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# Association between polymorphic variation in *VDR* and *RXRA* and circulating levels of vitamin D metabolites☆

E.A. Hibler[a,b,*], P.W. Jurutka[c,d], J.B. Egan[b], C. Hu[a], E.C. LeRoy[b], M.E. Martinez[a,b], P.A. Thompson[a,b], E.T. Jacobs[a,b]

[a] Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ 85724, USA
[b] Arizona Cancer Center, University of Arizona, Tucson, AZ 85724, USA
[c] Division of Mathematical and Natural Sciences, Arizona State University, Glendale, AZ 85069, USA
[d] Department of Basic Medical Sciences, University of Arizona College of Medicine-Phoenix, in partnership with Arizona State University, Phoenix, AZ 85004, USA

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ABSTRACT

The vitamin D metabolite 1,25(OH)$_2$D is the bioactive ligand of the vitamin D receptor (VDR). VDR forms a heterodimer with the retinoid X receptors (RXRs) that when bound to ligand influences the transcriptional control of genes that regulate circulating levels of vitamin D metabolites. Whether genetic variation in *VDR* or *RXRA* affects circulating levels of 1,25(OH)$_2$D or 25(OH)D has not been established. We used a single nucleotide polymorphism (SNP) tagging approach to evaluate the association between SNPs in *VDR* and *RXRA* and serum levels of 1,25(OH)$_2$D and 25(OH)D. A total of 42 tagSNPs in *VDR* and 32 in *RXRA* were analyzed in a sample of 415 participants. Principal components analyses revealed a gene-level association between *RXRA* and serum 1,25(OH)$_2$D concentrations ($P = 0.01$), but not 25(OH)D. No gene-level association was found for *VDR* with either serum biomarker. At the single-SNP level, a significant positive trend was observed for increasing 1,25(OH)$_2$D levels with each additional copy of the *A* allele for *RXRA* SNP rs9409929 ($P$-trend = 0.003). After a multiple comparisons adjustment, no individual SNP in *VDR* or *RXRA* was significantly associated with either outcome. These results demonstrate an association between genetic variation in *RXRA* and 1,25(OH)$_2$D serum concentrations.



## 1. Introduction

The active metabolite of vitamin D, 1,25(OH)$_2$D, is a hormone with structural and functional similarity to the classic steroid hormones, and is produced through a series of reactions after exposure to sunlight or consumption of dietary or supplemental vitamin D [1–4]. Upon exposure to UVB, 7-dehydrocholesterol is converted to previtamin D$_3$ in the epidermis [2–4]. In the liver, 25-hydroxylase (CYP2R1) acts to synthesize 25(OH)D for transport to the kidneys where it is hydroxylated by the enzyme 25-hydroxyvitamin D 1-alpha-hydroxylase (CYP27B1) to form 1,25(OH)$_2$D or cholecalciferol [1–6]. Circulating concentrations of 25(OH)D are used to measure vitamin D status because concentrations of 1,25(OH)$_2$D are tightly regulated in the body, due to its role in calcium homeostasis [7,8]. The actions of 1,25(OH)$_2$D are mediated by the vitamin D receptor (VDR). The VDR is a nuclear receptor that functions as a ligand-dependent transcription factor that can bind a number of vitamin D metabolites, though 1,25(OH)$_2$D has the highest affinity for the receptor and is the physiologically relevant ligand [1,4]. VDR must form a heterodimer with the retinoid X receptor (RXR) before it can exert any effect in the cell [4,9,10]. The binding of the ligand to VDR induces conformational changes that allow for protein-protein interaction, including formation of the VDR-RXR heterodimer, as well as interactions between VDR and transcriptional co-activator proteins like SRC-1 [4,9–11]. The RXR is an obligatory co-receptor for VDR to mediate transcription; however, RXR can also interact with many other receptors to exert a wide range of biological effects.

RXR, like VDR, is a ligand-activated transcription factor that plays a role in cell differentiation, cell growth, apoptosis, and it is also required for proper vertebrate embryonic development [12–14]. The retinoid receptors, including the retinoic acid receptors (RARs) and RXRs, also belong to the family of nuclear hormone receptors [12–15]. There are three isoforms of RXR, α, β, and γ [12,14,15]. *RXRA* was selected for analysis of genetic variation in the parent study of colorectal lesions because functional effects of RXR in colon cells have most often focused on RXRα [16–19]. 9-*cis* retinoic acid is the primary endogenous ligand for RXR which, upon binding, induces conformational changes that lead to the formation

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* Corresponding author at: Mel and Enid Zuckerman College of Public Health, P.O. Box 245163, Tucson, AZ 85724, USA. Tel.: +1 520 626 0341; fax: +1 520 626 9275.
*E-mail address:* ehibler@email.arizona.edu (E.A. Hibler).

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of either homodimers or heterodimers with a variety of receptors [12,14]. The binding of $1,25(OH)_2D$ to VDR induces allosteric conformational changes in RXR that facilitate the recruitment of coregulators [9,11]. There are numerous genes with a variety of physiologic effects that are then targeted by the VDR/RXR heterodimer, including those involved in the regulation of vitamin D metabolite concentrations via a classical endocrine feedback loop [1]. It is not known whether genetic variation in *VDR* or *RXRA* influences circulating levels of vitamin D metabolites and through what mechanisms such polymorphisms would act. Therefore, the purpose of this study was to determine if an association exists between polymorphisms in *VDR* and *RXR* and circulating concentrations of $1,25(OH)_2D$ or 25(OH)D.

## 2. Materials and methods

### 2.1. Study population

These analyses were performed using data from participants from the ursodeoxycholic acid (UDCA) trial conducted at the Arizona Cancer Center, which has been previously described [16]. The UDCA trial was a phase III randomized, double-blind, placebo-controlled trial conducted to test the effect of UDCA on recurrence of colorectal neoplasia [16]. There were 1192 participants who completed the trial; no effect of UDCA was observed. From this population a total of 568 participants were randomly selected to have serum vitamin D metabolite levels analyzed [20]. The statistical analysis for the current work included 487 participants who had both complete *VDR* and *RXRA* genotype and serum vitamin D metabolite data. The final sample was further restricted to 415 individuals who reported their racial/ethic group as white, in order to account for population stratification.

### 2.2. Genotyping and outcome ascertainment

Participants were genotyped using the Illumina Golden Gate platform (Illumina®, San Diego, CA) and tagSNPs were selected from Hapmap data release #16c.1, June 2005, on NCBI B34 assembly, dbSNP b124. The details of these processes have been previously described in detail [21]. The final statistical analysis included 42 *VDR* SNPs and 32 *RXRA* SNPs; 7 *VDR* SNPs and 9 *RXRA* SNPs were omitted for the analysis because they failed at least one of the QA/QC measures listed in Supplemental Table 1. Concentrations of vitamin D metabolites were measured at the lab of Dr. Bruce Hollis at the University of South Carolina, using established practices [22,23].

### 2.3. Statistical analysis

Vitamin D metabolites were analyzed as both continuous measures and binomial variables using common thresholds for vitamin D insufficiency including: 20, 25, and 32 ng/ml [24]. The statistical analysis included generation of principal components (PC) on the SNP data for each gene and then modeling with either linear or logistic regression models, depending upon the outcome being tested. A likelihood ratio test, comparing the model including PCs to an intercept-only model, was used for logistic regression models to generate a *P*-value testing the overall association between each gene and the outcome [25]. Individual SNPs were also examined in regression models and a multiple comparisons adjustment was applied [26]. Finally, the association between genotype and serum vitamin D metabolites was evaluated for any SNPs that showed a strong association prior to adjustment.

## 3. Results

Baseline characteristics of the participants are shown in Supplemental Table 2 and have been previously described in detail [16]. This includes mean serum concentrations for $1,25(OH)_2D$ and 25(OH)D, which were $35.1 \pm 9.7$ pg/ml and $26.2 \pm 9.3$ ng/ml, respectively for this sample. The results of the principal components analysis are presented in Table 1. Overall, genetic variation in *VDR* was not associated with levels of 25(OH)D ($P = 0.77$) or $1,25(OH)_2D$ ($P = 0.97$). In contrast, genetic variation in *RXRA*, while not associated with 25(OH)D ($P = 0.42$), was significantly associated with circulating concentrations of $1,25(OH)_2D$ ($P = 0.001$). Further

**Table 1**
Association between genetic variation in *VDR* and *RXRA* overall, and *RXRA* rs9409929, and continuous measures of circulating 25(OH)D and $1,25(OH)_2D$.

| | 25(OH)D | | | $1,25(OH)_2D$ | | |
|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | Coefficient | 95% CI | |
| ***RXRA*** | | | | | | |
| PC1 | 0.13 | −0.26 to 0.20 | | 0.18 | −3.74 to 4.1 | |
| PC2 | −0.44 | −1.19 to 0.31 | | −0.37 | −0.76 to 0.02 | |
| PC3 | 0.19 | −0.81 to 1.19 | | 0.19 | −0.85 to 1.23 | |
| PC4[a] | 1.27 | −0.04 to 2.58 | | −2.23 | −3.60 to −0.86 | |
| *P*-value[b] | | | 0.42 | | | 0.001 |
| ***VDR*** | | | | | | |
| PC1 | −0.13 | −1.03 to −2.84 | | −0.14 | −0.59 to 0.31 | |
| PC2 | 0.11 | −0.36 to 0.58 | | 0.21 | −0.30 to 0.71 | |
| PC3 | −0.24 | −0.87 to 0.39 | | −0.18 | −0.87 to 0.51 | |
| PC4 | −0.23 | −0.98 to 0.52 | | −0.19 | −0.97 to 0.76 | |
| PC5 | 0.11 | −0.91 to 1.13 | | 0.30 | −0.78 to 1.38 | |
| PC6 | 0.03 | −1.07 to 1.13 | | 0.22 | −0.97 to 1.41 | |
| PC7[a] | −1.06 | −1.12 to 1.00 | | −0.003 | −1.35 to 1.35 | |
| *P*-value[b] | | | 0.77 | | | 0.97 |
| | 25(OH)D (ng/ml), mean ± S.D. | | | $1,25(OH)_2D$ (pg/ml), mean ± S.D. | | |
| ***RXRA* rs9409929 genotype** | | | | | | |
| *GG* | $25.5 \pm 9.1$ | | | $34.0 \pm 9.4$ | | |
| *AG* | $26.5 \pm 9.6$ | | | $35.5 \pm 9.0$ | | |
| *AA* | $27.5 \pm 9.0$ | | | $38.5 \pm 12.4$ | | |
| *P*-trend | 0.092 | | | 0.003 | | |

[a] An 80% explained-variance threshold is used for including principal components (PC) in the model.
[b] *P*-value for each model is from a linear regression model with degrees of freedom equal to the number of principal components.

analysis of *RXRA* at the single-SNP level indicated that rs9409929 was strongly related to levels of $1,25(OH)_2D$ ($P = 0.003$), prior to the multiple comparisons adjustment. This led to examination of the association between genotype and vitamin D metabolite concentrations for that SNP, also presented in Table 1. A statistically significant trend for increasing $1,25(OH)_2D$ levels with additional copies of the *A* allele (*P*-trend = 0.003) for SNP rs9409929 was observed. This SNP was not significantly associated with 25(OH)D levels (*P*-trend = 0.092); however, it is likely that the study was not powered to detect this small change in circulating levels. There was no association for either gene and the binomial measures of vitamin D status (Supplemental Table 3), and no other individual *RXRA* or *VDR* SNP showed strong unadjusted associations with circulating levels of vitamin D metabolites (Supplemental Tables 4–7). After the multiple comparisons adjustment, no SNPs exhibited a statistically significant association with measures of vitamin D metabolites.

## 4. Discussion

Polymorphic variation in *VDR* has been extensively studied for associations with vitamin D status and disease outcomes. However, there is conflicting evidence for an association between polymorphisms in *VDR* and circulating levels of vitamin D metabolites. There are several commonly studied SNPs in *VDR* that include polymorphic endonuclease sites for *TaqI*, *BsmI*, *Apa1*, *FokI*, as well as a polymorphism in a binding site for Cdx-2, a homeodomain protein [27]. A group of SNPs (*BsmI*, *ApaI*, and *TaqI*) located in the 3′ region of the *VDR* gene show strong linkage disequilibrium and are often studied together in haplotypes. Earlier research showed that the *B*, *A*, and *t* alleles in these SNPs were associated, both alone and together, with increased expression of VDR and increased circulating levels of $1,25(OH)_2D$ [28,29]; although more recently, Ahn et al. demonstrated that no SNPs in *VDR* were associated with levels of either 25(OH)D or $1,25(OH)_2D$ [30]. There is also a trend in recent studies to examine the relationship between *VDR* and circulating levels of vitamin D metabolites in association with disease outcomes. Some have found an interaction between certain polymorphisms in *VDR* and circulating levels of metabolites, but fail to show a main effects association between the gene and vitamin D metabolite concentrations [31,32].

In contrast to *VDR*, the study of genetic variation in *RXR* has been limited, and to our knowledge only three studies have examined the association between *RXRA* SNPs and health outcomes. Wjst et al., reported significant associations between rs3132299 and $1,25(OH)_2D$ then rs877954 and 25(OH)D levels, however, different statistical methods were used in this study and no significant association was observed for these SNPs in the UDCA population [33]. In a study examining the risk of prostate cancer associated with variation in vitamin D pathway genes, Ahn et al. showed no association between polymorphisms in *RXRA* and circulating levels of 25(OH)D or $1,25(OH)_2D$ [30]. SNPs in *RXRA* were also studied for associations with insulin sensitivity and biliary tract cancers; however, this study did not examine vitamin D metabolites because RXR binds with PPAR in this metabolic pathway and not VDR [34]. Nonetheless, considering that a significant association between circulating $1,25(OH)_2D$ and *RXRA* was found in the current work, the possible mechanisms for this action should be further explored.

It is known that VDREs are present in promoter regions of genes that play a role in regulating circulating levels of vitamin D metabolites [1,35]. Two primary candidates are *CYP24A1* and *CYP27B1*. Vitamin D acts in an endocrine feedback loop to self-regulate $1,25(OH)_2D$ synthesis by suppressing transcription of CYP27B1, and also to initiate $1,25(OH)_2D$ catabolism by stimulating transcription of *CYP24A1* [1]. While genetic variation in *RXRA* could potentially influence VDR-RXR signaling, *RXRA* SNP rs9409929 is a *G* to *A* change in a non-coding region of chromosome 9 at position 249320, and is therefore unlikely to have functional effects [36]. However, it is possible that rs9409929 is in linkage disequilibrium with another SNP located in a region that controls expression of the gene or affects the stability of the mRNA. This SNP could thus be a marker for a different polymorphism that causes structural changes in the gene, and considering that RXRα is known to bind with a variety of receptors, the change could also influence competitive binding with VDR compared to other receptors. The partner for RXR helps determine which target genes are transcribed upon activation and, as a promiscuous receptor, its varied list of partners leads to a wide range of effects in the body. For example, when paired with the peroxisome proliferators-activated receptor (PPAR), the RXR has a role in insulin resistance; however, when paired with the retinoic acid receptor (RAR) it has been shown to induce myeloid cell differentiation [14,34]. If VDR were unable to bind with RXR, then it would be unable to stimulate transcription of *CYP24A1* and *CYP27B1*, thus interrupting the feedback loop and proper regulation of circulating levels of vitamin D metabolites. We plan to identify any SNPs in linkage disequilibrium with rs9409929 and then examine their possible functional effects using the assay system of Jurutka et al. [37].

There are limitations of this study that should be addressed in future research. The sample for the analyses only included individuals who self-reported race/ethnicity as white and, considering that vitamin D status is known to be heavily influenced by skin pigmentation, exploring associations within other racial groups is critical [24]. There is also a possibility that this study of participants with colorectal adenoma patients may not be generalizable to the general population; however, given the relatively high prevalence of these lesions in the population it is likely that the sample is fairly representative of this particular age group. Also, a larger sample size might be necessary to detect some of the more modest associations with various SNPs, and future studies will be designed to address this issue of statistical power. Finally, the statistical adjustment used to account for multiple comparisons may have been too stringent to allow for identification of additional SNPs that affect the relationship between *RXRA* and circulating levels of vitamin D metabolites. An alternative approach could include PC analysis followed by directed examination of individual SNPs included in that PC, as opposed to examining all available SNPs in a gene individually [25]. This method could lead to less chance of a Type II error, especially for genes with a large number of SNPs (like *VDR* or *RXR*), where the increased number of statistical tests leads to a more stringent adjustment of the *P*-value.

## 5. Conclusions

The results of this analysis suggest that genetic variation in *RXRA* may influence $1,25(OH)_2D$ homeostasis. This is the first study to find a relationship between genetic variation in *RXRA* and levels of this hormone. Though RXRα is known to play an integral role in the function of VDR, it is unclear how allelic variation in *RXRA* effects the action of the VDR/RXR heterodimer at the molecular level. This analysis should be replicated in different populations that are representative of the general population and incorporate additional methods for statistical testing.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jsbmb.2010.03.052.

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