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Effect of vitamin D–binding protein genotype on the development of asthma in children

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ABSTRACT

Background: Potential vitamin D–related influences on inflammatory diseases such as asthma are controversial, including the suggestion that vitamin D insufficiency is associated with increased asthma morbidity. Vitamin D–binding protein transports vitamin D metabolites in the circulation. Single nucleotide polymorphisms in the GC gene encoding vitamin D–binding protein are associated with circulating vitamin D metabolite levels in healthy infants and toddlers.

Objective: To test the hypothesis that GC single nucleotide polymorphisms encoding the D432E and T436K variants predict subsequent development of asthma in healthy children.

Methods: A retrospective medical record review was performed to determine the development of asthma in 776 children in whom GC genotype, vitamin D–binding protein concentration, and circulating 25-hydroxyvitamin D had been determined at 6 to 36 months of age. Demographic and detailed current clinical data were collected and criteria for asthma were recorded.

Results: GC genotype was available for 463 subjects. After an initial analysis of all subject data, the analysis was limited to the predominant Hispanic population (72.1%) to minimize potential confounding effects of ethnicity. Asthma was diagnosed in 87 children (26%). Subjects with the GC genotype encoding the ET/ET (Gc1s/Gc1s) variant had lower odds of developing asthma, representing a protective effect compared with subjects with the DT/DT (Gc1f/Gc1f) variant.

Conclusion: In the Hispanic population of inner-city New Haven, Connecticut, the ET/ET (Gc1s/Gc1s) genotype of vitamin D–binding protein might confer protection against the development of asthma compared with the wild-type genotype DT/DT (Gc1f/Gc1f).

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Introduction

Recently, there has been extensive interest in “nonclassic” functions of vitamin D, in contrast to the classic role of vitamin D in the regulation of total body calcium homeostasis. Because vitamin D has been implicated in the regulation of immune cells, such as T

and B lymphocytes, macrophages, and dendritic cells,^{1–3} the possibility of a role for vitamin D in the mediation of inflammatory diseases, including asthma, was considered.

Several studies have found that circulating 25-hydroxyvitamin D (25-[OH]D) levels are associated with risk for developing childhood asthma,^{2,3} wheezing,^{4–6} and asthma severity and asthma control.^{7–11} Maternal vitamin D intake during pregnancy has been found to be inversely related to asthma symptoms in early childhood.^{12,13} Higher 25-(OH)D levels have been associated with significantly lower odds of hospitalization for asthma, and low serum levels of this metabolite have been associated with increased rates of hospitalization for asthma, increased use of controller medications, and increased airway responsiveness.⁹ African American adolescents with asthma have been found to have significantly lower serum 25-(OH)D levels compared with control subjects without asthma.¹⁴ In contrast to these findings, there have been reports of a lack of relation between 25-(OH)D levels and

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asthma,^{5,15–17} raising the question of whether factors in the vitamin D metabolism pathway other than metabolite level might be a determining factor for asthma risk.

Vitamin D deficiency, as indicated by levels of 25-(OH)D lower than 20 ng/mL (50 nmol/L), is not infrequent in the general population¹⁸ or in children.¹⁹ Known risk factors for vitamin D deficiency include lack of sunlight exposure, nonwhite ethnicity and increased skin pigmentation, obesity, and indoor confinement.¹⁴ However, 25-(OH)D levels may be influenced by other unidentified factors, raising the distinct consideration of genetic influences on circulating levels. Candidate genes that have been identified as potential determinants of circulating 25-(OH)D in genome-wide association studies include *VDR* (encoding the vitamin D receptor), *CYP2R1* (encoding the microsomal 25-hydroxylase), and *GC* (encoding the vitamin D-binding protein [DBP], which binds circulating vitamin D metabolites).²⁰ *GC* is a highly polymorphic gene located at 4q11-13.²¹ Many variants of DBP have been characterized by isoelectric focusing,²² but attention has increasingly centered on the 2 most common genetic variants: D432E (rs7041–c1296TNG) and T436K (rs4588–c1307CNA). These single nucleotide polymorphisms (SNPs) in the coding region of exon 11 of *GC* encode the electrophoretically distinguishable proteins Gc1F/Gc1S and Gc2, respectively. The 2 variants show ethnic-specific allele frequencies based on large population studies²³ and have been shown to correlate with vitamin D metabolite levels.^{24–26} More recently, the authors reported that the T436K variant in DBP is an important determinant of 25-(OH)D levels in healthy infants and toddlers.²⁷ Therefore, they hypothesized that specific DBP variants associated with circulating 25-(OH)D levels would be associated with increased risk for developing asthma in children.

Methods

Study Population

The authors accessed data from 776 healthy children who were enrolled from 2005 to 2008 (at 6–36 months old) in a study examining determinants of circulating vitamin D metabolite levels. At enrollment the subjects were healthy and were specifically free from diseases or conditions that might affect overall nutritional status or bone metabolism. Children with a history of disorders that affected vitamin D or mineral metabolism or who received systemic glucocorticoids, who received at least the medium dose (fluticasone or equivalent 352 µg)²⁸ of inhaled corticosteroids for up to 4 years of age, and who had current or recent (within 1 month) use of anticonvulsants or other medications known to affect bone and mineral homeostasis were excluded from enrollment in the original study. The children received primary care services at 1 of 4 community-based primary care centers in New Haven, Connecticut. The ethnicity of the subjects was predominantly Hispanic but included black and white children. The study was approved by the Yale University institutional review board for clinical investigation.

Study Design

This retrospective medical record review was performed from 2010 to 2011 and included demographic data and detailed clinical information related to the development of asthma, asthma symptoms, and atopic disease. Evidence for asthma and confirmation of an asthma diagnosis that was present in the record were based on the National Heart, Lung, and Blood Institute Expert Panel Report 3 guidelines.²⁸ This included identifying symptom frequency and pulmonary function testing (impairment domain), exacerbations (risk domain), triggers, evidence of atopy, and family history. Subjects were excluded if they had developed any chronic respiratory or nonrespiratory disease other than asthma, had a history of prematurity (<32 weeks' gestational age), liver disease such as

hepatitis, or renal/urologic disease (eg, recurrent urinary tract infection), or used pharmacologic or prescription-level dosages of vitamin D or its metabolites.

Biochemical Analysis

At enrollment GC genotype, DBP concentration, and circulating levels of 25-(OH)D were determined. Serum 25-(OH)D was measured by radioimmunoassay kit methodology (DiaSorin, Stillwater, Minnesota). Plasma concentration of DBP was measured by immunonephelometry using a Behring Nephelometer (Behring Diagnostics, Westwood, Massachusetts), as described by Wians et al.²⁹

Genotype Analysis

The pD432E (rs7041) and pT436K (rs4588) GC SNPs were genotyped, with phase assignment based on allele-specific amplification of the pT436K site, followed by restriction endonuclease digestion of the pD432E site, as previously described.²⁷ Allele-specific amplification was carried out in a 20-µL reaction mixture containing 1× polymerase chain reaction buffer (Qiagen, Toronto, Ontario, Canada), 0.2 mmol/L each of the 4 deoxynucleoside triphosphates (dATP, dGTP, dTTP, and dCTP), 50 ng of genomic DNA, 0.5 U of HotStarTaq (Qiagen), and 0.3 to 1 µmol/L of the following primers: 5'-GGCATGTTTCACTTTCTGATCTC-3' (forward), 5'-ACCAGCTTTGCCAGTACCG-3' (wild-type reverse), and 5'-GCAAAGTCTGAGTGCTTGTATGCAGCTTTGCCAGTTGCT-3' (mutant reverse). The underlined bases in the primer sequences are mismatched nucleotides introduced to avoid cross-priming. After the initial DNA denaturation and HotStarTaq activation at 95°C for 15 minutes, the amplification went through 35 cycles of denaturation at 94°C for 20 seconds, annealing at 58°C for 20 seconds, and extension at 72°C for 20 seconds, with an increment of 1 second after each subsequent cycle, and a final extension at 72°C for 5 minutes at the finish. Eight microliters of amplified products was run in a 2% NuSieve gel (Lonza Group Ltd, Basel, Switzerland) containing ethidium bromide and then visualized using ultraviolet illumination. The pT436K wild-type allele produced a 246-bp band and the mutant allele produced a 270-bp band. Another 8 µL of amplicon was digested with *Hae*III (New England BioLabs, Ipswich, Massachusetts) at 37°C overnight and the digested products were analyzed by repeat electrophoresis in 2% NuSieve gel. The DNA bands containing the wild-type pD432E allele remained unchanged, whereas those with pD432E mutant allele were cut, producing 221-bp fragments.

Given the absence of any recombinants between the 2 polymorphic loci, assignment of a diplotype for each subject, based on the 3 haplotype alleles (wild-type, electrophoretic variant 1f; mutant 432E, electrophoretic variant 1s; mutant 436K, electrophoretic variant 2), was unambiguous.

Data Analysis

The χ^2 and *t* tests were conducted to compare the categorical or continuous characteristics between subjects with asthma and those without asthma accordingly. The Hardy-Weinberg equilibrium was tested within subjects with asthma, without asthma, and the entire population using the exact test method. If significant disequilibrium existed in subjects without asthma for a certain SNP, this marker was excluded from further analysis. Otherwise, haplotype was constructed according to genotyping results. For the haplotype of D432E/T436K, the reconstruction was completed directly because there was no existence of haplotype EK. The haplotypes of *VDR* (vitamin D receptor) and *CYP2R1* (encoding the vitamin D-25 hydroxylase that catalyzes synthesis of 25-[OH]D from native vitamin D) were reconstructed using the expectation-maximization algorithm in the Proc Haplotype procedure in SAS

Genetics (SAS Institute, Cary, North Carolina). SNPs for these 2 genes were selected based on previous studies that have shown a relation between them and 25-(OH)D levels. Five VDR SNPs were examined: Fok1 (rs2228570), Taq1 (rs731236), Bsm1 (rs1544410), Apa1 (rs7975232), and Cdx-2 (rs11568820).^{30,31} For CYP2R1 the rs10741657 SNP was examined because it had been previously identified as associated with 25-(OH)D levels.^{32–34} Multivariate logistical regression was performed for asthma outcome using haplotype, 25-(OH)D, and obesity. A backward model selection strategy was used. Only variables with a *P* value of estimate less than .2 were kept in the final model. The genotype effect on age, age at enrollment, DBP concentration, and circulating levels of 25-(OH)D at enrollment were examined using analysis of variance. All statistical analyses were performed using SAS 9.2 (SAS Institute). The significance level of the *P* value was at .05 (2-sided).

Results

Of the original sample of 776 subjects, 69 were excluded because of inadequate genotype information. Sufficient information to confirm or exclude the diagnosis of asthma using the National Heart, Lung, and Blood Institute Expert Panel Report 3 guidelines was available for 601 subjects. Subjects were initially divided into 2 groups by age (<5 and ≥5 years) because of the uncertainty of whether a diagnosis of asthma could be established in the younger children with the information available in the medical record. In 23 of the 161 younger children, the diagnosis of asthma could be confirmed. Therefore, these children were included in the analysis of the older group, resulting in 463 subjects. The age of the youngest subjects included in this analysis was 4 years.

Characteristics of subjects with and without asthma are listed in Table 1. There was no difference in sex distribution, age at initial enrollment, current age, or obesity between the 2 groups. The prevalence of asthma was less frequent in Hispanic subjects (87 vs 247) compared with other ethnicities. Because of the predominance of subjects of Hispanic ethnicity (72.1% of total), the analysis

was focused on this ethnic group to minimize any potential confounding effects of ethnicity. Therefore, in the final analysis, only the 334 Hispanic children were included.

As presented in Table 2, the diagnosis of asthma was confirmed in 87 of the 334 examined subjects (26.0%). There was no difference between the asthma and no-asthma groups in current age, age at enrollment, sex, or prevalence of obesity. Most subjects with asthma were classified as having intermittent asthma (58.3%). More subjects with asthma had evidence of atopy and wheezing with viral infection compared with the group without asthma (Table 2). The authors did not find a difference between groups regarding circulating levels of DBP or 25-(OH)D at enrollment.

To confirm the authors' previous finding of a relation between genotype and vitamin D,²⁷ they examined the relation among GC genotype, circulating levels of DBP, and circulating levels of 25-(OH)D (Table 3). They confirmed that circulating 25-(OH)D was affected by the SNP encoding the DBP T436K variant in an additive manner (TT > TK > KK, *P* = .019) and was not affected by D432E variance in this subset of Hispanic children (*P* = .76). Circulating DBP also was affected by T436K genotype (TT > TK > KK, *P* < .0001) and by the D432E variants in this group of subjects (EE > DE > DD, *P* = .02).

Then, the authors examined the odds of developing asthma as related to GC haplotype (Table 4). They found that the haplotype associated with variance at the D432E position was associated with the development of asthma. In particular, the E allele appeared to be protective in this regard; ie, subjects with haplotypes containing the E variant had lower odds of developing disease compared with those containing the D432 allele. Moreover, the effect was additive such that the proportion of children with asthma decreased with progressive substitution of the D allele (DD > DE > EE, *P* = .05).

Table 2

Demographics and vitamin D metabolite and DBP levels at original enrollment of Hispanic subjects with and without asthma^a

Characteristics	Total (N = 334)	With asthma (n = 87)	Without asthma (n = 247)	<i>P</i> value
Sex				.31
Female	177 (53.0)	42 (48.3)	135 (54.7)	
Male	157 (47.0)	45 (51.7)	112 (45.3)	
Current age (y)	5.9 (1.0)	5.8 (1.1)	5.9 (0.9)	.23
Age at enrollment (years)	1.7 (0.7)	1.7 (0.7)	1.8 (0.7)	.36
Age at diagnosis ^b	2.1 (1.4)	2.1 (1.4)	—	
Obese				.13
Yes	26 (7.8)	10 (11.5)	16 (6.5)	
No	308 (92.2)	77 (88.5)	231 (93.5)	
Asthma class				
Intermittent		49 (58.3)		
Mild persistent		20 (23.8)		
Moderate persistent		15 (17.9)		
Allergic rhinitis				<.0001
Yes	51 (15.3)	29 (33.3)	22 (8.9)	
No	282 (84.7)	58 (66.7)	224 (91.1)	
Allergies				.01
Food allergy	122 (36.5)	28 (32.2)	94 (38.1)	
Medical allergy	26 (7.8)	13 (14.9)	13 (5.3)	
No	186 (55.7)	46 (52.9)	141 (56.7)	
Eczema				.046
Yes	113 (33.8)	37 (42.5)	76 (30.8)	
No	221 (66.2)	50 (57.5)	171 (69.2)	
Wheezing with viral infections				<.0001
Yes		82 (94.3)	43 (17.6)	
No	207 (62.4)	5 (5.8)	202 (82.5)	
DBP at enrollment (mg/L)	198.8 (26.5)	194.1 (24.6)	200.5 (27.0)	.08
25-(OH)D at enrollment (nmol/L)	67.7 (26.4)	72.3 (45.7)	66.2 (14.7)	.23

Abbreviations: 25-(OH)D, 25-hydroxyvitamin D; DBP, vitamin D binding protein.

^aData are presented as number (percentage) for categorical variables and mean (SD) for continuous variables.

^bAsthma first diagnosed per medical record.

Table 1

Demographics of all subjects examined^a

Characteristics	Total (N = 463)	With asthma (n = 138)	Without asthma (n = 325)	<i>P</i> value ^b
Sex				.24
Female	242 (52.4)	66 (48.2)	176 (54.2)	
Male	220 (46.6)	71 (51.8)	149 (45.9)	
Ethnicity				.01
Hispanic	334 (72.1)	87 (63.0)	247 (76.0)	
Black/African American	98 (21.2)	40 (29.0)	58 (17.8)	
White/other	31 (6.7)	11 (8.0)	20 (6.2)	
Age (y)	5.8 (1.0)	5.6 (1.2)	5.9 (0.9)	.06
Age at enrollment (y)	1.8 (0.7)	1.7 (0.8)	1.8 (0.7)	.38
Age at diagnosis ^c	2.1 (1.4)	2.1 (1.4)	—	
Obese				.07
Yes	32 (6.9)	14 (10.2)	18 (5.5)	
No	430 (93.1)	123 (89.8)	307 (94.5)	
Asthma class				
Intermittent		78 (56.5)		
Mild persistent		26 (14.5)		
Moderate persistent		26 (14.5)		
N/A		8 (5.8)		
DBP at enrollment (mg/L)	196.8 (27.7)	192.8 (23.8)	198.7 (29.2)	.04
25-(OH)D at enrollment (nmol/L)	65.9 (24.3)	67.8 (37.3)	65.1 (16.0)	.43

Abbreviations: 25-(OH)D, 25-hydroxyvitamin D; DBP, vitamin D binding protein; N/A, not available.

^aData are presented as number (percentage) for categorical variables and mean (SD) for continuous variables.

^bBy χ^2 test for categorical variables and *t* test for continuous variables.

^cAsthma first diagnosed per medical record.

Table 3

Demographics, DBP, and 25-(OH)D level by genotype in Hispanic subjects

	T436K				D432E			
	TT (n = 207)	TK (n = 113)	KK (n = 14)	P value ^a	DD (n = 111)	DE (n = 176)	EE (n = 47)	P value ^a
Age (y)	5.9 (1.0)	5.9 (0.9)	6.1 (0.9)	.60	5.9 (1.0)	5.9 (0.9)	5.9 (1.0)	.98
Age at enrollment (y)	1.8 (0.7)	1.7 (0.7)	2.0 (0.7)	.25	1.7 (0.7)	1.8 (0.7)	1.7 (0.8)	.99
DBP	204.3 (26.4)	189.7 (24.0)	183.3 (23.3)	<.0001	194.3 (27.8)	198.9 (24.9)	203.8 (27.5)	.02
25-(OH)D at enrollment	70.9 (30.9)	62.1 (15.1)	65.1 (13.1)	.02	67.2 (41.4)	67.3 (14.2)	70.4 (13.7)	.76

Abbreviations: 25-(OH)D, 25-hydroxyvitamin D; DBP, vitamin D-binding protein.

^aAnalysis of variance comparing continuous variables.

Thus, with respect to the protein, homozygous Gc1s/Gc1s DBP was associated with lower odds of having asthma than the Gc1f/Gc1f DBP, and the heterozygous forms containing Gc1s (ET) were associated with lower odds than Gc1f/Gc1f. The authors did not find a significant effect of SNPs encoding T436K variants, and adjusting for obesity had no effect on this outcome (Table 4).

In contrast to the GC SNPs, there was no effect of the VDR or CYP2R1 SNPs examined for the presence of asthma. For VDR, only the Fok1, Taq1, and Bsm1 sites were examined as potential contributory variants, because the distribution of Apa1 and Cdx-2 showed significant Hardy-Weinberg disequilibrium.³⁵ For the 3 VDR SNPs and the rs10741657 variant in CYP2R1, no significant differences in allele frequencies were observed between subjects with asthma and controls, suggesting that these SNPs in vitamin D-related genes were not genetically associated with the risk of asthma in this group of subjects.

Discussion

In this study the authors found that the GC polymorphic bases giving rise to the major electrophoretic isoforms of DBP (rs4588 and rs7041) are significant determinants of asthma risk in inner-city Hispanic children. They showed the effects of these GC variants on the risk for asthma development, effects that were independent of circulating 25-(OH)D levels collected at the time of initial enrollment. Specifically, these data suggest that the Gc1s allele (ET) confers a protective effect against the development of asthma.

Serum DBP, also known as GC globulin, is a multifunctional protein known for its role in the transport of vitamin D metabolites. In addition to binding and transporting vitamin D, other described functions include activation of macrophages, augmenting the chemotactic effect of C5a for macrophages and neutrophils, and scavenging actin.³⁶ These latter functions have been shown in the lung and in other organ systems. In a recent study of adults with chronic obstructive pulmonary disease, circulating DBP levels were inversely correlated with lung function, and sputum DBP was

found to contribute to macrophage activation.³⁷ Other studies also have shown a role for DBP in chronic obstructive pulmonary disease.^{38–40}

Until recently, little attention has been afforded the role of DBP in asthma, primarily because of the varying results observed in the few studies examining this issue.^{36,41,42} However, new evidence for a role of DBP in asthma has become available. For example, in adults with asthma, DBP levels were found to be elevated in bronchoalveolar lavage fluid of subjects after allergen challenge, independent of vitamin D metabolite levels.⁴³ Then, these researchers showed in a murine model of ovalbumin sensitization/challenge that treatment with an antibody to DBP decreased airway hyper-reactivity and airway inflammation in a dose-dependent manner, further supporting a role for DBP.⁴³ In another study, DBP variants were associated with asthma in a Han Chinese population, with the DK haplotype (Gc2) predicting increased risk for asthma compared with wild-type DT (Gc1F).⁴⁴ In the present study, subjects harboring the ET haplotype showed significantly lower odds of developing asthma compared with the wild-type haplotype (DT) in this population of Hispanic children. Thus, the protein variant Gc1s/Gc1s (ET/ET) would be associated with the lowest odds of asthma compared with wild-type Gc1F/Gc1 (DT/DT). This difference might be related to the different populations represented in these studies, ie, Hispanic children vs Han Chinese adults. As in the present study, the genotypes associated with the development of asthma were not associated with circulating 25-(OH)D levels. Also comparable to the present study, there was no relation between the development of asthma and polymorphisms examined in other sites of the vitamin D pathway (VDR and CYP2R1). The authors are aware of only 2 other studies in children examining DBP effects on asthma. In 1 study,⁴⁵ children with severe, therapy-resistant asthma had higher levels of DBP in bronchoalveolar lavage fluid than did children with moderate asthma or nonaffected controls. These investigators identified a negative association among bronchoalveolar lavage DBP content, asthma control testing, spirometry, and inhaled corticosteroid use, supporting the possibility that DBP might play a role in childhood asthma. In the other study of a small group of

Table 4

Comparison of odds of having asthma between variants in vitamin D-binding protein in Hispanic subjects

	With haplotype, n	With asthma, n (%)	Crude		Adjusting for obesity	
			OR (95% CI)	P value	OR (95% CI)	P value
D432E				.03		.02
ET/DT (Gc1S/1F)	115	30 (26.1)	0.63 (0.41–0.95)		0.62 (0.41–0.94)	
ET/ET (Gc1S/1S)	47	8 (17.0)	0.39 (0.17–0.90)		0.38 (0.17–0.88)	
T436K				.30		.27
DK/DT (Gc2/1F)	52	16 (30.8)	0.78 (0.49–1.24)		0.77 (0.48–1.23)	
DK/DK (Gc2/2)	14	3 (21.4)	0.61 (0.24–1.55)		0.59 (0.23–1.51)	
Double heterozygote				.06		.049
DK/ET (Gc2/1S)	61	14 (23.0)	0.49 (0.23–1.02)		0.48 (0.23–0.99)	
Reference				—		—
DT/DT (Gc1F/Gc1F)	45	16 (35.6)	1.00		1.00	

Abbreviations: CI, confidence interval; OR, odds ratio.

Egyptian children,⁴⁶ the researchers examined the rs2282679 SNP in GC; they found that the G allele was more frequent in children with asthma compared with controls, and that disease was more severe in children who had 2 G alleles compared with those with TT (wild type) or GT, suggesting that the wild-type T allele was protective.

The mechanism by which mutations in DBP affect asthma risk cannot be discerned from the present study. Acknowledging the fact that the vitamin D metabolite levels that were analyzed were obtained at original enrollment, much before the subjects exhibited evidence of asthma, the authors did not identify a relation between serum levels of vitamin D metabolite and asthma, suggesting that the effect of DBP on circulating vitamin D is not the operative mechanism. However, different isoforms of GC have been shown to have different binding affinities for 25-(OH)D (Gc1 F and S > Gc2),⁴⁷ which may result in differences among genotypes in tissue availability of vitamin D.²⁴ Alternatively, DBP has a variety of direct effects on the immune system, including macrophage activation.²¹

To determine whether the effect risk for asthma was specifically related to DBP polymorphisms or to variance in SNPs at other sites along the vitamin D pathway, the authors examined candidate SNPs in VDR and CYP2R1, which have been shown to have some association with asthma.^{48–50} In a study of young African Americans, certain VDR variants were associated with increased IgE levels and aeroallergen sensitization, higher night-time asthma morbidity scores, and lower baseline spirometric scores.⁵¹ Furthermore, a homozygous variant of the CYP2R1 gene (rs10766197) was associated with increased risk of asthma, whereas a variant of the gene encoding CYP24A1 (rs2248137; responsible for the breakdown of 1,25[OH]₂D and 25-[OH]D) was associated with lower vitamin D levels but not with risk of asthma.⁵¹ The authors did not find any difference in the genotype and allele frequencies at these 2 sites, suggesting that these SNPs do not affect the risk of developing asthma in this population of Hispanic children.

In summary, the authors identified a DBP genotype (ET/ET [Gc1s/Gc1s]) that is protective against the development of asthma in a population of inner-city Hispanic children. Whether the protective effect of this genotype occurs in other ethnic groups will need to be studied further, in addition to elucidating the mechanism by which such protection is incurred.

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