Genetic Variants In Genes That Are Part Of The Vitamin D Metabolic Pathway Are Not Associated With Serum Vitamin D Levels In African American Children

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Disclosures:

Introduction: INTRODUCTION: Vitamin D deficiency is a common finding among children in the United States and its prevalence is increasing. African American children are at particularly high risk, as darker skin pigmentation limits the cutaneous synthesis of vitamin D. Childhood vitamin D deficiency is implicated in the pathogenesis of a number of diseases, including rickets, type I diabetes and asthma, and also with increased odds of pediatric forearm fracture. Thus, vitamin D deficiency may play a significant role in the increase in the rates of pediatric forearm fracture across children of all races over the past thirty years. While most of the environmental factors influencing vitamin D status have been delineated, including sun exposure, diet and skin melanin concentrations, the genetic determinants of vitamin D status are less clearly defined.

Recent genome-wide association studies (GWAS) have identified a number of genetic variants that are associated with circulating serum 25-hydroxyvitamin D [25-(OH)D] levels in European populations. Fewer studies have focused on the genetics of vitamin D status in African Americans. In this study, we investigated the association between eleven single nucleotide polymorphisms (SNPs) located within four genes involved in the vitamin D metabolic pathway are associated with vitamin D levels, bone mineral density (BMD), and fracture risk in African American children.

Methods: MATERIALS & METHODS: We utilized Taqman genotyping assays to determine variant genotypes within genomic DNA isolated from blood samples of 142 African American children ages 5 to 9 who were recruited as part of a forearm fracture study. Demographic data was recorded for all participants. Cases (n=71) had an isolated forearm fracture (radius, ulna or both) and age-matched control patients (n=71) had no self-reported history of prior fracture. SNPs were analyzed for association with phenotypes, including total bone mineral density, body mass index, 25(OH)D levels, and dietary vitamin D intake. Bone mineral density (BMD) was measured using dual energy X-ray absorptiometry (Hologic QDR Discovery A Densitometer). Whole body and lumbar spine scans were performed and results were reported as areal BMD z scores. The observed frequency of each genotype was compared with the expected frequency of the population in Hardy Weinberg equilibrium using a chi square test with one degree of freedom. Associations between genotypes and phenotypes were performed using ANCOVA models with gender as a covariate. Associations between SNPs and fracture status were tested using logistic regression adjusted for gender. All regression models used a dominant genetic model comparing homozygous rare allele individuals to heterozygous and homozygous common allele individuals combined.

Table 1: Significant associations with fracture status

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Cases</th>
<th>Controls</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10766197</td>
<td>GG</td>
<td>52</td>
<td>39</td>
<td>1.15-5.05</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>AG/AA</td>
<td>16</td>
<td>29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: RESULTS: None of the SNPs investigated in this study were associated with vitamin D level, dietary vitamin D intake or body mass index in African American children. The SNP located in the intron region of the CYP24A1 gene (rs2762942) was associated with total bone mineral density when gender was used as a covariate. Specifically, the AG/GG alleles were associated with a higher total bone mineral density. In addition, a SNP located within CYP2R1 (rs10766197) was associated with fracture status. The AG/AA alleles were associated with a higher incidence of fracture when adjusted for gender.
Discussion: None of the SNPs investigated in this study were associated with vitamin D levels in African American children. A number of twin studies show that genetics may account for up to 70% of the variation in serum 25(OH)D levels. Our study sought to further describe the role of genetics in determining vitamin D status in African Americans. A SNP located in CYP24A1, which encodes 24-hydroxylase, an enzyme that inactivates 1,25(OH)2D, was associated with total BMD. Individuals with carrying a copy of the rare allele (G) may more slowly or incompletely inactivate 1,25(OH)2D, which could promote bone mineralization and improve bone health. In addition, a SNP located in CYP2R1 was associated with fracture risk in individuals with a copy of the rare allele (G). However, this SNP was not associated with vitamin D levels or BMD. This reveals the complexity of the genetics of vitamin D deficiency and fracture risk. An important limitation of this study is the small sample size in comparison to other major GWAS studies. Future studies are needed to elucidate the extent to which genetic factors contribute to fracture risk and vitamin D deficiency and how risk differs among populations.

Significance: This study emphasizes the complexity of the relationship between vitamin D deficiency, fracture rates, and bone mineral density.

Acknowledgments: This study is funded in part by the National Institutes of Health National Center for Research Resources (1K23 RR024467-01), the Children’s National Medical Center General Clinical Research Center (5-M01-RR-020359-02), Children’s National Medical Center Board of Visitors, the DC-Baltimore Research Center on Child Health Disparities (5P20MD00165), The Dairy Research Institute, NICHD/NINDS 5R24HD050846-08: NCMRR-DC Core Molecular and Functional Outcome Measures in Rehabilitation Medicine.

References: NA

ORS 2014 Annual Meeting
Poster No: 0552