Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Significant association between *TaqI* and *FokI VDR* gene polymorphisms and chronic spontaneous urticaria in a Colombian Caribbean population

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Received 7 June 2022; Accepted 21 October 2022
Available online 29 October 2022

KEYWORD
Schronic spontaneous urticaria;
gene;
polymorphisms;
urticaria;
vitamin D receptor

Abstract
Introduction: Chronic spontaneous urticaria (CSU) is an inflammatory skin disease related to poor quality of life. Previous studies have found that vitamin D deficiency and vitamin D receptor (*VDR*) *TaqI*, *BsmI*, *FokI*, and *ApaI* gene single-nucleotide polymorphisms (SNPs) influence immune response and susceptibility to skin disorders.
Aim: To explore the role of *VDR* SNPs, and the association of vitamin D serum levels in a sample of Colombian Caribbean CSU patients. *Methods*: It is a case-control study. A group of CSU patients (n = 100) was compared with healthy individuals as a control group (n = 100). *VDR* polymorphisms were genotyped by quantitative polymerase chain reaction and Taqman® probes. Allelic, genotypic, and haplotype associations were estimated. Serum vitamin D levels were measured using enzyme-linked-immunosorbent serologic assay.
Results: Compared to the control group, the presence of G allele in *TaqI* and A allele in *FokI* SNPs of *VDR* gene was found to be a risk factor for CSU (odds ratio (OR) estimated using logistic regression adjusted by gender: 2.08 and 1.61, respectively, all P values < 0.05). The individuals who carry *GCCA* haplotype showed decrease in vitamin D levels (11.34 ng/mL; P = 0.002) with the G allele of *TaqI* and A allele of *FokI* gene SNPs.
Conclusion: We reported for the first time the association of *TaqI* [rs731236] and *FokI* [rs2228570] *VDR* gene SNPs showing as a risk factor for CSU in a sample of multiethnic patients from the Colombian Caribbean population.

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https://doi.org/10.15586/aei.v50iSP2.696

Introduction

Urticaria is a frequent mast cell-driven disease characterized by wheals or angioedema, or both.[1] The classification of urticaria subgroups is mainly based on clinical criteria: the acute form affects 20% and chronic urticaria (CU) affects up to 5% of the general population. These forms of urticaria differ in etiology, pathophysiology, and underlying mechanisms.[1,2] CU is diagnosed if the disease has been continuously or intermittently present for at least 6 weeks,[2] thus having a significant impact on the quality of life because of its regular recurrence and constant sensation of itching.[3,4]

Depending on whether the skin lesions can be induced by a specific trigger or appear spontaneously, CU is classified as either chronic inducible urticaria (CIndUs) or chronic spontaneous urticaria (CSU).[2,3] Interaction between the immune and neuroendocrine systems is the core of several inflammatory disorders of the skin, including CSU.[5] However, its underlying mechanisms are poorly understood.[3,6]

Vitamin D influences allergen-induced pathways in innate and adaptive immune systems and has a potential immunomodulatory role in skin disorders.[7] In addition, vitamin D may have clinical significance in determining susceptibility to autoimmune diseases through regulating multiple immune cells.[8–10] Its activity is mediated through its active form 1,25-dihydroxy vitamin D3 ($1,25(OH)_2D_3$), combined with vitamin D receptor (VDR), which further results in a conformational change and leads to dimerization of retinoid X receptor.[8]

The stimulation of VDR and retinoic acid receptor at cellular level can induce apoptosis, cell differentiation, intrinsic immunity, macrophage response modulation, proliferation, and survival of mast cells.[8,9,11,12] Moreover, vitamin D can suppress dendritic cell maturation, inhibition of T helper 1 (Th1) cell proliferation by decreasing Th1 cytokine secretion, and inhibit B-lymphocyte function resulting in reduced production of immunoglobulin E (IgE).[8,9,13]

Several single nucleotide polymorphisms (SNPs) have been reported in various exons of the *VDR* gene with a potential role in the susceptibility to various diseases, including rheumatoid arthritis, skin disorders, diabetes, and cancer.[14–18] However, data are still lacking on the relationship between *VDR* gene SNPs and Colombian Caribbean CSU patients. In this study, we conducted a case-control study involving 200 individuals to explore the potential role of the *VDR* gene SNPs (*FokI*, *BsmI*, *ApaI*, and *TaqI*) in Colombian Caribbean CSU patients, aiming to assess whether *VDR* gene polymorphism could affect CSU susceptibility. The effects of *VDR* gene SNPs on vitamin D levels were also studied.

Material and Methods

Subjects

This study included 100 patients with CSU and 100 healthy controls from the Colombian Caribbean population. All patients conformed to the EAACI/GA-LEN/EDF/-WAO diagnostic criteria.[19] Demographic data of the CSU patients were collected. Written informed consent was obtained from all patients prior to participating in this study. The ethics committee of the Universidad Del Norte (Health Sciences Division) approved this study.

Patients received H1-antihistamines as required to obtain sufficient symptom control and oral corticosteroids as a rescue therapy in severe exacerbations. Medications for difficult to control CSU included H2-antihistamines, leukotriene receptor antagonist, immunosuppressive agents (e.g., cyclosporine), and anti-IgE monoclonal antibody (omalizumab).

DNA extraction and genotyping

Four tubes were used to collect 10 mL of whole blood samples from each subject in both control and CSU groups. Two tubes were used for serum separation to measure the serum vitamin D level. The sera were stored at −70°C until the test was performed. DNA was extracted using the QIAamp® DNeasy kit (Qiagen, Germany). Additional tubes of blood were used to determine the genotype of *FokI* [rs2228570 A/G], *BsmI* [rs1544410 C/T], *ApaI* [rs7975232 A/C], and *TaqI* [rs731236 A/G] SNPs in the *VDR* gene. Genotyping was performed using real-time quantitative polymerase chain reaction (qPCR) with commercial TaqMan® SNP kits (Applied Biosystems, Foster City, CA, USA). A reaction mixture of 5 µL was used: 2.4 μL of DNA (~10 ng/μL), 2.5 μL of Master Mi, x-2x, and 0.125 μL of TaqMan genotyping-40x probes specific to each SNP. The conditions of real-time qPCR were as follows: 10 min at 95°C, followed by 40 cycles of 15 sat 92°C and 1 min at 60°C per cycle. The genotyping assignment was made automatically by the allelic discrimination application with an amplification quality of ≥90% per sample. All real-time qPCRs of the genotypes were carried out using the RT-PCR ABI Prism 7300 system (Applied Biosystems).

Estimation of serum levels of vitamin D

Serum vitamin D levels were measured using a commercial enzyme-linked-immunosorbent serologic assay (ELISA) kit according to manufacturer instructions (Immunodiagnostic Systems Ltd., Boldon, Tyne and Wear, UK). Serum vitamin D levels were classified according to the Institute of Medicine (IOM) cut-off point as follows: <10 ng/mL of 25(OH)D corresponds to deficient levels; 25(OH)D = 10–<30 ng/mL as insufficient; 25(OH)D = ≥30–<100 ng/mL as sufficient; and 25(OH)D ≥ 100 ng/mL as possible vitamin D poisoning.[20]

Statistical analysis

All calculations were performed using the SPSS® v24 software (IBM Corp., USA). Continuous variables were presented as the mean values ± standard deviation or median (interquartile range). Categorical variables were described as percentage values. Allelic and genotypic frequencies and the Hardy-Weinberg (H-W) genetic equilibrium were estimated using the software Arlequin v3.5. Differences in allele and genotype frequencies between patients and

control groups were assessed by χ^2 tests with Bonferroni correction. Odds ratios (OR) for genotypes and alleles were estimated using logistic regression models, and 95% confidence interval (95% CI) was adjusted by gender.

Association analyses between polymorphisms and serum concentrations of vitamin D were performed using both Mann-Whitney U and Kruskal-Wallis tests as appropriate. Analysis with categorical vitamin D data was performed using Pearson's χ^2 test. (Fisher's exact test was applied if the expected frequencies were <5). Haplotype analyses were done using Haplo.stats v1.6.8 (R version 3.0.2; http://www.r-project.org), Haplo.cc (logistic regression models for estimating risk OR [95% CI] excluding haplotypes with frequencies <3%), and Haplo.glm (generalized linear regression model for estimating associations) statistical packages; $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study sample

General characteristics of patients and controls are shown in Table 1. The patient and control groups were matched by age (mean age of CSU patients: 40.1 ± 16.6 years; mean age of controls: 39 ± 15.4 years).

Genotype and allele frequencies

The frequencies of genotypes in the CSU patient and control groups are shown in Table 2. With the exception of *ApaI* in the control group and *TaqI* in the CSU group, the other two genotyped SNPs were in H-W equilibrium for both CSU patients and controls (all $P > 0.05$). There was a significant difference between the frequencies of genotypes in CSU and control patients for *TaqI* and *FokI* SNPs (all $P < 0.05$). Presence of G allele in *TaqI* and A allele in *FokI* SNPs of the *VDR* gene was found to be a risk factor for CSU patients. In *TaqI*, the *GG* and *AG* genotypes increased the risk of CSU (ORs = 3.1 and 3.3, respectively). Similarly, the *AG* genotype in *FokI* SNP was found to increase the risk of CSU (OR = 2.33).

Haplotype and linkage disequilibrium analysis

Linkage disequilibrium (LD) analysis showed that *TaqI*, *ApaI*, and *BsmI* were in significant LD with each other ($D' = 0.85$, $r^2 = 0.54$), but not with *FokI* (Figure 1). The *GACG* haplotype formed by *TaqI*, *ApaI*, *BsmI*, and *FokI* was found to be a risk factor for CSU patients (OR = 13.5; 95% CI: 2.0–92). There were significant differences in *AACG* and *ACCG* haplotypes between CSU patients and controls ($P = 0.040$ and 0.001, respectively; Table 3).

VDR gene haplotype and vitamin D levels

The effect of *VDR* polymorphisms on serum 25(OH)D levels were explored. We compared serum 25(OH)D levels of individuals carrying different *VDR* gene haplotypes. *ACCG* haplotype was the most frequent and was taken as a reference for this analysis. Presence of the G allele of *TaqI* in individuals with *GACG* haplotype induces a decrease of 7.61 ng/mL ($P = 0.044$) in vitamin D levels. A decrease of 10.78 ng/mL ($P = 0.029$) was observed with the presence of the A allele of *FokI* in individuals with *ACTA* haplotype. The concomitant presence of the G allele of *TaqI* and the A allele of *FokI* additively increased the effect of these genetic variants on vitamin D levels, and individuals who carried the *GCCA* haplotype reported a decrease of 11.34 ng/ mL ($P = 0.002$; Table 4).

Discussion

Although CSU is a common skin disease, its pathogenesis is poorly understood.[1] The activation and release of histamine by mast cells and basophils is an important cause of this disease;[3] moreover, autoimmunity has been related as a causative role in CSU.[6,21] A gradually increasing evidence has linked decreased serum vitamin D levels with allergic diseases, such as dermatitis, atopic dermatitis, asthma, and urticaria.[8,14,22,23] Although the mechanisms related to the vitamin D effects in allergic diseases are not clear, vitamin D deficiency may result in excess inflammation leading to simultaneous degranulation of mast cells.[24]

Table 1 General characteristics of patients and controls in this study.

Parameter	CSU n (%)	Controls n (%)	OR	95% CI	*P* Value
Age (Mean ± SD)	40.1 ± 16.6	39 ± 15.4			0.364
Duration of disease (months)	16.3 ± 4.56				
Gender					
Male	18 (18)	43 (43%)	3.43	1.8–6.5	0.000*
Female	82 (82)	57 (57)			
Vitamin D (ng/mL)					
Mean ± SD	29.2 ± 16.6	37.1 ± 10.6			0.000*
Deficiency (<10 ng/mL)	1 (1)	4 (4)	0.65	0.6–6.4	
Insufficient (10–30 ng/mL)	67 (67)	13 (13)	13.9	6.4–29.8	0.000*
Sufficient (30–100 ng/mL)	32 (32)	81 (81)	1	-	

SD: standard deviation; CI: confidence interval; OR: odds ratio estimated using logistic regression adjusted by gender. *$P < 0.05$, Chi-square test and Mann-Whitney U test.

Table 2 Distribution of *VDR* (*FokI*, *BsmI*, *ApaI*, and *TaqI*) gene SNPs in CSU patients (n = 100) and controls (n = 100).

VDR gene	CSU n (%)	H-W	Controls n (%)	H-W	OR	95% CI	*P* Value¥
TaqI [rs731236]							
AA	27 (27)	0.013*	56 (56)	0.519	1	–	0.000*
AG	61 (61)		36 (36)		3.3	1.79–6.4	
GG	12 (12)		8 (8)		3.1	1.1–8.9	
A	115 (57.5)		148 (74)		1	–	0.000*
G	85 (42.5)		52 (26)		2.08	1.34–3.23	
ApaI [rs7975232]							
AA	32 (32)	0.354	24 (24)	0.037*	1	–	0.103
AC	45 (45)		60 (60)		0.5	0.25–1.07	
CC	23 (23)		16 (16)		0.88	0.37–2.1	
A	109 (54.5)		108 (54)		1	–	1.00
C	91 (45.5)		92 (46)		0.89	0.5–1.35	
BsmI [rs1544410]							
TT	9 (9)	1	7 (7)	0.90	1.24	0.41–3.7	0.672
CT	42 (42)		38 (38)		1.22	0.66–2.23	
CC	49 (49)		55 (55)		1	–	
C	140 (70)		148 (74)		0.86	0.54–1.35	0.436
T	60 (30)		52 (26)		1	–	
FokI [rs2228570]							
AA	16 (16)	0.614	12 (12)	0.203	1.92	0.78–4.7	0.036*
AG	51 (51)		37 (37)		2.33	1.23–4.42	
GG	33 (33)		51 (51)		1	–	
A	83 (42)		61 (30.5)		1.61	1.05–2.47	0.029*
G	117 (59)		139 (69.5)		1	–	

H-W: exact test of Hardy-Weinberg equilibrium by 100.000 steps of Markov chain and 1000 dememorization steps; OR: odds ratio estimated using logistic regression adjusted by gender; ¥Exact test of population differentiation by 100.000 steps of Markov chain and 1000 dememorization steps; *$P < 0.05$.

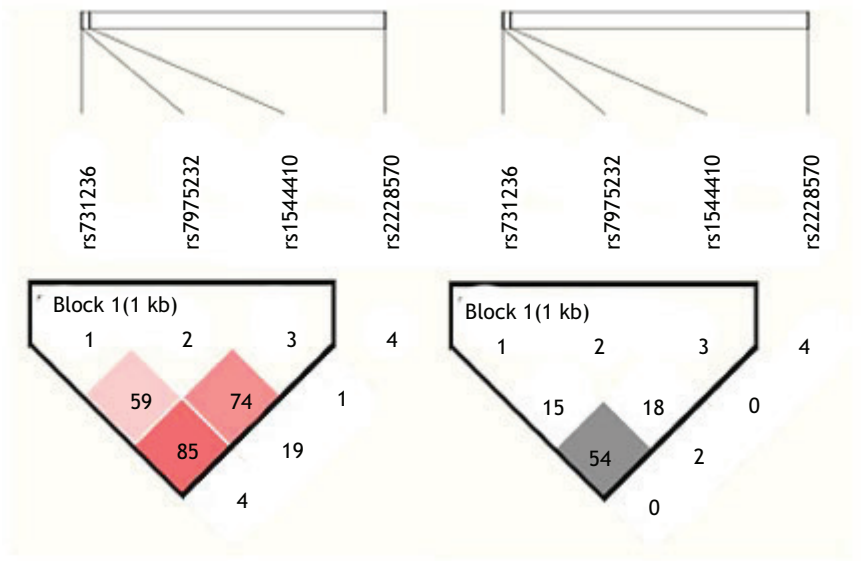

Figure 1 Linkage disequilibrium plot between *VDR* (*FokI*, *BsmI*, *ApaI*, and *TaqI)* genes. The markers rs731236, rs7975232, and rs1544410 represent *VDR TaqI*, *ApaI*, and *BsmI* genes, respectively. Blocks are framed in black. Each square plots a D'value between a pair of polymorphic loci.

It is presumed that vitamin D influences both innate and adaptive immunity. In the innate immune system, it improves antimicrobial defenses by stimulating the expression of antimicrobial peptides such as cathelicidin and human β-defensin.[25] In the adaptive immune system, vitamin D inhibits the production and activation of interleukin (IL)-1, IL-6, IL-12, interferon gamma (IFN-γ), and expression and secretion of normal T cells.[24] On the other hand, a concentration of 25(OH)D_3 in the serum-free medium can activate T cells to express CYP27B1 and then convert

Table 3 Distribution of haplotypes formed by *VDR* (*TaqI*, *ApaI*, *BsmI*, and *FokI*) gene SNPs in CSU patients (n = 100) and controls (n = 100).

TaqI	*ApaI*	*BsmI*	*FokI*	CSU (%)	Control (%)	OR	95% CI	*P* Value¥
A	A	C	A	7	6	1.16	0.52–2.5	0.700
A	A	C	G	15.1	23	0.588	0.35–0.97	0.040*
A	C	C	A	13.6	14.1	0.95	0.5–1.6	0.87
A	C	C	G	16.9	29.9	0.46	0.29–0.75	0.001*
G	A	C	G	7.3	0.6	13.5	2.0–92	0.000*
G	A	T	A	8.2	10.3	0.76	0.38–1.5	0.442
G	A	T	G	16.9	13.1	1.34	0.7–2.3	0.293

¥P-values; global P-value (VDR loci): 6.83e-8; haplotype frequencies < 3% were excluded; *$P < 0.05$

$25(OH)D_3$ to $1,25(OH)_2D_3$,[13] and this mechanism enabled them to rapidly increase the level of vitamin D required for regulating immune response.[26]

Many studies have demonstrated significant differences in vitamin D levels in CSU patients and controls.[18,27-29] In alignment with our results, meta-analysis conducted by Tsai et al.[29] and Wang et al.[30] showed that vitamin D levels were significantly lower in CSU patients than in controls. The cause of vitamin D deficiency in CSU patients was likely due to multifactorial adaption of a more sedentary indoor lifestyle, sun exposure, Fitzpatrick skin type, body mass index (BMI), changing dietary habits, genetic polymorphism, gene on gene interactions, and ethnic differences.[8,24] Particularly, the population of the Colombian Caribbean region consists of a multi-ethnic mix gene pool, and it is the result of the crossover of native Latin Americans, Europeans, and Afro descendant,[31,32] which may have influenced vitamin D levels.

Studies related to genetic association have confirmed the association between *VDR* gene SNPs and allergic diseases.[7,14,33] However, genetic studies addressing CSU are scarce. *VDR* gene is located on the long arm of chromosome 12 (12q13.11). Several SNPs have been reported in various exons of *VDR* gene, which are probably associated with a higher risk of CSU.[18,19] Most of these SNPs are located in the 3' region, which is evaluated by restriction enzymes (*Taq1*, *ApaI*, and *BsmI*); these SNPs participate in adjusting the stability of *VDR* mRNA.[16] Except for *FokI*, which is located on exon 2, the others are located between exon 8 and exon 9.[18] Ma et al. demonstrated the association between *VDR* gene *FokI* (rs2228570) SNP and CSU risk in a Chinese population.[19] Unlike our study, they did not report a significant relationship between serum vitamin D levels and *FokI* SNP in *VDR* gene. In a Kurdish population having CSU, Nasiri-Kalmarzi et al. demonstrated that *BsmI* (rs1544410) SNP was a risk factor for CSU and that changes in the Vitamin D pathway in the level of gene or protein could be a risk factor for the progression of CSU.[27] Similarly to our study, Khoshkhui et al. discovered a significant association between *TaqI* SNP and susceptibility to CSU in an Iranian population[18].

Conclusion

In our study, as far as we know, we have reported for the first time the association of *TaqI* [rs731236] and *FokI* [rs2228570] *VDR* gene SNPs as a risk factor for CSU in a sample of multiethnic patients from the Colombian Caribbean population. A larger sample size and multicenter studies are required to confirm these associations. Moreover, further functional studies are required to clarify the mechanisms of *TaqI* and *FokI* polymorphism on the risk of CSU and its effect on vitamin D levels.

Conflict of Interest

None.

Author Contributions

All the authors contributed equally to the submitted work, and approved the final manuscript for its publication.

Table 4 Haplotype association of *VDR* gene SNPs with general serum levels of vitamin D.

TaqI	*ApaI*	*BsmI*	*FokI*	Frequency (%)	Vitamin D levels (ng/mL)	β coefficient	Standard error	*P* Value¥
Vitamin D [ng/mL]								
A	*C*	*C*	*G*	23.37	37.05	Ref	2.73	0.000*
A	*A*	*C*	*A*	6.53	36.90	−0.16	3.47	0.964
A	*A*	*C*	*G*	19.56	38.39	1.34	2.10	0.524
A	*C*	*C*	*A*	13.25	32.75	−4.31	3.06	0.161
A	*C*	*T*	*A*	2.22	26.28	−10.78	4.90	0.029*
G	*A*	*C*	*G*	3.89	29.44	−7.61	3.75	0.044*
G	*A*	*T*	*A*	9.19	36.59	−0.46	2.79	0.869
G	*A*	*T*	*G*	15.11	32.90	−4.15	2.48	0.096
G	*C*	*C*	*A*	4.67	25.72	−11.34	3.60	0.002*

¥Empirical P-values; Ref: reference haplotype; haplotype frequencies < 2% were excluded. *$P < 0.05$

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