1. Introduction

The vitamin D endocrine system is central to the control of bone and calcium homeostasis. The active form of the vitamin D is 1,25-dihydroxyvitamin D (calcitriol), the circulating level

of which is tightly regulated and acts through a specific receptor to mediate its genomic actions on almost every aspect of calcium homeostasis. Furthermore, it has also been shown that vitamin D plays an important role in other metabolic pathways, such as those involved in the immune response and cancer (Fig. 1) [1]. Vitamin D, derived from the diet or by bioactivation of 7-dehydrocholesterol, is inert and must be activated to exert its biological activity. Vitamin D3 is produced in the skin by an

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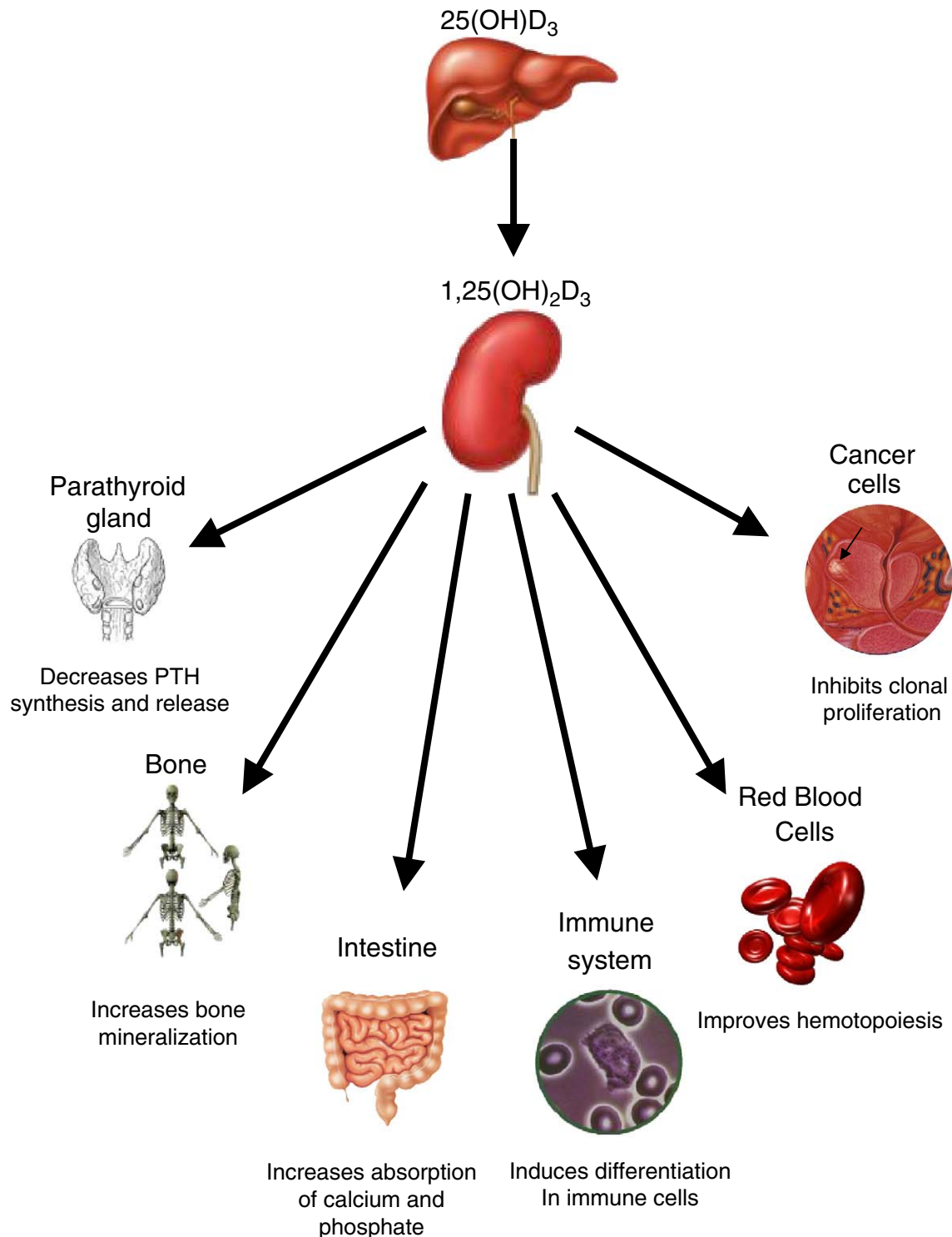


Fig. 1. Effects of vitamin D on target cells.

ultraviolet light-induced photolytic conversion of 7-dehydrocholesterol to previtamin D₃ [2,3] followed by thermal isomerization to vitamin D₃ [4,5]. The first step in the metabolic activation of vitamin D is hydroxylation of carbon 25. This reaction occurs primarily in the liver, although other tissues including skin, intestine, and kidney have been reported to catalyze 25-hydroxylation of vitamin D. The second and more important step in vitamin D bioactivation, the formation of 1,25

(OH)₂D₃ from 25(OH)D₃ occurs, under physiological conditions, mainly in the kidney [5]. The renal enzyme responsible for producing 1,25(OH)₂D₃, 25(OH)D-1α-hydroxylase, is located in the inner mitochondrial membrane and is a cytochrome P-450 monooxygenase requiring molecular oxygen and reduced ferredoxin [6]. In recent years, many reports have demonstrated that the kidney is not unique in its ability to convert 25(OH)D₃ to 1,25(OH)₂D₃. Numerous cells and tissues express 1α-

hydroxylase in vitro; however, in humans, these extrarenal sources of 1,25(OH)₂D₃ only contribute significantly to circulating 1,25(OH)₂D₃ levels during pregnancy, in chronic renal failure, and in pathological conditions such as sarcoidosis, tuberculosis, granulomatous disorders, and rheumatoid arthritis.

Most of the biological activities of 1,25(OH)₂D₃ are mediated by a high-affinity receptor that acts as a ligand-activated transcription factor. The major steps involved in the control of gene transcription by the vitamin D receptor (VDR) include ligand binding, heterodimerization with retinoid X receptor (RXR), binding of the heterodimer to vitamin D response elements (VDREs), and recruitment of other nuclear proteins into the transcriptional preinitiation complex. Thus, genetic alterations of the VDR gene could lead to important defects on gene activation, affecting calcium metabolism, cell proliferation, immune function, etc., which could be explained by changes in the protein sequence. For instance, deleterious mutations in the VDR gene cause 1,25-dihydroxivitamin D resistant rickets, a rare monogenetic disease [7]. More subtle sequence variations (polymorphisms) in the VDR gene also occur more frequently, but the significance of it has not been systematically analyzed and the effects on the VDR protein levels and function are unknown.

A polymorphism is a genetic variant that appears in at least 1% of the population. These changes can occur in non-coding parts of the gene (introns), so they would not be seen in the protein product. Changes in these regulatory parts of the gene would then affect the degree of expression of the gene, and thus the levels of the protein. For instance, changes in the 5'-promoter of the VDR gene can affect mRNA expression patterns and levels, while 3' untranslated region (UTR) sequence variations can affect the mRNA stability and protein translation efficiency. However, the changes can take place in exonic parts of the DNA, then leading to changes in the protein sequence. Nonetheless, changes in exonic sequences of the DNA which do not alter the protein structure are also possible, and are called synonymous polymorphisms. Often these changes create or abolish sites for restriction enzymes to cut the DNA. Digestion with the enzyme then produces DNA fragments of a different length which can be detected by electrophoresis. These polymorphisms are called Restriction Fragment Length Polymorphisms (RFLPs). Developments in DNA sequencing now make it easier to look for allelic versions of a gene by sequencing samples of the gene taken from different members of a population (or from a heterozygous individual).

The discovery of genetic variants linked with susceptibility of diseases can be the key to advances in preventive medicine. In general, we use association studies to test whether a polymorphism occurs more frequently in the cases studied than in the controls. If a relationship with the disease emerges from association studies, this finding would strongly support the idea that the candidate gene is in some way involved in the disease. The interpretation of the association studies however is sometimes hindered by the fact that most of the polymorphisms used have an unknown functional effect, so it is expected a linkage to truly functional polymorphisms elsewhere in the same or a nearby gene. Thus, in addition to knowing which

polymorphisms are present in a candidate gene area, it is important to understand how they relate to each other, both in a genetic and in a functional level.

The existence of several RFLPs in the VDR gene has been described using different restriction enzymes. Examples of these include the *Tru9I* [8], *TaqI* [9], *BsmI* [10], *EcoRV* [10] and *ApaI* [11]. All these RFLPs are located between the 8 and 9 exons and lay in an area with unknown function. A different case of RFLP is the so-called *FokI*. This polymorphism was described in the early nineties [12,13] in the exon 2, and consisted of a T to C change. The change is inside a start codon (ATG), so when the C variant is present, an alternative start site is used leading to a protein with different size. Most of the experiments conducted so far point to the fact that the shorter form of the protein (424 aa) is more active than the long form (427 aa) in terms of its transactivation activity as a transcription factor. However, it seems to be a gene-specific and cell type-specific effect. Thus, some genes and some cell types will be more sensitive to the effect of the polymorphism than others [14].

Using the sequencing approach, a number of new polymorphisms have been found. For instance, Brown et al. [15] found a C to T change near the exon 2 and a insertion/deletion of a G after exon 7. Arai et al. in 2001 [16] detected a new polymorphism (*Cdx2*) using the same technique in Japanese women. This polymorphism consisted in a G to A change in the promoter region of the VDR gene. That change is within the binding site for an intestinal-specific transcription factor called *CDX2*. Recently the polymorphism has also been described among different racial groups [17].

The 3' UTR of the VDR gene is also a source of several different polymorphisms. However, conflicting reports over the number and position of the polymorphisms exist in the literature. Morrison et al. [9] and Durrin et al. [18] reported 13 and 7 different polymorphisms, respectively. Surprisingly, only two sequences were common in both papers.

As we stated before, the association of a certain polymorphism with a phenotype does not necessarily mean that the polymorphism is causing it. The association of alleles of different polymorphisms with each other within a population is called linkage disequilibrium (LD) [19]. The low level of recombination over time in a certain area of a gene, leads to the presence of certain polymorphisms with a high level of association. In practice this means that we can predict the presence of a certain allele by the presence of an adjacent linked one. In cases of high levels of LD, this leads to blocks of alleles that are present together forming what we call a haplotype. Those blocks vary in size, having an average size of 10–20 kb, and they could be very useful to determine the causes of certain genetic diseases. One of the advantages is that we only need to determine the presence of a few polymorphisms to know the presence of all the alleles associated with the haplotype. Then, once we know which haplotype carries the risk allele, we can use different techniques to determine which polymorphism is truly responsible for the phenotype observed. Several studies have been performed to determine the degree of LD among the known polymorphisms of the VDR gene. So far, the information available is very limited but a strong degree of LD has been

found among the *TaqI*, *BsmI*, *EcoRV* and *ApaI* RFLPs [9] with five different haplotypes [20]. Furthermore, Uitterlinden et al. [21] have shown a strong LD between the *BsmI* RFLP and a polymorphism present in the 3' UTR (VNTR) [22]. Thus, the study of the LD among the different VDR polymorphisms could give new insights in the etiology of certain diseases.

In a recent paper, Nejentsev et al. [23] sequenced 94 kb in a 164 kb region of chromosome 12q12-q14 around the VDR gene. They found 245 polymorphisms that seem to be in three LD blocks. Polymorphism within each block showed little, if any, LD with polymorphisms in a different block. They compared the LD blocks among four different populations, finding remarkable similarity on the LD patterns in all the European populations but not with the African population. Therefore, they concluded that European populations show relative advantage to detect initial disease association, because fewer tag polymorphisms are required to characterize a common variation. They also showed that African populations have higher haplotype diversity. Analysis of additional haplotypes may further help the fine mapping of a casual variant. Therefore, genetic analysis in populations of different origin would facilitate the study of complex diseases.

Very recent studies have started to shed some light on the functional effects of polymorphisms in the non-coding regions of the VDR gene. Fang et al. [24] analyzed 15 haplotypes in the 5' 1a/1e, 1b promoter region and in the 3' UTR and they found very strong association with risk of bone fracture. Furthermore, they performed functional analysis showing that variants carrying the 1e/1a promoter with increased risk had lower mRNA levels. They also showed that, in an osteoblast cell line, the presence of the 3' UTR risk haplotype caused a 30% increase in mRNA decay. D'Alesio et al. [25] analyzed two polymorphisms in the promoter region of the VDR gene (G-1521C and A-1012G). They found that one base change in any of the variant sites led to a dramatic change in protein-DNA complex formation and a smaller height from 11 years of age up to adult height.

2. VDR polymorphism and renal patients

The effect of VDR polymorphisms in renal failure has been widely explored due to the complex role played by vitamin D in those patients. One of the main complications in patients with chronic renal failure is the development of secondary hyperparathyroidism (sHPT). The complex calcitriol-VDR regulates parathyroid cell proliferation and parathyroid hormone (PTH) synthesis [26,27]. Thus, the interaction of calcitriol with its receptor inhibits PTH synthesis as well as parathyroid gland cell proliferation. Patients with uremic sHPT were treated with vitamin D metabolites during decades in order to correct the hypercalcemia and, therefore, to inhibit sHPT. After discovering the presence of VDR on parathyroid gland, the treatment shifted to bolus of calcitriol to act directly over the parathyroid gland. However, some of the patients were resistant to the treatment. After years of experience we have learned that, in sHPT, the parathyroid gland suffers nodular growth, and that the density of VDR in the nodules is lower than in the surrounding hyperplastic cells [28].

The discovery of the VDR on parathyroid cells opened a new and exciting field of research. Thus, in 1995 Carling et al. [29] reported a relationship between *BsmI* polymorphism and primary HPT. These results led our laboratory to hypothesize that VDR polymorphisms could be involved in sHPT due to chronic renal failure (CRF). In the meantime, a rapid communication of Tsukamoto et al. [30] reported a higher incidence of the *b* allele on hemodialysis patients with sHPT. Then, our laboratory designed a bigger study minimizing the impact of the time on hemodialysis as an important risk factor for the development of sHPT [31]. Furthermore, we divided our population of patients in two groups depending on the PTH levels. We did not find any differences in *BsmI* polymorphism distribution between the high PTH group and normal population. However, we found a higher presence of the *B* allele in the group of patients with low PTH levels. Thus, even after being exposed to the same conditions than the other group, patients with the *B* allele presented a *relative hypoparathyroidism*. It is important to add that we had previously excluded from this group patients with any other factor affecting parathyroid function (diabetes, parathyroid hypofunction, hyperalbuminemia and hypercalcemia). These results have been also confirmed by other investigators [32,33].

The main limitation of the former study was that the cohort of patients had a long history of sHPT and was already on hemodialysis. Furthermore, it is known that in these patients the onset of the alterations in mineral metabolism as well as in the parathyroid function is in very early stages. Therefore, we tried to analyze the influence of the polymorphism in patients with different degrees of CRF and to relate it to the levels of calcitriol. After excluding the main risk factors we also showed that patients with the *BB* genotype had lower levels of PTH in every stage of CRF. Furthermore, this was accompanied with higher calcitriol levels [34].

In order to define the clinical implications of these findings, we analyzed the response of patients with different genotype to a single bolus of calcitriol [35]. We found that patients with the *BB* genotype showed a higher reduction on PTH levels than patients with the *bb* genotype, even after correcting by calcium and phosphorus levels. In this same line of reasoning, we also demonstrated that patients with *BB* genotype could develop severe sHPT and a need for parathyroidectomy, but required a longer time on dialysis than patients with the *bb* genotype [36].

In other of our studies, the *bb* genotype was overrepresented among hemodialysis survivors [37]. The Cox analysis in the population showed that *BB* patients had a mortality risk 4 times higher than *bb*, but the mechanisms implicated in this advantage are still unknown. Patients with a *BB* genotype had lower PTH levels, which are per se a risk factor for increased mortality. However, the presence of VDR on vascular and cardiac tissue implies new target organs where VDR polymorphisms could be influencing mortality. Furthermore the association of *BsmI* genotype with hemoglobin levels [38] and bone mineral loss [39] could explain the increase in survival of some of the patients.

It is very difficult to determine the increase in the risk of developing sHPT associated with having a specific *BsmI*

genotype. Firstly, because of the different and, sometimes, contradictory results found in the literature [40,41]. Secondly, due to the fact that the risk calculation is performed with many variables, and some of those change within different studies (sample size, study design, etc.). However, almost all the reports published indicate that there is some influence of *BsmI* genotype on the sHPT progress. In an ideal scenario in which we would try to prevent sHPT in early stages of CRF, the use of *BsmI* polymorphism to evaluate the risk of the patients to develop sHPT could be an option.

The association of *BsmI* genotype with PTH levels has also been tested after kidney transplantation. In this case, all the reports published so far agree in the association of the *bb* genotype with higher PTH levels [42,43]. However, the presence of the *bb* genotype seems to be related to a better recovery of bone mineral density 3 months after transplant [44,45].

The rest of genotypes have not been so extensively studied in renal failure. There is only one report linking the *FF* genotype of *FokI* polymorphism with higher PTH levels in predialysis patients [46]. Due to the higher sensitivity of the *FF* phenotype to 1,25(OH)₂D₃, it would be reasonable to expect the opposite result. However, the authors argue that, before the onset of renal failure, the patients with the *FF* phenotype had a stronger suppression of the PTH levels. Thus, after the renal failure and the decrease of 1,25(OH)₂D₃ levels, the lack of constrain on PTH secretion would lead to higher increases on PTH levels in the *FF* patients. In predialysis patients, levels of 1,25(OH)₂D₃ are low. Thus, the authors argue that the higher sensitivity of the *FF* genotype will be suppressing the PTH levels on. The authors explained the effect and one more associating the *t* allele of the *TaqI* polymorphism with the risk of suffering post-transplant diabetes mellitus (DM) [47]. In addition, the *aa* genotype of the *ApaI* polymorphism has been linked to higher PTH and osteocalcin levels in patients in predialysis [48], and with a higher sensitivity to detect changes in calcium and, therefore, to regulate PTH secretion [49].

3. VDR polymorphisms and bone biology

In 1992, Morrison described for the first time a relationship between the *BsmI* polymorphism and osteocalcin levels. In that work, the presence of the homozygous allele *bb* was related to a higher bone mass density (BMD) in normal population and in twin pairs. This paper, together with a second published in *Nature* in 1994 [9], in which the presence of the *BB* genotype was related with lower BMD in postmenopausal women, grounded the basis of dozens of papers published in the following years.

The studies have been performed in normal population [9,21,50], in twin pairs [9,51], in premenopausal women [52–55], in postmenopausal women [53,56–59,12], in elderly women [12,60,61], in healthy women [62] and in women with osteoporosis [62] or even comparing black and white women [54]. All these studies have been performed in population of different origin like caucasian (British [53,56], Italian [60], Finnish [57], North American [54,58,59,62],

Swedish [61], Dutch [21], Australian [10], German [63] and French [52]), Oriental [50] and South American [12,64].

All these studies reported conflicting results, some of them confirming [65–68,56,69,70], other finding no relationship [21,51,59,61,71,72] or even reporting an opposite effect [53]. These discrepancies could be explained by differences in diet [58,73], genotype distribution in different populations [74,9] or even by the sample size used in each study. Overall, what seems to be accepted is that the effect of *BsmI* genotype on BMD is relatively small (2–3%) and strongly influenced by some other non-genetic factors like diet.

Recently, two meta-analysis performed by Thakkinstian et al. [75,76] collecting all data published from 1994, demonstrated a positive association between the *b* allele and bone mass density. Furthermore it was showed that the haplotypes *Bat* and *BAt* were significantly associated with osteoporosis. The authors also pointed out a series of methodological issues which need to be addressed in this kind of studies. Readers are encouraged to consult both articles for further information.

The relationship between bone biology and some other polymorphisms of the VDR gene has also been reported. For instance, the *FokI* polymorphism has also been associated with differences in BMD but, whereas some papers linked the presence of the longer form of the protein with lower BMD [77,12,78–81], some other reached opposite conclusions [82,83,70]. The *CDX-2* polymorphism has also been related with BMD in Japanese population, being the allele *G* associated with lower BMD in lumbar spine [16,84].

In 1997 two almost simultaneous papers described for the first time the possible relationship between VDR polymorphisms and the risk of suffering osteoarthritis. In one of them, Keen et al. [85] associated the presence of the *T* allele of the *TaqI* polymorphism with a higher risk of suffering osteoarthritis in the knee. Uitterlinden et al. [86] studied haplotypes of the *BsmI*, *ApaI* and *TaqI* polymorphisms and reached the conclusion that the *bAT* haplotype was associated with reduced prevalence of knee osteoarthritis. These results could not be confirmed in a posterior study by Huang et al. [87] in Japanese women. Nonetheless, the study by Huang et al. demonstrated that the protective haplotype was very uncommon among Japanese population. Furthermore, Loughlin et al. [88] were also unable to find a relationship between the *TaqI* polymorphism and the risk of suffering osteoarthritis.

In 1998 Aerssens et al. [89] demonstrated that *BsmI* polymorphism had no effect on the prevalence of osteoarthritis in Belgian women with hip replacement. These results were confirmed by Granchi et al. [90] in a cohort of 143 Caucasian patients. Furthermore, in this work they found an association between haplotypes of the *BsmI* and the *PvuII* polymorphism of the collagen 2A gene. However, this association could not be confirmed later in a bigger study [91].

4. VDR polymorphisms and cancer

An association has been described between 1,25(OH)₂D₃ and susceptibility to and outcome of some cancers, like breast, prostate and colon cancers. The relationship includes vitamin D

serum levels as well as VDR polymorphisms. As in the case of bone biology, the results are controversial and, in some cases, even contradictory. These apparent contradictions could be explained by differences in vitamin D levels, racial heterogeneity and sample size.

In 1997, Ingles et al. [22] published one of the first reports finding a relationship between the polyA polymorphism of the VDR gene (one of the UTR polymorphisms) and prostate cancer in the US population. One year earlier, a paper of Taylor et al. [92] showed the relationship between the *TaqI* polymorphism and an increased risk of prostate cancer, being the phenotype that presented the restriction site (*tt*) the one with a lower risk. However, in this case, the *tt* genotype also correlated with higher levels of 1,25(OH)₂D₃. Those results were confirmed several years later in European patients by Correa-Cerro et al. [93]. In the meantime, some other reports showing no association between *TaqI* and/or polyA and prostate cancer were also published. Kibel et al. [94] and Cheteri et al. [95] showed no association between both polyA or *TaqI* polymorphisms and death by prostate cancer in US patients. In Europe, a recent report by Gsur et al. [96] did not find an increased risk of prostate cancer associated with *TaqI* polymorphism. However, in this case the control group was not a normal population but patients with benign prostate hyperplasia. In Japan, a lack of association between *TaqI* and prostate cancer risk has also been demonstrated [97,98].

In the case of other VDR polymorphisms, we can find the same conflicting results in the literature. *FokI* has been found to be related to prostate cancer in some cases [99] whereas in some others no relationship has been reported [93,100,95]. The case of *BsmI* is similar. Whereas in Japanese and African American populations a relationship has been reported [98,101]. No influence of the *BsmI* and risk of prostate cancer has been found in North Americans [95] or Chinese [100]. In addition, in a recent report of Ntais et al. [102] in which a meta-analysis of 28 different studies was performed, no relationship was found between any of the former VDR polymorphisms and prostate cancer susceptibility.

Breast cancer is the most common malignant tumor in women. Therefore, a great effort is being done trying to determine the genetic risk factors involved in the process. As with prostate cancer, conflictive results have been reported regarding the possible relationship between breast cancer and VDR polymorphisms. The majority of the reports present in the literature found no relationship between the risk of breast cancer and *TaqI* polymorphism [103,104], but some of them presented a link between *TaqI* polymorphism and risk of metastases [105,106] and only one reported a strong relationship [107]. The *BsmI* shows an opposite pattern with relationship detected in three reports [108–110] and no link in only one [106]. In the case of *FokI* the consensus is higher, and most of the reports showed no association with increased risk of breast cancer [107,110,109] or association only in certain racial groups [22]. All the studies performed so far investigating the relationship between polyA [22,109] or *ApaI* [107,106] with the risk of breast cancer showed a link between the polymorphisms and the possibility of presenting a tumor.

The number of papers analyzing VDR polymorphisms in other cancer types is significantly lower. In colon carcinoma, a couple of reports showed association with *BsmI* polymorphism [111,112] whereas conflictive results are found regarding *FokI* [113,114]. The *FF* genotype of the *FokI* polymorphism has been also associated with reduced risk of malignant melanoma [115] and a link has also been found between renal carcinoma and *TaqI* [116].

Recently, Halsall et al. [117] described a new polymorphism in the exon 1a transcription start site (A-1012G). In the same paper they showed that the *A* allele was overrepresented in malignant melanoma and that it was related to metastases, specially when combined with the *f* allele of the *FokI* polymorphism. They concluded that the a-1012G polymorphism could have an additive prediction power together with the classical Breslow thickness.

5. VDR polymorphism and nephrolithiasis

The relationship between calcium handling and VDR polymorphism was one of the first connections studied. Apart of the effects on bone formation and mineralization, a deficient calcium handling in the body could lead to different alterations, like an increase in absorption and excretion. Nephrolithiasis is a multifactorial pathology resulting from the interaction between environmental influences and hormonal and genetic factors. The tendency to form calcium oxalate kidney stones is directly related to urinary concentrations of calcium and oxalate, and inversely to citrate and magnesium.

In a paper in 1999, Ruggiero et al. [118] related the phenotype *bb* of the *BsmI* polymorphism with a higher urinary calcium excretion and thus, to an increase of risk of stone formation. In the same line of reasoning, Mossetti et al. [119] published a paper showing a decrease of citrate urinary excretion in individuals with the *bb* phenotype, confirming the theory of a higher risk of kidney stones in the population presenting the *b* allele. Like in previous cases, these results were not confirmed in all the studies [120,121]. In the *TaqI* polymorphism we found the same kind of conflictive results. Nishijima et al. [122] showed an association of the *t* allele with a higher calcium excretion and, therefore, to a higher stone formation. However, the results of Mossetti et al. [119] prove a link between the *T* allele and hipocyturia and thus to stone forming conditions. Of course, there is also a report demonstrating no association between *TaqI* polymorphism and stone formation [120]. *FokI* and *ApaI* have also been investigated in this condition. The link has been established in some cases [120,123] whereas in others it was not confirmed [122,124].

6. VDR polymorphism and diabetes

The involvement of vitamin D has been suggested in the etiology of both independent and dependent DM. On the one hand, type 1 DM is recognized as a T-cell-mediated autoimmune disease [125]. In addition, vitamin D compounds are known to suppress T-cell activation by binding to the VDR [126–128] and thus, VDR gene polymorphisms are likely to be related to T-cell-mediated autoimmune disease. On the other hand, it has been

described that, in experimental animals, vitamin D is necessary for the maintenance of glucose tolerance and normal insulin release [129], both of which are defective in type 2 DM. Furthermore, β -cells possess VDR [129,130] and insulin secretion is impaired in vitamin D deficiency and restored by 1-25(OH) vitamin D [131].

Not surprisingly, the results obtained by different investigators vary. In type 1 DM, *BsmI* polymorphism has been linked to susceptibility to present the disease in Southern Indians [132], Taiwanese [133], Croatians [134] and Japanese [135]. In Finnish [136] and Chilean [137] populations the link could not be established. Following the same pattern *ApaI*, *TaqI* and *FokI* were found associated to type 2 DM in some reports [133,134] and not related in some others [133,136,137]. We should highlight a recent report by Nejentsev et al. [138] in which the association between 98 different SNPs and type 2 DM susceptibility was analyzed in more than 3000 families in the UK. The results of this paper showed that none of the sequences studied had any major effect in type 1 DM.

In type 2 DM a link between *BsmI* and the onset of the disease has been found in Hungarians [139] and Germans [140] but not in French [141], Bangladeshi [142] or Polish [143]. Similar results have been found regarding the other most common polymorphisms [143,142,141].

7. VDR polymorphism and other diseases

The association between the VDR polymorphisms and some other diseases has also been studied. Our group reported an association between *BsmI* genotype and blood pressure in healthy men, with higher levels of blood pressure in healthy men and women with the *b* allele [144]. However, in Korean lead workers, an opposite relationship has been reported [145]. Ortlepp et al. reported an increase in susceptibility to calcific aortic valve stenosis [146] in individuals with the *B* allele, but also a lack of relationship between the *BsmI* polymorphism and the severity of coronary artery disease [147]. However, the same group has recently reported an increase in susceptibility to myocardial infarction [148] associated to the presence of the *B* allele. These results are in harmony with those of Kammerer et al. [149] reporting an association of the *BB* genotype with a higher intimal-medial thickness in carotid artery.

Furthermore, we can find in the literature studies on autoimmune disorders like lupus, cirrhosis, hepatitis, Crohn, Graves' disease and multiple sclerosis. Ozaki et al. [150] and Huang et al. [151] described a positive relationship between the *B* allele of the *BsmI* polymorphism and the incidence of systemic lupus erythematosus in Japanese and Chinese. The same Chinese group provided evidence of a lack of relationship between the *FokI* polymorphism and the disease [152]. In the case of Crohn's disease, a link has been suggested between the *TaqI*, *ApaI* and *FokI* polymorphisms and the susceptibility to suffer the disease [153]. Furthermore, a link between *BsmI* and *FokI* with primary biliary cirrhosis and autoimmune hepatitis has also been found [154,155]. In multiple sclerosis patients, a higher presence of the *ba* haplotype has been found [156,157]. In addition it has also been described an effect of *TaqI* [158] and

FokI [159] polymorphisms on the risk of having multiple sclerosis. However, the effects of *ApaI* and *TaqI* were not confirmed in Canadian population [160]. The results obtained in patients with Graves' disease vary depending of the ethnicity. In Japanese, the *F* allele of the *FokI* polymorphism was over-represented among patients with the disease [161]. Furthermore, the same group reported that the presence of the *B* and the *A* alleles caused an increased risk to suffer the disease [162]. In Caucasian population, Collins et al. [163] found no association of any of the polymorphisms studied (10 polymorphism, including *BsmI* and *ApaI*) with increased susceptibility to suffer Graves' disease. However, in eastern Croatians the presence of the *BB* or *AA* genotypes was reported to be protective [164]. In German and Polish the *b* and the *F* allele, respectively, were associated with increased risk [165].

Bellamy et al. [166] reported that African patients with the *tt* genotype had some protection against tuberculosis. The following year, Selvaraj et al. [167] published that the very same genotype was associated with increased susceptibility to suffer the disease, but only in women. To add more confusion, Wilkinson et al. [168] demonstrated that the influence of the genotype was detected only with low serum levels of 25(OH) D_3 . Since then a number of papers have been published reporting different results in susceptibility [169,170], or even response to treatment [171–173]. However, a recent report by Lewis et al. [174] carried out a systematic review and meta-analysis and found that results were inconclusive and studies were underpowered.

A number of papers have been published showing a link between *BsmI*, *ApaI* and *TaqI* haplotypes and the risk of having primary hyperparathyroidism (pHPT). Most of them were published by Carling et al. in a Swedish population, and showed a higher incidence of the *baT* haplotype in patients with adenoma [175] and in postmenopausal women with pHPT [176]. Nevertheless, no relationship was found in Spanish [177] or Canarian population [178].

There is a recent paper by Halsall et al. [117] in which they found that, in patients without a family history for psoriasis, the presence of the *A* allele of the A-1012G polymorphism will confer protection against suffering psoriasis. This protection would be further increased in combination with the *F* allele of the *FokI* polymorphism. Furthermore, the response to the treatment with vitamin D derivatives would also be better in patients with the *A AFF* genotype.

8. Conclusions

In summary, a vast amount of information has been collected through the years regarding the association of vitamin D polymorphisms with susceptibility to suffer different diseases. Unfortunately, the results obtained so far are conflictive, and the role of VDR polymorphisms remains obscure. What seems to be clear is that the influence of the polymorphisms may not be related to changes in the protein structure, but to differences in stability and/or translation efficiency of the RNA, or even to changes in a totally different gene. In this last case, the VDR polymorphisms would act as a marker of truly functional

polymorphisms elsewhere. It is also likely that differences in race, diet or even latitude could alter the influence of the polymorphisms on the susceptibility to diseases, diluting the effects observed in other populations. Furthermore, the lack of understanding of the cellular and molecular processes influenced by the polymorphisms makes the observational studies very difficult to interpret.

Therefore, the use of VDR polymorphisms as diagnostic tools, or even as markers for a higher propensity to suffer some diseases, is still a matter of debate. Further effort must be placed in understanding the molecular and cellular variations affected by the polymorphisms and in performing observational studies in bigger populations. In these studies, special attention should be paid to the effects of environmental contributions for the better understanding of the role of VDR polymorphisms. Furthermore, the study of the different haplotypes, instead of single polymorphisms, could eliminate some of the inconsistencies found so far. Until then, the role of VDR polymorphisms will still be a topic for discussion.

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