EXTENDED REPORT

Combined role of vitamin D status and *CYP24A1* in the transition to systemic lupus erythematosus

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ABSTRACT

Objective We examined whether measures of vitamin D were associated with transitioning to systemic lupus erythematosus (SLE) in individuals at risk for SLE.

Methods 436 individuals who reported having a relative with SLE but who did not have SLE themselves were evaluated at baseline and again an average of 6.3 (±3.9) years later. Fifty-six individuals transitioned to SLE (≥4 cumulative American College of Rheumatology criteria). 25-Hydroxyvitamin D (25[OH]D) levels were measured by ELISA. Six single-nucleotide polymorphisms in four vitamin D genes were genotyped. Generalised estimating equations, adjusting for correlation within families, were used to test associations between the vitamin D variables and the outcome of transitioning to SLE.

Results Mean baseline 25[OH]D levels (p=0.42) and vitamin D supplementation (p=0.65) were not different between those who did and did not transition to SLE. Vitamin D deficiency (25[OH]D <20 ng/mL) was greater in those who transitioned compared with those who did not transition to SLE (46% vs 33%, p=0.05). The association between 25[OH]D and SLE was modified by *CYP24A1* rs4809959, where for each additional minor allele increased 25[OH]D was associated with decreased SLE risk: zero minor alleles (adjusted OR: 1.03, CI 0.98 to 1.09), one minor allele (adjusted OR: 1.01, CI 0.97 to 1.05) and two minor alleles (adjusted OR: 0.91, CI 0.84 to 0.98). Similarly, vitamin D deficiency significantly increased the risk of transitioning to SLE in those with two minor alleles at rs4809959 (adjusted OR: 4.90, CI 1.33 to 18.04).

Conclusions Vitamin D status and *CYP24A1* may have a combined role in the transition to SLE in individuals at increased genetic risk for SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterised by a number of immunological abnormalities, including autoantibody production, acute and chronic inflammation of numerous tissues, and recurring rash and fever. The aetiology of SLE remains largely unidentified, although a combination of genetic and environmental influences is most likely.

One plausible environmental risk factor in SLE pathogenesis may be vitamin D. Lower levels of 25-hydroxyvitamin D (25[OH]D) have been associated with various autoimmune diseases, including other rheumatological conditions.[1 2] Studies within patients with SLE indicate that lower 25[OH]D levels may correlate with increased disease activity,[3–16] although inconsistently.[17–24] Variation within the vitamin D receptor gene (*VDR*), the vitamin D receptor protein that binds the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), has been associated with higher SLE disease activity in females[25] and higher damage score.[26]

Whether vitamin D is related to risk of developing SLE has not been clearly established. Several measures have been used to assess the association between vitamin D and SLE, including serum levels of 25[OH]D, vitamin D intake assessed from diet and supplement use, and variation in vitamin D genes. Individuals with SLE have lower levels of 25[OH]D[14 19 20 27–31] compared with those without SLE, although it is possible that this may be a consequence rather than a risk factor of the disease. Neither vitamin D intake in adulthood[32] nor in adolescence[33] was associated with increased risk of SLE in the Nurse's Health Study. However, examining vitamin D intake alone may reflect only a small portion of an individuals' vitamin D status as it does not account for 25[OH]D produced as a result of exposure to the sun nor the genetic control of vitamin D metabolism. A number of genes play a role in transporting 25[OH]D and 1,25$[OH]_2$D (*GC*), converting 25[OH]D to 1,25$[OH]_2$D (*CYP27B1*), degradation of 1,25$[OH]_2$D (*CYP24A1*) as well as enabling the action of 1,25$[OH]_2$D (*VDR*). Case–control studies have examined the association between *VDR* polymorphisms and SLE with conflicting results, finding associations in some populations,[25 34–36] but not others.[37–42] No studies have examined the role of *GC*, *CYP27B1* or *CYP24A1* and the risk of SLE.

Previous studies were limited to a single measure of vitamin D status, whether vitamin D levels, vitamin D intake or vitamin D genes. We assembled a unique cohort of individuals who reported having a relative with SLE, putting them at increased genetic risk for SLE,[43 44] but who did not meet SLE classification[45] at their baseline visit. Within this cohort, we examined whether vitamin D at baseline was prospectively associated with transitioning to SLE at follow-up, using plasma 25[OH]D levels, reported vitamin D supplement use and genetic variants within four vitamin D metabolism genes encoding enzymes involved in the activation, metabolism and binding/activation of vitamin D.

METHODS

Study population

All protocols were approved by the Institutional Review Boards at the Oklahoma Medical Research Foundation, the Medical University of South Carolina and the University of Colorado Denver. Study participants were enrolled in the Lupus Family Registry and Repository (LFRR)[46] or Systemic Lupus Erythematosus in Gullah Health (SLEIGH)[47] studies and provided informed consent prior to enrolment. Letters were sent to individuals who reported having a relative with SLE and who did not meet ≥4 American College of Rheumatology (ACR)[45] criteria for SLE at the time of their LFRR or SLEIGH baseline visit. These individuals were invited to enrol in a follow-up study to gather information regarding interim development of symptoms consistent with SLE or transition to classified SLE. Of the 3823 individuals recontacted, 436 individuals enrolled in this follow-up study. Compared with those who were not enrolled, individuals enrolled in this study were younger (53.7 vs 59.7 years), had shorter time between contact (6.1 vs 8.0 years), were more likely to be female (83.7% vs 66.9%) and more likely to be European American (73.8% vs 52.9%). Of the 436 individuals enrolled, 393 individuals were first-degree relatives of an individual with confirmed SLE, 11 were second-degree relatives (aunts, uncles, grandparent, grandchild) and 5 were more distantly related (cousin, grandniece). Although this cohort was recruited because they reported a family member with SLE, in 27 individuals the lupus diagnosis of their family member could not be confirmed.

Identical questionnaires and laboratory tests were completed at baseline and follow-up (mean time between contact 6.3 ±3.9 years). Detailed demographic, environmental, clinical and therapeutic data were collected by questionnaire[46] and participants completed the SLE portion of the Connective Tissue Disease Screening Questionnaire.[48] Body mass index (BMI) was calculated as reported weight (kg)/height (m^2). Peripheral blood samples were obtained from all study participants and processed for serum, plasma and DNA. Antinuclear antibodies (ANA) were detected using a HEp-2 indirect immunofluorescent assay (positive titre ≥1:120) and anti-dsDNA was detected using *Crithidia luciliae* (positive titre ≥1:30) according to manufacturer's instructions (INOVA Diagnostics, San Diego, California, USA) in the College of American Pathologists-certified OMRF Clinical Immunology Laboratory. Medical records were obtained for individuals who reported signs and symptoms of SLE and reviewed by a rheumatology-trained physician or nurse for ACR classification criteria. Individuals were classified as having transitioned to SLE if they met ≥4 cumulative ACR criteria, in which medical record-verified ACR criteria could accumulate towards the total count of ACR, and did not need to be all present at the same time. We identified 56 individuals who transitioned to SLE at follow-up. The most common ACR criteria were ANA positivity (96%), arthritis (73%), malar rash (59%), immunological disorder (55%) and photosensitivity (52%).

Vitamin D measures

Plasma levels of 25[OH]D were determined in duplicate using a commercial enzyme immunoassay (Immunodiagnostic Systems, Scottsdale, Arizona, USA) according to manufacturer's instructions. In order to examine season of blood draw, we classified blood draws taken in June–August as summer, those taken from September–November as autumn, those taken in December–February as winter and those taken from March–May as spring. Vitamin D deficiency was defined as 25[OH]D <20 ng/mL. Vitamin D supplementation use was assessed by self-reported medication history within the last year and defined as a yes/no variable.

Six single-nucleotide polymorphisms (SNPs) in four vitamin D genes (*GC* (rs7041), *CYP27B1* (rs10877012), *CYP24A1* (rs4809959) and *VDR* (rs1544410, rs11568820 and rs7975232)) were genotyped using the Immunochip and were read on the Illumina iScan in the OMRF Genomics Core.[49] Genotypes were called via Opticall[50] using the default options with the addition of -nointcutoff option in order to manually remove intensity outliers. Each SNP was tested for consistency with Hardy–Weinberg proportions using a one-degree of freedom χ^2 goodness-of-fit test with a p value of 0.05 considered as evidence of a departure from Hardy–Weinberg equilibrium; all six SNPs were in Hardy–Weinberg equilibrium. SNPs were analysed using an additive model, treating the number of minor alleles as a continuous variable with the OR representing an increase (or decrease) in risk for each minor allele.

Ancestry was determined by principal component analysis of the full Immunochip data after pruning out poor genotyping and SNPs in high-linkage disequilibrium. The first three principal components sufficiently differentiated between the different races within our cohort and were included as covariates in the genetic analyses.

Statistical methods

All analyses were performed in SAS V.9.4 (Cary, North Carolina, USA). t Tests for continuous variables and χ^2 tests for categorical variables were used to determine differences between individuals who transitioned to SLE (n=56) and individuals who did not transition to SLE (n=380). Mean 25[OH]D levels were assessed with confirmed cutaneous ACR criteria (malar or discoid rash and photosensitivity) by t test. Within this cohort, individuals within the same family could be enrolled; family size ranged from 1 to 6 family members, with 23% of our population with at least one other family member enrolled. We therefore accounted for the correlation among these family members in our analyses.

Generalised estimating equations, accounting for correlation within families, were used to assess associations between our dichotomous outcome of transitioning to SLE at follow-up, and our predictor variables of (1) 25[OH]D as a continuous variable, (2) vitamin D deficiency as a dichotomous variable and (3) vitamin D supplementation as a dichotomous variable. The models were adjusted for age, sex, race and season of blood draw. BMI at baseline did not add significantly to these models and was not included as a covariate. When examining association with the vitamin D gene SNPs, we additionally adjusted for ancestry by including the first three PCs from our principal components analysis of the Immunochip data (as described above). Effect modification between vitamin D levels and SNPs in the vitamin D genes was tested by addition of interaction terms to the models. ORs and 95% CIs were determined for all models. The significance threshold was defined as $\alpha<0.05$. Because our analyses were based on a priori hypotheses with SNPs previously found to be associated with 25[OH]D levels and other autoimmune diseases, p values were not corrected for multiple testing.

RESULTS

Description of study cohort by SLE transition status

We compared individuals who transitioned to SLE at follow-up with those who did not transition with respect to demographics, number of ACR criteria and vitamin D status (table 1). Age and BMI were similar between those who transitioned to SLE and

Table 1 Description of the study participants by systemic lupus erythematosus transition status

Variable	Transitioned N=56	Did not transition N=380	p Value
Age at baseline: mean (median)±SD	47.4 (48.5)±12.1	47.2 (48.0)±15.8	0.93
Age at follow-up: mean (median)±SD	53.2 (55.0)±12.0	53.5 (55.0)±15.5	0.89
Years to follow-up: mean (median)±SD	5.9 (5.1)±3.5	6.3 (5.4)±3.9	0.50
Sex: female	49 (87.5%)	316 (83.2%)	0.41
Race			
EA	43 (76.8%)	279 (73.4%)	0.55
AA	9 (16.1%)	55 (14.5%)	
Other*	4 (7.1%)	46 (12.1%)	
BMI at baseline: mean (median)±SD	28.5 (28.5)±7.4	28.1 (26.9)±6.8	0.71
Number of confirmed ACR criteria at baseline	2.3 (2.0)±0.7	0.9 (1.0)±0.8	**<0.001**
ANA positive at baseline	43 (76.8%)	183 (48.2%)	**<0.001**
Vitamin D supplementation at baseline: yes	6 (10.7%)	49 (12.9%)	0.65
25[OH]D (ng/mL) at baseline: mean (median)±SD	23.0 (21.5)±9.7	24.1 (23.7)±9.5	0.43
Vitamin D deficient† at baseline: yes	26 (46.4%)	126 (33.2%)	**0.05**
Season‡ of blood draw at baseline:			
Summer	18 (32.1%)	89 (23.4%)	0.15
Autumn	14 (25.0%)	102 (26.8%)	
Winter	18 (32.1%)	103 (27.1%)	
Spring	6 (10.7%)	86 (22.6%)	

Bold typeface indicates significant results ($p < 0.05$).
*Other includes Native American (n=8), Asian (n=1) and Hispanic (n=2).
†Vitamin D deficient defined as 25[OH]D <20 ng/mL.
‡Summer is June–August, autumn is September–November, winter is December–February and spring is March–May.
25[OH]D, 25-hydroxyvitamin D; AA, African American; ACR, American College of Rheumatology; ANA, antinuclear antibodies; BMI, body mass index; EA, European American.

those who did not transition to SLE, and the majority of individuals in both groups were European American and female. Individuals who transitioned had a greater number of confirmed ACR criteria and were more likely to be ANA positive at baseline compared with those who did not transition ($p<0.001$). Reported vitamin D supplement use at baseline was similar between groups. Adjusting for age, sex, race and season of blood draw, taking vitamin D supplements at baseline was not associated with transitioning to SLE at follow-up (adjusted OR 0.70, 95% CI 0.28 to 1.79). While mean 25[OH]D levels were not different between those who transitioned to SLE and those who did not transition to SLE, a greater proportion of individuals who transitioned to SLE were vitamin D deficient compared with those who did not transition ($p=0.05$).

Vitamin D levels interact with *CYP24A1* in risk of developing SLE

We examined the interaction between 25[OH]D and genetic variants in vitamin D metabolism on the risk of transitioning to SLE as these genes play a role in transporting 25[OH]D (and $1,25[OH]_2D$) (*GC*), converting it to $1,25[OH]_2D$ (*CYP27B1*), degrading of $1,25[OH]_2D$ (*CYP24A1*), as well as the action of $1,25[OH]_2D$ (*VDR*) (figure 1). While SNPs in *GC*, *CYP27B1*, *CYP24A1* and *VDR* were not significantly associated with transitioning to SLE on their own, adjusting for age, sex and ancestry, we detected a significant interaction between *CYP24A1* and vitamin D. The association between 25[OH]D level and transitioning to SLE was modified by *CYP24A1* rs4809959 (interaction $p=0.001$). For each additional minor A allele, an increased 25[OH]D level was associated with a greater decreased SLE risk: zero minor alleles (OR 1.03, 95% CI 0.98 to 1.09), one minor allele (OR 1.01, 95% CI 0.97 to 1.05), two minor alleles (OR 0.91, 95% CI 0.84 to 0.98), adjusting for age, sex and ancestry (figure 2A). Similarly, the association between vitamin D deficiency and transitioning to SLE was modified by this same SNP (interaction $p=0.02$), where vitamin D deficiency was significantly associated with increased risk of SLE in individuals with two copies of the minor allele (OR 4.90, 95% CI 1.33 to 18.04), adjusting for age, sex and ancestry (figure 2B). Based on the proportion (0.286) who transitioned in the exposed group (ie, vitamin D deficiency and two minor alleles) and the proportion (0.091) who transitioned in the unexposed group (ie, no vitamin D deficiency and zero minor alleles), we calculated the attributable risk per cent for the interaction of vitamin D deficiency and *CYP24A1* as 68.1%.

In addition to adjusting for ancestry, we also explored the potential of spurious genetic associations due to population stratification by limiting our analyses to European Americans (n=294) to make the population more homogeneous. After

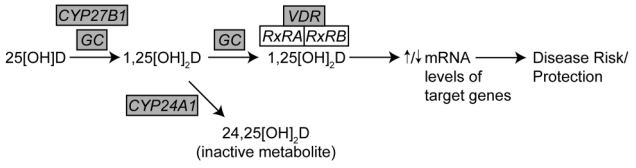

Figure 1 Vitamin D metabolic pathway. Vitamin D-related genes are represented by the grey boxes. *GC*, group-specific component (vitamin D binding protein). Vitamin D is bound to vitamin D binding protein (encoded by the *GC* gene) in the blood and transported to the liver, where it is converted to 25-hydroxyvitamin D (25[OH]D). This is then transported to the kidney via vitamin D binding protein, where it is converted into the active metabolite 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) by 1-α hydroxylase (encoded by the *CYP27B1* gene), which affects several immunomodulatory pathways that can affect disease risk. When $1,25[OH]_2D$ is sufficiently available, some of it is converted to the inactive 24,25-dihydroxyvitamin D ($24,25[OH]_2D$) by 1-α, 25 dihydroxyvitamin D 24-hydroxylase (encoded by the *CYP24A1* gene) in the kidney.VDR, vitamin D receptor.

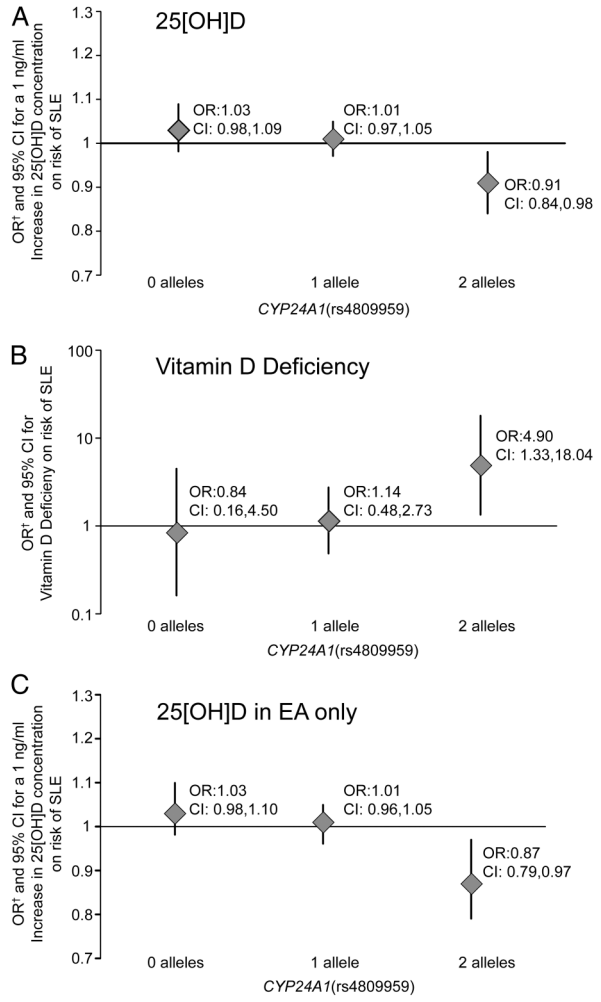

Figure 2 The association between vitamin D at baseline and transitioning to systemic lupus erythematosus (SLE) differs by number of *CYP24A1* rs4809959 minor A alleles. All models are adjusted for age, sex and ancestry. (A) Lower 25-hydroxyvitamin D (25[OH]D) levels are significantly associated with transitioning to SLE in individuals with two copies of the minor allele at rs4809969. Interaction p value: p=0.001. OR 0.91 (0.84 to 0.98). (B) Vitamin D deficiency is significantly associated with transitioning to SLE in individuals with two copies of the minor allele at rs4809969. Interaction p value: p=0.02. OR 4.90 (1.33 to 18.04). (C) After limiting analyses to European Americans, lower 25[OH]D levels are still significantly associated with transitioning to SLE in individuals with two copies of the minor allele at rs4809969. Interaction p value: p=0.03. OR 0.87 (0.79 to 0.97).

adjusting for age, sex and ancestry, we found similar results in European Americans as we found with our full cohort, including the effect modification with between 25[OH]D and risk of SLE by the number of A alleles at *CYP24A1* rs4809959 (figure 2C).

Vitamin D levels associate with *CYP24A1* independent of clinical features

Specific ACR criteria may influence sun exposure behaviour. We examined whether presence of these criteria at baseline were associated with 25[OH]D levels and found that levels did not differ by presence of rash nor photosensitivity (table 2).

As number of ACR criteria and ANA positivity were strong predictors of our outcome of transitioning to SLE (table 1), we investigated whether including each as a variable in our models influenced the association between the *CYP24A1* rs4809959 and 25[OH]D interaction and transitioning to SLE. The interaction between 25[OH]D levels and rs4809959 was still significant when including either number of ACR criteria ($p_{interaction}$=0.03) or ANA positivity ($p_{interaction}$=0.01), indicating that the association of 25[OH]D levels and *CYP24A1* is independent of number of baseline ACR criteria and ANA positivity.

Table 2 Baseline 25-hydroxyvitamin D (25[OH]D) levels are not associated with cutaneous American College of Rheumatology (ACR) criteria

ACR criteria	Baseline 25[OH]D ng/mL Mean±SE (n=436)	p Value
Malar or discoid rash		
No (n=397)	24.1±9.4	0.27
Yes (n=39)	22.3±10.0	
Photosensitivity		
No (n=399)	23.8±9.6	0.52
Yes (n=37)	24.9±8.6	

DISCUSSION

25[OH]D is most commonly measured in clinical settings. It has been shown to be the best predictor of an individual's vitamin D status with a half-life of 2–3 weeks compared with the 4–6 hours of $1,25[OH]_2D$ and is a measure of vitamin D from dietary intake, adipose stores and synthesis from sun exposure.[51] 25[OH]D levels have also been shown to predict $1,25[OH]_2D$ levels.[52] However, measures of vitamin D status alone may not accurately represent the risk for SLE, and assessing the effect in combination with genes involved in vitamin D transport, binding and metabolism may allow more accurate assessment of SLE risk in relatives. We found that vitamin D status and *CYP24A1* may have a combined role in transitioning to SLE in individuals at increased genetic risk for SLE. In individuals with two copies of the minor allele at rs4809959, increasing 25[OH]D levels were associated with decreased risk of transitioning to SLE, and vitamin D deficiency was associated with increased risk of transitioning to SLE. This association did not appear to be a result of confounding by number of ACR criteria, nor possible sun-avoidance behaviour at baseline, and was robust to population stratification. Measurement of an individual's vitamin D status, along with the presence of genetic variation within vitamin D metabolism genes, may help identify individuals at increased risk of transitioning to SLE.

SLE develops through multiple steps that result in the loss of self-tolerance, development and accumulation of autoantibody specificities, and onset of clinical disease. Given that *CYP24A1* encodes the enzyme responsible for initiating the degradation of $1,25[OH]_2D$, these results may indicate genetic evidence for a pathogenic role for low levels of $1,25[OH]_2D$ in SLE. rs4809959 in *CYP24A1* is located within an intron, indicating variation may result in splice-site variation or disrupt non-coding regulatory components to affect disease susceptibility, rather than directly disturbing protein structure and function.

Vitamin D deficiency is a risk factor for several chronic inflammatory or autoimmune conditions.[1 2] In rheumatic diseases in particular, $1,25[OH]_2D$ regulates both innate and adaptive immunity, potentiating the innate response,[53–56] which has been shown to precede the development of autoimmunity in SLE,[57] but reducing adaptive immunity,[53–56] including reduced T cell activation[58] and working in conjunction with glucocorticoids on

the inhibition of lymphocyte proliferation.[56] Vitamin D deficiency seems to play a role in increasing B cell activation[14 59] and therefore autoantibody production, and long-term supplementation with vitamin D increased the number of T-regulator cells in individuals with SLE.[60] 1,25[OH]$_2$D has inhibitory effects on many of the immunological response pathways associated with SLE, including the proliferation of B cells, antibody production[61] and altered inflammatory and regulatory pathways.[62] In addition, 1.25[OH]$_2$D has been shown to downregulate pro-inflammatory cytokines in macrophages by decreasing aromatase activity.[63] Lower 25[OH]D levels and vitamin D deficiency, and therefore reduced 1,25[OH]$_2$D levels, may result in an increased risk of transitioning to SLE through these pathways.

Previous studies examining the association of vitamin D status on the risk of SLE had several limitations. Most were cross-sectional and did not assess the prospective risk of vitamin D status on transitioning to SLE. In addition, all were limited to a single measure of vitamin D status, thereby only assessing a portion of an individual's vitamin D status. Therefore, prior studies may not have had a complete picture of the involvement of vitamin D. One clear advantage to our study is the ability to examine different measures of vitamin D status and the interaction between them. Indeed, we found the effect of 25[OH]D on risk of transitioning to SLE was modified by the number of minor alleles in *CYP24A1*. Among those with vitamin D deficiency and two minor alleles, the per cent of the incidence of transitioning to SLE that can be attributed to vitamin D deficiency and having two minor alleles was 68.1%. Although this study is limited by not having a direct measure of 1,25[OH]$_2$D, a previous study found that patients with SLE had lower 25[OH]D levels but similar 1,25[OH]$_2$D levels and vitamin D binding protein levels compared with controls.[31] It is possible that while the individuals with SLE have lower 25[OH]D levels, this is not a good measurement of immunological susceptibility to SLE unless it is taken within the context of *CYP24A1* genotype as this may have the greatest impact on levels of the physiologically important 1,25[OH]$_2$D. Individuals with SLE have multiple risk factors for 25[OH]D deficiency. Along with the development of rashes that can be exacerbated by ultra-violet (UV) exposure, photosensitivity may lead to sun avoidance in patients with SLE and decreased production of vitamin D in the skin. We found no associations between lower 25[OH]D levels and increased number of confirmed ACR criteria, nor associations specifically with photosensitivity and rash in this population at baseline. SLE also affects other organ systems, including the kidneys, where 25[OH]D is converted to its metabolically active form 1,25[OH]$_2$D, possibly leading to decreased levels of vitamin D in these individuals.[64] Only one individual had medical record confirmed renal criteria at baseline, however, indicating that this is likely not an issue within this cohort.

Approximately 75% of our study population is European American, which has a slower rate of transition to classified disease,[65 66] as well as damage accumulation,[67] than other race/ethnic groups, which may explain the later age at onset of lupus in our cohort. Studying a more diverse at-risk population would allow one to explore the extent to which the observed interaction between vitamin D levels and SNPs and its association with transitioning to SLE applies to other racial and age groups. In addition, following individuals prospectively will allow for one to study time to SLE diagnosis, allowing for a clearer understanding of how vitamin D deficiency is affecting development of SLE.

To our knowledge, this is the first study to examine effect modification between 25[OH]D and genes in the vitamin D pathway on SLE risk. Our results indicate that *CYP24A1*, central in the degradation of the physiologically active 1,25[OH]$_2$D, is important in the association of lower levels of 25[OH]D and increased risk of SLE. Future studies examining 1,25[OH]$_2$D levels and the risk of SLE are warranted, as is the effect of two copies of the minor A allele at rs4809959 on both 25[OH]D and 1,25[OH]$_2$D levels. In addition, there should be further exploration of the pathophysiological pathways responsible for the vitamin D and SLE association, including expression of *CYP24A1* variants in organs and tissues involved in SLE, such as the skin, heart, lungs, blood vessels, brain, kidneys and connective tissue. In conclusion, vitamin D status and *CYP24A1* may have a combined role in transitioning to SLE in individuals at increased genetic risk for SLE and could be used to help inform prevention efforts.

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Competing interests None declared.

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Combined role of vitamin D status and *CYP24A1* in the transition to systemic lupus erythematosus

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