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Vitamin D receptor (VDR) polymorphisms and skin cancer

A systematic review

Nicole Denzer, Thomas Vogt and Jörg Reichrath*

Department of Dermatology; The Saarland University Hospital; Homburg, Germany

Key words: VDR, polymorphism, skin cancer, vitamin D, melanoma, basal cell carcinoma, squamous cell carcinoma

Abbreviations: BCC, basal cell carcinoma; BMD, bone mineral density; bp, base pair; CM, cutaneous melanoma; CI, confidence interval; LD, linkage disequilibrium; MM, malignant melanoma; NMSC, non-melanoma skin cancer; OR, odds ratio; p, percentile exceeding probability; RFLP, restriction fragment length polymorphism; SCC, squamous cell carcinoma; SK, solar keratosis; SNP, single nucleotide polymorphism; TNM classification, tumor staging classification; UVR, ultraviolet radiation; VDES, vitamin D endocrine system; VDR, vitamin D receptor

Skin cancer is the most common cancer in humans. There are several types of skin cancer that include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). The associations of VDR polymorphisms with skin cancer risk are not well characterized so far. Only a few epidemiologic studies have directly addressed the relationship between VDR polymorphisms and the incidence and prognosis of MM. To make the most of the available information on VDR polymorphisms and skin cancer (MM, BCC and SCC), we undertook a systematic review of published studies. In conclusion, data summarized in this review support the concept that the vitamin D endocrine system (VDES) is of importance for pathogenesis and progression of MM and other types of skin cancer.

Introduction

Skin cancer is the most common cancer in humans. There are several types of skin cancer that include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). The key environmental risk factor in the development of non-melanoma skin cancer (NMSC) is ultraviolet (UV) radiation, in particular UV-B with a wavelength range between 280 and 320 nm.[1,2] The UV-B radiation induces photochemical changes in the skin that may lead to skin cancer.[1,2] Interestingly, recent evidence indicates that the cutaneous production of vitamin D may exert a protective effect against the development of skin cancer. Sunlight causes DNA damage but also induces production of vitamin D whose metabolite 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$ or calcitriol] has significant protective effects against the development of various types of cancer.[3,4]

*Correspondence to: Jörg Reichrath; Email: joerg.reichrath@uks.eu
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$1,25(OH)_2D_3$ acts via binding to a corresponding intranuclear receptor (VDR).[5,6] VDR belongs to the superfamily of transacting transcriptional regulatory factors, which includes the steroid and thyroid hormone receptors as well as the retinoid-X receptors and retinoic acid receptors.[7,8] VDR is encoded by a relatively large gene (>100 kb) located on chromosome 12q12-14.[5,9] The VDR gene encompasses two promoter regions, eight protein-coding exons (2–9) and six untranslated exons (1a–1f).[5] It has an extensive promoter region capable of generating multiple tissue-specific transcripts.

It has been demonstrated that VDR requires heterodimerization with auxiliary proteins for effective DNA interaction.[8,10,11] These auxiliary proteins have been identified as the retinoid-X receptors (RXR)-α, -β and -γ.[8,10,11]

MM cells have been demonstrated to express the VDR, and the anti-proliferation and pro-differentiation effects of $1,25(OH)_2D_3$ have been shown in cultured melanocytes, MM cells and MM xenografts.[12] Moreover, $1,25(OH)_2D_3$ has been shown to exert an inhibitory effect on the spread of MM cells and it has been noticed that MM patients have low serum levels of $1,25(OH)_2D_3$. In addition to these findings, VDR polymorphisms have been shown to be associated with both the occurrence and outcome of MM.[12]

To date, more than sixty VDR polymorphisms have been discovered that are located in the promoter, in and around exons 2–9 and in the 3'UTR region.[13,14] The analysis of the importance of these VDR polymorphisms for various diseases has been proven to be difficult. As a result, only few polymorphisms of this large gene have been studied extensively so far. Most of them are restriction fragment lengths polymorphisms (RFLP) with an unknown functional effect. In some cases, it has been indicated that they may be linked to truly functional polymorphisms elsewhere in the VDR gene (or in a nearby gene), which may explain some of the associations observed.[13]

The associations of VDR polymorphisms with skin cancer risk are not well characterized so far. Only a few epidemiologic

Table 1. Summary of the studies investigating the association between VDR SNP´s and skin cancer

Reference	SNP	Type of cancer	Study type	Cases (total)	Controls (total)	Country
Original papers						
Randerson-Moor et al. 2009	TaqI, BsmI, FokI, ApaI, Cdx2, GATA	MM	CCS	1343	980	UK
Gapska et al. 2009	TaqI, BsmI, FokI, A-1012G	MM	PCCS	763	1540	Poland
Halsall et al. 2009	A-1012G	MM	CCS	176	80	UK
Barroso et al. 2008	TaqI, FokI, BglI	MM	CCS	283	245	Spain
Reviews						
Gandini et al. 2009	BsmI, FokI	MM, NMSC	review	1437 (MM) 563 (NMSC)	1889 854	UK, USA, Italy USA
Köstner et al. 2009	TaqI, BsmI, FokI, A-1012G	MM, NMSC	review	2039 (MM) 563 (NMSC)	2492 854	UK, USA, Italy USA
Mocellin et al. 2008	TaqI, BsmI, FokI, A-1012G, Cdx2	MM	review	2152	2410	UK, USA, Italy

MM = malignant melanoma, NMSC = non-melanoma skin cancer, CCS = case-control study, PCCS = population based case-control study.

studies have directly addressed the relationship between VDR polymorphisms and the incidence and prognosis of MM. To make the most of the available information on VDR polymorphisms and skin cancer (MM, BCC and SCC), we undertook a systematic review of published studies.

Results

We included data from four original reports (refs. 15–18)and three reviews (refs. 19–21) publishing data for VDR polymorphisms and the risk of skin cancer. The reviews included the following additional studies: Hutchinson et al.[12] (in reviews by Mocellin et al.,[18] Köstner et al.[20] and Gandini et al.[21]), Halsall et al.[22] (in review by Mocellin et al.[19]), Santonocito et al.[23] (in reviews by Mocellin et al.,[19] Köstner et al.[20] and Gandini et al.[21]), Han et al.[24] (in reviews by Mocellin et al.,[19] Köstner et al.,[20] and Gandini et al.,[21]), Povey et al.[25] (in review by Mocellin et al.[19]), Li et al.[26] (in review by Köstner et al.[20]), Li et al.[27] (in reviews by Mocellin et al.,[19] Köstner et al.[20] and Gandini et al. [21]). The main characteristics of the studies are reported in **Table 1**. The total cases of MM were 5,319, of NMCS (BCC/SCC) were 563 and of controls were 5,858. The following SNP's were studied: TaqI (3 studies and 2 reviews), BsmI (2 studies and 3 reviews), FokI (3 studies and 3 reviews), ApaI (1 study), A-1012G (3 studies and 1 review), BglI (1 study) and Cdx2 (1 study and 2 reviews).

TaqI polymorphism. The TaqI polymorphism (rs731236) is a restriction fragment length polymorphism (RFLP) at codon 352 in exon 9 of the VDR gene. Depending on the presence or absence of a Taq1 restriction site in each allele, products are digested into 2 fragments of 495 and 245 bp (T allele: absence of the restriction site) or 3 fragments of 290, 245 and 205 bp (t allele: presence of the restriction site). Individuals are generally classified as TT, Tt or tt. The TT allele has been shown to be associated with lower circulating levels of active vitamin D_3 (refs 28–30). The TaqI polymorphism leads to a silent codon change (from ATT to ATC, which both result in an isoleucine at codon 352).[28]

The TaqI polymorphism was investigated in three papers and in two reviews (**Table 1**). It was reported that the TaqI allele t was significantly less frequent among melanoma cases than among controls [0.370 vs. 0.429 ($p < 0.01$)].[27] This suggested that t might protect carriers against melanoma or T might put them at risk. The genotypes Tt + tt were constantly less frequent among melanoma cases than among controls ($p < 0.05$) and were associated with a significantly lower melanoma risk for Tt + tt vs. TT genotypes [adjusted OR (CI) 0.68 (0.56, 0.83)].[27]

However, the three studies summarized in **Table 1** did not observe any significant over-representation of the TaqI polymorphism among the MM cases. Gapska et al. were unable to find any statistical association of the TaqI polymorphism with any distinct clinical signs (age of onset, primary tumor localization, familial aggregation, tumor type, Breslow's depth).[16] But they demonstrate a statistically significant association of the VDR haplotype: rs731236_A (TaqI) and rs1544410_T (BsmI). This haplotype was present in 1.9% of melanoma cases and in 0.5% of controls (OR = 3.2, 95% CI 1.42–4.7, $p = 0.02$).[16] However in one study, homozygosity for variant allele at the TaqI restriction site was significantly associated with higher Breslow thickness (OR = 31.5).[12]

BsmI polymorphism. The BsmI polymorphism (rs1544410) is an RFLP in intron 8 at the 3' end of the VDR gene and is considered to be a silent SNP without changing the amino acid sequence of the encoded protein.[31] However, the BsmI polymorphism may affect gene expression through regulation of mRNA stability.[32]

The BsmI polymorphism was investigated in two original articles and in three reviews (**Table 1**).

The BsmI allele B was significantly less frequent among melanoma cases than among controls [0.394 vs. 0.431 ($p = 0.03$)].[27] This suggested that B might protect carriers against melanoma or b might put them at risk. The genotypes Bb + BB were constantly less frequent among cases than among controls ($p < 0.05$) and were associated with a significantly lower melanoma risk for

Bb + BB vs. bb genotypes [adjusted OR (CI) 0.68 (0.56, 0.83)].[27] Significant associations were found between the Bsm1 bb genotype frequency and the tumor thickness (Breslow) of MM (p = 0.001).[23] This result was confirmed by multivariate logistic regression analysis. Analyzing SCC, the BB genotype was significantly associated with increased cancer risk (OR = 1.51).[24] Moreover, an interaction between the Bsm1 polymorphism and total vitamin D intake was observed in SCC patients with >2-fold higher risk seen in women with the BB genotype and high vitamin D intake (OR = 2.38, p interaction = 0.08).[24]

There is a strong linkage disequilibrium (LD) between the BsmI, ApaI and TaqI polymorphisms (D = 0.97) with three haplotypes accounting for 97% of all haplotypes (G-C-T 45%, A-A-C 40%, G-A-T 12% for the BsmI-ApaI-TaqI haplotype).[17] But there was no evidence of any association between any haplotype and melanoma status.[17]

FokI polymorphism. Of particular interest is the FokI polymorphism (rs2228570, formally known as rs10735810) located at the first potential start site[33,34] which can be detected by a RFLP using the Fok1 restriction enzyme.[35] It alters an ACG codon that is located ten base pairs upstream from the translation start codon and results in the generation of an additional start codon. If the translation initiating starts from this alternative site (thymine variant), it results in the generation of a longer VDR protein of 427 amino acids. This polymorphism is referred to as the f allele.[34] However, the f allele exerts less transcriptional activity,[36] with the F variant being 1.7-fold more active.[35,37,38] To date, the Fok1 polymorphism is the only known VDR gene polymorphism that results in the generation of an altered protein.

The FokI polymorphism was investigated in three original articles and in three reviews (**Table 1**).

The FokI f allele was identified as a risk allele for MM and NMSC.[17,19,20,21] For the association of the Ff and ff genotypes vs. wild-type genotype with MM or NMSC risk, the summary relative risks (SRR) were 1.11 (0.95–1.31) and 1.30 (1.03–1.63) respectively.[21] Using the Breslow thickness as outcome measure in melanoma cases, variant alleles could be associated with increased Breslow thickness including the tt/ff genotype (Taq1 t and Fok1 f) which turned out to be associated with tumors thicker than 3.5 mm (OR = 31.5, p = 0.001).[12]

However, the indication that the f allele may be a risk allele for melanoma or other types of skin cancer could not be confirmed by several other studies (ref. 15: MM, ref. 16: MM, ref. 23: MM; ref. 27: CM; ref. 24: MM, NMCS). Gapska et al. investigated the melanoma risk in the Polish population. But none of the investigated VDR variants alone or as compound carriers of two or more of the VDR genotypes were associated with MM risk. There were no major differences between the prevalences of the examined variants among patients with MM on UV-exposed and UV-non exposed skin areas, as well as among early-onset and late-onset cases.[16] Santonocito et al. found no association between the Fok1 genotype frequency and MM along with Breslow thickness.[23] Li et al. stated that the Fok1 polymorphism is not an independent risk factor but is interacting with skin color (p = 0.029), moles (p = 0.017) and number of first-degree relatives with any cancer (p = 0.013) in modifying melanoma risk.[27] Associations of haplotype combinations including FokI, TaqI and BsmI polymorphisms with melanoma risk and their interaction with known risk factors were also analyzed by Li et al.[27] In result, only the combined genotype TT/Bb + BB/Ff + ff (adjusted OR = 2.35) could be associated with increased risk when compared to TT/bb/Ff + ff genotype. On the other hand, the haplotype combinations tBF (adjusted OR = 0.52) and tBf (adjusted OR = 0.51) were associated with a 50% risk reduction when compared to Tbf. Furthermore, the combined genotypes Tt + tt/Bb + BB/Ff + ff (adjusted OR = 0.69) and Tt + tt/Bb + BB/FF (adjusted OR = 0.58) turned out to be associated with risk reduction for MM.

ApaI polymorphism. The ApaI polymorphism (rs7975232) is located as the BsmI polymorphism in intron 8 at the 3' end of the VDR gene.[39]

The ApaI polymorphism was investigated in melanoma in one original article (**Table 1**). It was reported that the BsmI, ApaI and TaqI polymorphisms were in strong LD. Following three haplotypes were seen accounting for 97% of all haplotypes: G-C-T 45%, A-A-C 40%, G-A-T 12% for the BsmI-ApaI-TaqI haplotype (Randerson-Moor et al. 2010). But there was no evidence of any association between any haplotype and melanoma status.[17]

A recent study has assessed the possible implications of the ApaI polymorphism for solar keratosis (SK) prevalence.[40] SKs are established biomarkers for SCC,[41,42] representing SCC in situ. In individuals with fair skin, the prevalence of SK was higher in the homozygote groups with AA or aa than in the heterozygote group with Aa (eight-fold vs. five-fold) compared with heterozygote groups.[40] So the heterozygote genotype Aa may protect individuals against being affected by SK, in conjunction with skin color or tanning ability.

A-1012G and G-1520C polymorphisms. The A-1012G polymorphism (rs4516035) is characterized by an adenine (A) to guanine (G) substitution which is located at position 1,012 in the 1A promoter region.[22] It was reported that the A allele has a protective effect on susceptibility to non-familial psoriasis and an enhanced effect on vitamin D analog treatment.[43]

The A-1012G polymorphism was investigated in two original articles and in two reviews (**Table 1**). The G-1520C polymorphism was investigated in one original article (**Table 1**).

The A-1012G polymorphism is lying within the core sequence of a putative glutamyl-transfer RNA amidotransferase subunit A 3 (GATA-3) binding site in the A allele. In the G allele this binding site is not present.[44] GATA-3 is an important transcription factor directing the polarization of naïve T-cells to T-helper 2-type lymphocytes (Th-2).[45] $1,25(OH)_2D_3$ has been shown to upregulate the GATA-3 gene expression and the GATA-3 protein promotes polarization to Th-2.[46] GATA-3 may produce a positive feedback loop and amplify the GATA-3-induced polarization. So, the A-1012G polymorphism is believed to play an effective role in the anticancer immune response.[22] It was shown that the A-1012G polymorphism was strongly associated with MM risk.[22] With GG as reference, the A allele was more than 2-fold more frequent in MM patients

(OR = 2.5) and when there was homozygosity for this allele (AA genotype) the melanoma risk increased more than 3-fold (OR = 3.3).[22] Additionally, the A allele was put into relationship with a thicker Breslow thickness group (p = 0.04) and the development of metastasis (p = 0.008).[22] The probability of metastasis at five years was, according to Kaplan Maier, 21% for the AA variant and 9% for the AG variant when compared to the GG genotype. The effect on metastasis was independent of tumor thickness, and the A-1012G polymorphism was considered to have predictive potential, additional to Breslow thickness. Finally, an interaction between the A-1012G and Fok1 polymorphism (p = 0.025) was noticed, which enhanced the effect of the A allele of the A-1012G polymorphism on metastasis increasing the probability of metastasis for the AAff genotype at 5 years up to 57%.[22]

Recently, a further polymorphism in the 1A promoter region was found. The G-1520C polymorphism (rs7139166) is characterized by a guanine (G) to cytosine (C) substitution at position 1,520 and is in a marked LD with the A-1012G polymorphism ($p < 1 \times 10^{-9}$).[18] It was suggested that there is a further GATA binding site in the G allele but not in the C allele[18] and that the A allele of the A-1012G polymorphism might be correlated with the G allele of the G-1520C polymorphism. So the G-1520A-1012 haplotype might produce a pair of GATA-3 binding sites and might be a greater risk factor for MM.[18] But first investigations showed that the A allele of the A-1012G polymorphism was more frequent in MM patients (p = 0.011) while frequencies of the G-1520C alleles were very similar between patients and controls (p = 0.756).[18] The CA haplotype was a risk factor for MM (p = 0.0001) while the CG haplotype protected the carriers (p = 0.014).[18] But like the A allele of the A-1012G polymorphism the G allele of the G-1529C polymorphism was also associated with MM metastasis (p = 0.015).[18]

BglI polymorphism. The BglI polymorphism (rs739837) is located 303 bp downstream of the stop codon in exon 9. It was investigated in one original article (**Table 1**).

Data on the BglI polymorphism and skin cancer or cancer in general are still very limited. Barroso et al. observed no statistically association with MM and the BglI polymorphism.[15] Only a marginally significant association with fair skin color (p = 0.048) and with Fitzpatrick's phototype I/II (p = 0.070) was seen.[15]

Cdx2 polymorphism. The Cdx2 polymorphism (rs11568820) was found through sequence analysis of a targeted area.[35] It is a guanine (G) to adenine (A) sequence variation in the promoter area (1e promoter) of the VDR gene, more specifically in a binding site for an intestinal specific transcription factor which is called Cdx2.[47] First, it has been found among Japanese women, but it has been shown to be present also among Caucasians as well as other race groups.[48] The A allele has been demonstrated to be more active by binding the Cdx2 transcription factor more strongly and by having more transcriptional activity.[35] It has been assumed that in consequence, the A allele may result in a higher VDR expression in the intestine and therefore in an increased bone mineral density (BMD) through a better intestinal absorption of calcium.[35,48,49]

The Cdx2 polymorphism was investigated in one original article and in one review (**Table 1**).

There was only one study in the review which analyzed the Cdx2 polymorphism.[24] But no association between this polymorphism and risk for any type of skin cancer was observed. Recently Randerson-Moor et al. found a strong LD between the Cdx2 and the A-1012G polymorphisms (D = 0.97).[17] Following three common haplotypes were seen: G-G 42%, G-A 36% and A-A 21% for the Cdx2 and A-1012G variants respectively.[17]

Materials and Methods

Search strategy and data extraction. A systematic review of original articles analyzing the association between VDR polymorphisms and skin cancer risk was performed by searching the PubMed database. The search strategy included the following keywords (variously combined): malignant melanoma, basal cell carcinoma, squamous cell carcinoma, non-melanoma skin cancer (NMSC), VDR, vitamin D receptor, polymorphism, risk, allele and gene. Original and review articles that were published from January 2008 up to December 2010 were sought, and the review articles were used as additional sources for original articles. Cited references from selected articles also were reviewed as appropriate. Data have been extracted taking the following information from each report: authors, journal and year of publication, country of origin, racial descent of study population, number of cases and controls for each VDR genotype. The studies were heterogeneous in terms of number of cases and controls, racial composition and analyzed polymorphisms.

Conclusion

Data summarized in this review show that the vitamin D endocrine system may be of importance for pathogenesis and progression of MM and NMSC. In particular, TaqI, BsmI and FokI polymorphisms of the VDR gene are associated with MM risk. A strong LD has been noticed at the 3' end of the VDR gene for the BsmI, ApaI and TaqI RFLP's.[50] The most frequent haplotypes were baT (48%) and Bat (40%).[13] In vitro functional studies have demonstrated that the baT haplotype inserted into transfection constructs resulted in lower reporter gene activity compared with Bat and was associated with low VDR messenger RNA levels.[29,51] This reduction in vitamin D activity may lead to an increased melanoma risk.

Furthermore, there is a slight indication of a role of ApaI polymorphism in NMSC development.

However, it has to be noted that, besides VDR polymorphisms, other factors also influence the integrity of the skin's VDES, and may thereby influence skin cancer risk and prognosis. It has been reported that vitamin D serum levels may influence MM risk or prognosis.[52,53] Serum 25(OH)D levels were significantly reduced in stage IV melanoma patients as compared to stage I melanoma patients (p = 0.006).[52] A trend toward a greater tumor thickness of the primary cutaneous melanomas was seen in the patients with low (<10 ng/ml) serum 25(OH)D levels (median: 2.55 mm)

as compared to those with 25(OH)D serum levels >20 ng/ml (median: 1.5 mm), although this difference was not statistically significant (p = 0.078).[52] The patients with low 25(OH)D serum levels (<10 ng/ml) had earlier distant metastatic disease (median: 24.37 months) as compared to those with 25(OH)D serum levels >20 ng/ml (median: 29.47 months), although this difference was also not statistically significant (p = 0.641).[52]

In conclusion, data summarized in this review support the concept that the VDES is of importance for pathogenesis and progression of MM and other types of skin cancer.

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References

1. English DR, Armstrong BK, Kricker A, Fleming C. Sunlight and cancer. Cancer Causes Control 1997; 8:271-83.
2. Ravanat JL, Douki T, Cadet J. Direct and indirect effects of UV radiation on DNA and its components. J Photochem Photobiol B 2001; 63:88-102.
3. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. The role of vitamin D in cancer prevention. Am J Public Health 2006; 96:252-61.
4. Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. Curr Med Res Opin 2008; 24:139-49.
5. Baker AR, McDonnell DP, Hughes M, Crisp TM, Mangelsdorf DJ, Haussler MR, et al. Cloning the expression of full length cDNA encoding human vitamin D receptor. Proc Natl Acad Sci USA 1988; 85:3294-8.
6. Stumpf WE, Sar M, Reid FA, Tanaka Y, DeLuca HF. Target cells for 1,25-dihydroxyvitamin D_3 in intestinal tract, stomach, kidney, skin, pituitary and parathyroid. Science 1979; 209:1189-90.
7. Haussler MR, Mangelsdorf DJ, Komm BS, Terpening CM, Yamaoka K, Allegretto EA, et al. Molecular biology of vitamin D hormone. Recent Prog Horm Res 1988; 44:263-305.
8. Kliewer SA, Umesono K, Mangelsdorf DJ, Evans RM. Retinoic X receptor interacts with nuclear receptors in retinoic acid, thyreoid hormone and vitamin D_3 signalling. Nature 1992; 355:446-9.
9. Labuda M, Fujiwara TM, Ross MV, Morgan K, Garcia Heras J, et al. Two hereditary defects related to vitamin D metabolism map to the same region of human chromosome 12q13-4. J. Bone Miner Res 1992; 7:1447-53.
10. Yu VC, Deisert C, Andersen B. RXRβ: A coregulator that enhances binding of retinoic acid, thyroid hormone and vitamin D receptors to their cognate response elements. Cell 1991; 67:1251-66.
11. Leid M, Kastner P, Lyons R. Purification, cloning and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. Cell 1992; 68:377-95.
12. Hutchinson PE, Osborne JE, Lear JT, Smith AG, Bowers PW, Morris PN, et al. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. Clin Cancer Res 2000; 2:498-504.
13. Uitterlinden AG, Pols HA, Burger H, Huang Q, Van Daele PL, van Dujin CM, et al. A large-scale population-based study of the association of vitamin D receptor gene polymorphisms with bone mineral density. J Bone Miner Res 1996; 11:1241-8.
14. Fang Y, van Meurs JB, d'Alesio A, Jhamai M, Zhao H, Rivadeneira F, et al. Promoter und 3'-untranslated region haplotypes in the vitamin D receptor gene predispose to osteoporotic fracture: the Rotterdam study. Am J Hum Gent 2005; 77:807-23.
15. Barroso E, Fernandez LP, Milne RL, Pita G, Sendagorta E, Floristan U, et al. Genetic analysis of the vitamin D receptor gene in two epithelial cancers: melanoma and breast cancer case-control studies. BMC Cancer 2008; 8:385.
16. Gapska P, Scott RJ, Serrano-Fernandez P, Mirecka A, Rassoud I, Górski B, et al. Vitamin D receptor variants and the malignant melanoma risk: a population-based study. Cancer Epidemiol 2009; 33:103-7.
17. Randerson-Moor JA, Taylor JC, Elliott F, Chang YM, Beswick S, Kukalizch K, et al. Vitamin D receptor gene polymorphisms, serum 25-hydroxyvitamin D levels and melanoma: UK case-control comparisons and a meta-analysis of published VDR data. Eur J Cancer 2009; 45:3271-81.
18. Halsall JA, Osborne JE, Epstein MP, Pringle JH, Hutchinson PE. The unfavorable effect of the A allele of the vitamin D receptor promoter polymorphism A-1012G has different mechanisms related to susceptibility and outcome of malignant melanoma. Dermatoendocrinol 2009; 1:54-7.
19. Mocellin S, Nitti D. Vitamin D receptor polymorphisms and the risk of cutaneous melanoma: a systematic review and meta-analysis. Cancer 2008; 113:2398-407.
20. Köstner K, Denzer N, Müller CS, Klein R, Tilgen W, Reichrath J. The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. Anticancer Res 2009; 29:3511-36.
21. Gandini S, Raimondi S, Gnagnarella P, Doré JF, Maisonneuve P, Testori A. Vitamin D and skin cancer: a meta-analysis. Eur J Cancer 2009; 45:634-41.
22. Halsall JA, Osborne JE, Potter L, Pringle JH, Hutchinson PE. A novel polymorphism in the I A promoter region of the vitamin D receptor is associated with altered susceptibility and prognosis in malignant melanoma. British Journal of Cancer 2004; 91:765-70.
23. Santonocito C, Capizzi R, Concolino P, Lavieri MM, Paradisi A, Gentileschi S, et al. Association between cutaneous melanoma, Breslow thickness and vitamin D receptor BsmI polymorphism. Br J Dermatol 2007; 156:277-82.
24. Han J, Colditz GA, Hunter DJ. Polymorphisms in the MTHFR and VDR genes and skin cancer risk Carcinogenesis 2007; 28:390-7.
25. Povey JE, Darakhshan F, Robertson K, Bisset Y, Mekky M, Rees J, et al. DNA repair gene polymorphisms and genetic predisposition to cutaneous melanoma. Carcinogenesis 2007; 28:1087-93.
26. Li C, Liu Z, Zhang Z, Strom SS, Gershenwald JE, Prieto VG, et al. Genetic variants of the vitamin D receptor gene alter risk of cutaneous melanoma. J Invest Dermatol 2007; 127:276-80.
27. Li C, Liu Z, Wang LE, Gershenwald JE, Lee JE, Prieto VG, et al. Haplotype and genotypes of the VDR gene and cutaneous melanoma risk in non-Hispanic whites in Texas: a case-control study. Int J Cancer 2008; 122:2077-84.
28. Hustmyer FG, Deluca HF, Peacock M. Apa1, Bsm1, EcoRV and Taq1 polymorphisms at the human vitamin D receptor gene locus in Caucasians, Blacks and Asians. Hum Mol Genet 1993; 2:487.
29. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, et al. Prediction of bone density from vitamin D receptor alleles. Nature 1994; 367:284-7.
30. Ma J, Stampfer MJ, Gann PH, Hough HL, Giovannucci E, Kelsey KT, et al. Vitamin D receptor polymorphisms, circulating Vit D metabolites and risk of prostate cancer in United states physicians. Cancer Epidemiol Biomarkers Prev 1998; 7:385-90.
31. Morrison NA, Yeoman R, Kelly PJ, Eisman JA. Contribution of transactivating factor alleles to normal physiological variability: vitamin D receptor gene polymorphism and circulating osteocalcin. Proc Natl Acad Sci USA 1992; 89:6665-9.
32. Jurutka PW, Whitfield GK, Hsieh JC, Tompson PD, Haussler CA, Haussler MR. Molecular nature of vitamin D receptor and its role in regulation of gene expression. Rev Endocrin Metab Disord 2001; 2:203-16.
33. Gross C, Eccleshall TR, Mallory PJ, Villa ML, Marcus R, Feldman D. The presence of a polymorphism at the translation initiation site of the vitamin D receptor gene is associated with low bone mineral density in postmenopausal Mexican American women. J Bone Miner Res 1996; 11:1850-5.
34. Saijo T, Ito M, Takeda E, Huq AH, Naito E, Yokota I, et al. A unique mutation in the vitamin D receptor gene in three Japanese patients with vitamin D dependent rickets type II: utility of single strand conformation polymorphism analysis for heterozygous carrier detection. Am J Hum Genet 1991; 49:668-73.
35. Arai H, Miyamoto K, Taketani Y, Yamamoto H, Iemori Y, Morita K, et al. A vitamin D receptor gene polymorphism in the translation initiation codon: effect on protein activity and relation to bone mineral density in Japanese women. J Bone Miner Res 1997; 12:915-21.
36. Whitfield GK, Remus LS, Jurutka PW, Zitzer H, Oza AK, Hope T, et al. Are human vitamin D receptor polymorphisms functionally significant? In: Vitamin D Endocrine system, Structural, Biological, Genetic and Clinical Aspects. Norman AW, Bouillon R, Thomasset M, Eds. Riverside, CA: University of California 2000; 817-23.
37. Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, et al. The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. Mol Endocrinol 2000; 14:401-20.
38. Colin EM, Weel AE, Uitterlinden AG, Buurman CJ, Birkenhager JC, Pols HA, van Leeuwen JP. Consequences of vitamin D receptor gene polymorphisms for growths inhibition of cultured human peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D_3. Clin Endocrinol 2000; 52:211-6.
39. Faraco JM, Morrison NA, Baker A, Shin J, Frossard PM. Apa1 dimorphism at the human vitamin D receptor gene locus. Nucleid Acids Res 1989; 117:2150.
40. Carless MA, Kraska N, Lintell RE, Neale AC, Griffiths LR. Polymorphisms of the VDR gene are associated with presence of solar keratoses on the skin. British Journal of Dermatology 2008; 159:804-10.
41. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000; 42:8-10.
42. Evans C, Cockerell CJ. Actinic keratosis: time to call a spade a spade. South Med J 2000; 93:734-6.
43. Halsall JA, Osborne JE, Pringle JH, Hutchinson PE. Vitamin D receptor gene polymorphisms, particularly the novel A-1012G promoter polymorphism, are associated with vitamin D_3 responsiveness and non-familial susceptibility in psoriasis. Pharmacogenet Genomics 2005; 15:349-55.

44. Schug J, Overton GC. Modeling transcription factor binding sites with Gibbs Sampling and Minimum Description Length encoding. Proc Int Conf Intell Syst Mol Biol 1997; 5:268-71.
45. Rengarajan J, Szabo SJ, Glimcher LH. Transcriptional regulation of Th1/Th2 polarization. Immunol Today 2000; 21:479-83.
46. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin D_3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001; 167:4974-80.
47. Yamamoto H, Miyamot K, Li B, Taketani Y, Kitano M, Inoue Y, et al. The caudal-related homeodomain Cdx-2 regulates vitamin D receptor gene expression in the small intestine. J Bone Minar Res 1999; 14:240-7.
48. Fang Y, van Meurs JB, Bergink AP, Hofman A, van Dujin CM, van Leeuwen JP, et al. Cdx-2 polymorphism in the promoter region of the human vitamin D receptor gene determines susceptibility to fracture in the elderly. J Bone Miner Res 2003; 18:1632-41.
49. Uitterlinden SG, Fang Y, van Meurs JB, Pols HA, van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. Gene 2004; 338:143-56.
50. Durrin LK, Haile RW, Ingles SA, Coetzee GA. Vitamin D receptor 3'-untranslated region polymorphisms: lack of effect on mRNA stability. Biochim Biophys Acta 1999; 1453:311-20.
51. Carling T, Rastad J, Akerström G, Westin G. Vitamin D receptor (VDR) and parathyroid hormone messenger ribonucleic acid levels correspond to polymorphic VDR alleles in human parathyroid tumors. J Clin Endocrinol Metab 1998; 83:2255-9.
52. Nürnberg B, Gräber S, Gärtner B, Geisel J, Pföhler C, Schadendorf D, et al. Reduced serum 25-hydroxyvitamin D levels in stage IV melanoma patients. Anticancer Res 2009; 29:3669-74.
53. Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, et al. Serum 25-hydroxyvitamin D_3 levels are associated with breslow thickness at presentation and survival from melanoma. J Clin Oncol 2009; 27:5439-44.