Disproportionate vitamin A deficiency in pregnant women of specific ethnicities in the United States and ethnic differences in allele frequencies of polymorphisms of vitamin A-related genes

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Short report

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Abstract

Background

Vitamin A is an essential micronutrient that plays critical roles in many biological functions of the body. The current national prevalence rate of vitamin A deficiency (VAD) in the United States is reported to be very low (<1%). However, our recent study in an urban city of the U. S. (the Bronx study) revealed that pregnant women in the Bronx have much higher proportions of VAD than the national prevalence rate. Given that Hispanics (56%) and non-Hispanic Blacks (29%) are the major racial and ethnic groups in the Bronx, we hypothesized that VAD could be more prevalent among pregnant women from specific ethnicities in the U.S. We therefore re-analyzed two independent datasets of serum retinol levels, i.e., the data from the the Bronx study and the National Health and Nutrition Examination Survey (NHANES). Moreover, as known polymorphisms have been associated with vitamin A status, we also assessed the differences of minor allele frequencies of these polymorphisms between ethnic groups in publicly available datasets, such as the Allele Frequency Aggregator (ALFA), the Population Architecture using Genomics and Epidemiology (PAGE), and the 1000 Genomes project.

Findings

We found that in both datasets of pregnant women non-Hispanic Black and Hispanic ethnicities have high proportions of VAD compared to non-Hispanic White pregnant women, and this VAD prevalence rate was much higher of the currently estimated national prevalence level. Interestingly, non-Hispanic Black pregnant women showed comparably high proportions of VAD in both datasets. However, pregnant women with Latin American/Afro-Caribbean ancestry in the Bronx dataset have strikingly high proportion of VAD compared to Latin American/Mexican ancestry in NHANES dataset (p= 1.973e-10, 95%CI 0.04 - 0.22, Fisher's exact test). Furthermore, from the ALFA and the PAGE data analysis, we showed that the known single nucleotide polymorphism (SNP) located near the *RBP4* gene (rs10882272) associated with lower serum retinol levels occurs at higher frequencies in Latin American/Afro-Caribbean ancestry and non-Hispanic Black/African populations compared to Latin American/Mexican ancestry and European populations. In addition, the analysis of minor allele frequency (MAF) of 39 previously reported SNPs associated with vitamin A metabolism showed significantly higher MAF variations between populations of different ancestries than that of randomly selected SNPs (p=0.030, permutation test with 1,000 iterations).

Conclusions

We confirmed that VAD rates in the pregnant women differ between different ethnicities, and that pregnant women in minority groups in the U.S. have much higher VAD rates than the estimated national prevalence level. Moreover, our analysis suggested that ethnic differences in allele frequencies of polymorphisms of vitamin A-related genes might contribute to the observed VAD rate differences. Further genome-wide association studies are needed to assess the influences of specific genetic variation and the different VAD status between different ethnic groups.

Main Text

The essential micronutrient vitamin A plays critical roles in vision [1, 2], immune system [3, 4], cell growth and differentiation [5–8], as well as in the development of multiple organs, including the lung, heart, eyes, and kidneys (reviewed in [9, 10]). Since vitamin A is an essential micronutrient, limited access to vitamin A-rich food or supplements severely affects tissue and blood levels of vitamin A in humans [11]. While the current prevalence rate of vitamin A deficiency (VAD) - defined as serum retinol levels lower than 1.05 μmol/l - is estimated to be less than 1% in the United States (U.S.) (CDC's Second Nutrition Report [12]), it has been suggested that this rate might vary between different ethnic groups and races [13]. Interestingly, an epidemiological study based on the NHANES dataset, collected from 2003 to 2006, demonstrated that non-Hispanic Black women of childbearing age have a higher rate of VAD [14]. However, this dataset was collected almost two decades ago. Morevoer, in general, populations-level studies of vitamin A are not up to date in developed countries, including the U.S. [15].

Recently, we reported a high VAD proportion rate among pregnant women in the Bronx, NY, USA [16], where the ethnic diversity and the poverty rate is much higher than in the rest of the nation [17, 18]. Although the original study addressed the effects of bariatric surgery on serum vitamin A levels during pregnancy, the most surprising result was that more than 60% of the pregnant women who did not undergo the bariatric surgery (control group) had serum retinol levels during the third-trimester lower than 1.05 μmol/l [16], meeting the criteria for vitamin A deficiency. This proportion of vitamin A deficient women in the Bronx was much higher than that of non-White women of the same age group recently reported by Hanson et al. [19]. As Hispanics (56%) and non-Hispanic Black (29%) are the major race and ethnic groups in the Bronx [18], our findings [16] prompted us to re-analyze the disproportionality of VAD status in the Hispanic and non-Hispanic Black pregnant women from the Bronx study. Here we used Student's t-test for continuous variables, Fisher's exact test for categorical variables, and a permutation test to assess the significance level of the deviations of allele frequency of previously reported vitamin A related gene polymorphisms between the ethnic groups compared to background noise. An alpha of 0.05 was used as the cutoff for significance. All statistical analyses were performed using R version 4.0.2 [20]. In the Bronx dataset, women planning to breasfeed with singleton pregnancy with and without a history of bariatric surgery (either Roux-en-Y or gastric sleeve) were recruited [16]. Demographic data included race/ethnicity, education, pre-pregnancy and at delivery body mass index, gestational weight gain and parity. Pregnancy outcome included gestational age at delivery, mode of delivery, and neonatal weight [16]. We used the third-trimester serum retinol levels that were available for 67 women out of the 96 participants in the Bronx study [16]. We found no significant association between missing data status and other covariates. While maternal serum levels of beta-carotene, the most abundant dietary vitamin A precursor [11], and cord blood serum retinol were significantly associated with maternal VAD status ($p=0.041$ and $p=0.007$, respectively), other known covariates, including the bariatric surgery status, did not show significant associations (**Table 1**). We then re-analyzed the third trimester serum retinol levels in the Bronx dataset by ethnic group, specifically using the self-reported ethnicities (non-Hispanic Black, Hispanic, or other race) as the ethnicities [16]. Our results showed that the proportion of VAD in Hispanic women was 65.9% (29 out of 44 Hispanic participants), in non-Hispanic Blacks was 53.3% (8 of 15

African American participants), and for other ethnicities was 37.5% (3 in 8 participants). Among the Hispanic participants (n=44), vitamin A deficient women tended to be younger than the vitamin A sufficient women (p=0.088), but education levels, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG) were not associated with the VAD status (p=0.876, p=0.195, and p=0.935, respectively). Whereas the poverty levels were not assessed in the Bronx study cohort [16], the degree of education and poverty level are generally negatively correlated in the Bronx, NY (poverty rate with educational attainment of less than High School is 36.6%, High School is 23.4%, and College is 19.5%, 2019 1-year estimates, U.S. Census) [18]. Therefore, we inferred that the poverty levels in the Bronx study were likely similar between vitamin A deficient and sufficient women, and that the poverty level might not have been directly associated with VAD status between ethnicities, in this cohort. Also, no clinical evidence was available for these VAD pregnant females as they were not assessed [16]. Nevertheless, overt symptoms of VAD were not expected given their subclinical vitamin A deficient status (based on serum levels). Therefore, despite the relatively limited sample size of the Bronx study, our analysis revealed that the proportions of VAD in Hispanic and non-Hispanic Black pregnant women were much higher than the estimated levels in the U.S. regardless of the history of bariatric surgery (**Additional file 1**).

Next, we analyzed serum retinol levels of pregnant women from the NHANES dataset (2001-2002, 2003-2004, and 2005-2006) by ethnicities using the reported race/ethnicity (RIDRETH1) information in the Sample Person Demographics Files [21]. While the NHANES data were collected almost two decades ago, this remains the latest nationwide serum vitamin A level assessment in the U.S.. In the NHANES dataset the proportion of VAD among Hispanic (Mexican American) pregnant women was half that of non-Hispanic Black pregnant women, 14.9% and 32.0% respectively ($p< 0.0001$, Fisher's exact test, **Additional file 1**; 966 pregnant women). According to the U. S. Census Bureau the poverty income ratio (PIR) of 1.0 defines the minimum income needed to avoid poverty and thus it is used as measure of poverty threshold [18]. Blumberg et al. [22] reported that individuals in poverty income ratio (PIR)>1.85 subgroup had a lower prevalence of inadequacy for most nutrients compared to the subgroups PIR ≦ 1.85 [22]. Given that in the Bronx about 45% of people live below PIR ≦ 1.85 [18], we focused our analysis of the NHANES dataset on pregnant women aged 17-42 (similar to the age range of the Bronx study) with a PIR less than 1.85. While VAD status and PIR≦1.85 were significantly associated in non-Hispanic Black women in total (aged 17-42, Fisher's exact test $p<0.005$, 95 percent confidence interval (95%CI) 1.37-4.45), this association was not observed in pregnant women of all races [Hispanic (Mexican American), Fisher's exact test p= 0.6494 (95%CI 0.53-4.57); non-Hispanic Black, Fisher's exact test p=0.12 (95%CI 0.83-6.73); non-Hispanic White, p=0.684 (95%CI 0.49-2.71)]. Taken together these data suggest that the higher VAD rates among pregnant women between these minority groups (Hispanic and non-Hispanic Black) might be independent of their poverty levels also in NHANES data set. Interestingly, the proportions of VAD in non-Hispanic Black pregnant women were not significantly differ between the NHANES and the Bronx datasets (p=0.26, 95%CI 0.14-1.74), however, the proportions of VAD in Hispanic (Mexican American) pregnant women in poverty from the NHANES dataset were significantly lower than that of Hispanic pregnant women in the Bronx dataset (p= 1.973e-10, 95%CI 0.04 - 0.22). Of note, while the major origins

of Hispanic populations in the Bronx are Latin Americans with Afro-Caribbean ancestry (39.4% Dominicans and 36.4% Puerto Ricans, U.S. Census data [18]), the Hispanic participants of the NHANES were Mexican Americans. Thus, these data strongly argue for an ancestry/ethnicity-specific impact on serum retinol levels and vitamin A status of pregnant women.

Genetic contributions to the levels of circulating retinol have been reported in European populations. Specifically, a family study in France showed that the heritability estimate for serum retinol concentration (30.5%) was much larger than the variability accounted for by household, i.e., individuals living in the same house (14.2%) [23]. Moreover, in the GWAS Catalog [24], two single nucleotide polymorphisms, (SNPs) (rs10882272 T/C and rs1667255 C/A), located near the retinol binding protein 4 (*RBP4*) and transthyretin (*TTR*) genes, respectively, identified from a genome-wide association study of 5,006 "Caucasian" males, are listed as associated with serum retinol levels [25]. The association of rs10882272 was replicated in independent samples, including 3,792 females and 504 males [25]. However, as the rate of VAD in the individuals studied was low, the authors were not able to test the association of the genetic variation with VAD [25].

Unfortunately, genomic data are not available for the Bronx nor for the NHANES study. Therefore, to assess the potential genetic contribution to the vitamin A status, we analyzed the deviations of allele frequency of previously reported vitamin A-related gene polymorphisms [25–27] between ethnic groups from publicly available population allele frequency datasets, such as the Allele Frequency Aggregator (ALFA) [28], the Population Architecture using Genomics and Epidemiology (PAGE [29], BioProject Accession: PRJNA168052), and the 1000 Genomes [30] projects. The ALFA pipeline consists of the allele frequency for variants in dbGaP that includes genomic data with subjects from 12 diverse populations worldwide [28]. The PAGE consortium dataset includes genetic variations representing seven ethnic groups, i.e., African Americans, Asian Americans, American Indians, European Americans, Hispanic Americans, and Native Hawaiians, from the United States-based cohorts [29]. Importantly, the Hispanic American cohorts in PAGE contains subjects from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), with one of the HCHS/SOL research centers located in the Bronx, NY [29, 31]. The associations of genetic variants with gene expression levels, defining expression quantitative trait loci (eQTL), were obtained from the Genotype-Tissue Expression project, GTEx [32]. To assess if the two above-mentioned genetic polymorphisms could be associated with VAD status differences between different racial/ethnic groups, we first compared the low serum retinol allele frequencies of rs10882272 and rs1667255 between different ethnic groups in ALFA and PAGE. While we did not observe significant differences in major allele frequencies of rs1667255 between Hispanic groups (**Additional file 2**), the allele frequencies of rs10882272 showed significant variation between different ethnic groups, as we predicted. The frequency of the allele associated with low serum retinol (rs10882272: frequency for C allele) was much higher in African (0.620, 62%) and African American (0.617) compared to European (0.383) and Asian (0.106) individuals in the ALFA dataset (**Figure 1a**). Similarly, the PAGE dataset results showed that the risk allele frequencies were higher in Latin Americans with Afro-Caribbean ancestry [Puerto Ricans (0.455), Dominicans (0.502) and Cubans (0.410)] compared to Mexicans (0.260), Central Americans (0.288), South Americans (0.278) or Native Americans (0.357) (**Figure 1b**). The ethnic groups

with the higher VAD proportions showed a higher frequency of the allele associated with low serum retinol levels. The rs10882272 variant is located in the 3' UTR of the free fatty acid receptor 4 (*FFAR4*) gene and downstream of the *RBP4* gene. The *FFAR4* gene encodes a GPCR receptor (GPCR120) for free long-chain fatty acids, including omega-3 [33, 34]. *FFAR4*/GPCR120 is expressed in various cell types, including pituitary, lung, macrophages, adipocytes, intestinal neuroendocrine cells and pancreatic cells. Thus, it participates in a number of physiological processes, including energy regulation, insulin sensitivity, immunological homeostasis and anti-inflammatory responses [35]. RBP4 is the sole specific carrier for retinol in the bloodstream [2, 36]. Predominantly expressed in the hepatocytes, RBP4 binds retinol to mobilize vitamin A from the liver, the primary body storage site of the vitamin, towards the peripheral tissues [2]. Furthermore, we tested if the rs10882272 is an expression quantitative trait locus (eQTL) for its nearby genes using a publicly available database (the Genotype-Tissue Expression project, GTEx) [32]. In the GTEx data, we detected the associations between the rs10882272 variations and the expression levels of RBP4 in the liver, where the gene is highly expressed [37], with the presence of the allele associated with low serum retinol levels also associated with increased expression of *RBP4* (normalized effect size: 0.137, p=0.00012, and m-value 0.987). For *FFAR4,* we detected the association in lung (normalized effect size: 0.126, p=8.5e-6, and m-value 1.00), but not in pituitary (normalized effect size: 0.0334, p=0.5, and m-value 0.809). The pituitary showed the highest expression of *FFAR4* in the GTEx data.

Another polymorphism associated with differences in serum retinol levels between different ethnic groups is rs738409 [27], which is located in the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene. *PNPLA3* encodes a gene involved in the mobilization of retinyl esters stored in stellate cells [27, 38]. The rs738409 polymorphism is a missense variant, with the C to G nucleotide substitution changing the amino acid I[ATC] to M[ATG]. The *PNPLA3* I148M missense variant is a loss-of-function mutation [27], and associations between the variant and the risk of nonalcoholic fatty liver disease (NAFLD) have been reported [39–41]. The frequency of the mutant allele varies between ethnic groups (African American (0.144), Cuban (0.28), Dominican (0.26), Mexican (0.50) and Puerto Rican (0.34); PAGE dataset**, Additional file 2**). Of note, individuals homozygous for *PNPLA3* I148M have lower circulating levels of RBP4 [27]. Changes in circulating levels of RBP4 have been linked to pathological conditions and variations in nutritional intake [42–45]. Interestingly, reported associations of the circulating levels of RBP4 and NAFLD are conflicting, and a recent meta analysis reported that circulating RBP4 levels may indeed not be associated with NAFLD [46]. Thus, we speculate that the associations between PNPLA3 I148M variants and circulating RBP4 levels might be independent of NAFLD status. In animal models, while retinol deficiency leads to accumulation of RBP4 in liver, likely by inhibiting its secretion from this organ, hepatic RBP4 mRNA levels show no differences between vitamin A deficiency and sufficiency [47, 48]. Further studies are needed to test the associations of these SNPs with circulating RBP4 levels, serum retinol levels, and disease status.

In addition to the three above-mentioned SNPs, several GWAS and candidate gene association studies have identified other polymorphisms associated with serum retinol and beta-carotene levels as well as with the beta-carotene bioactivities [26]. We therefore also assessed the allele frequency deviations of the

39 SNPs associated with circulating vitamin A levels [26] between different ethnic groups in the 1000 Genomes Project [30]. The deviations of allele frequencies of those vitamin A-related SNPs between different ethnic groups are listed in the **Additional file 2**. The average of the allele frequency standard deviation among ethnic groups was 0.122, significantly higher than randomly selected sets of 39 SNPs from the 1000 Genomes data (p=0.030, permutation test with 1,000 iterations, **Additional file 1**). Since serum retinol level variations between different ethnic groups have been reported, this result is not surprising. However, this is the first systematic analysis of the allele frequency variations of the vitamin A-related SNPs among different ethnic groups.

Looker *et al.* reported serum retinol level differences among three Hispanic groups using the Hispanic Health and Nutrition Examination Survey (HHANES) conducted from 1982-1984 [49]. The authors found that Mexican Americans have a higher VAD prevalence rate than Puerto Ricans or Cubans in both adults and children. This study was performed almost four decades ago when the participants' nutrient status might have differed from currently. The CDC's Second Nutrition Report in 2012 showed that serum vitamin A concentrations increased between 1999-2000 and 2005-2006 in the United States (geometric mean, 52.8 μg/dl to 54.7 μg/dl). Moreover, serum retinyl palmitate levels, an indicator of newly ingested vitamin A, were dramatically increased during this period in Mexican Americans (geometric mean 0.759 ug/dl in 1999-2000 to 1.85 ug/dl in 2005-2006) [50]. The differences observed in 1982-1984 might reflect the lower dietary intake of vitamin A at that time rather than genetic variations. An updated population-based measurement of serum retinol levels is clearly needed.

We acknowledge that there are several limitations to our study: the sample size of the Bronx cohort (n=97) was limited, the poverty levels and clinical information on VAD-related outcome of the Bronx cohort are not available, the serum retinol data of NHANES were collected almost two decades ago, and the genotype information of all participants is not available in both cohorts. Further genome-wide association studies with demographic information, including food accessibility/intake in multiethnic cohorts, are needed to assess the influences of genetic variation and the different VAD status between different ethnic groups. While the WHO does not recommend routine vitamin A supplementation to pregnant women, they recommend vitamin A supplementation to pregnant women in a given geographical area if ≥20% of pregnant women have serum retinol levels <0.70 μmol/L [51]. Our re-analysis of the Bronx study showed that more than 40% of pregnant women have serum retinol <0.70 μmol/L, strongly suggesting that urgent actions need to be taken to reduce the VAD, especially in unusually susceptible ethnic groups, to reduce the risk of adverse health conditions of the mother [52] and diseases of offspring later in life [53, 54].

In summary, while VAD in developed countries is believed to be a rare condition, there is a substantial proportion of VAD pregnant women of certain ethnic groups, even in wealthy, developed countries. Moreover, our results showed that genetic polymorphisms may be contributing to the VAD status differences between ethnic groups, at least in pregnant women. Further understanding of this association will ultimately enable adequate food interventions based on the genetic information that could be crucial to improve maternal vitamin A status during pregnancy in these higher risk groups.

Abbreviations

eQTL: expression quantitative trait loci

GWAS: Genome-Wide Association Study

NHANES: National Health and Nutrition Examination Survey

PAGE: Population Architecture using Genomics and Epidemiology

VAD: vitamin A deficiency

Declarations

Ethical Approval and Consent to Participate:

We used publicly available data, no ethical approval is required.

Consent for publication:

Not applicable.

Availability of data and materials:

The serum retinol and demographic information of the Bronx dataset, originally published in the J Perinat Med (PMID:30231012), are available by request. The National Health and Nutrition Examination Survey (NHANES) datasets were downloaded from the NHANES repository (https://www.cdc.gov/nchs/nhanes/index.htm) and merged file in accordance with the NHANES guidelines and recommendations.

Competing interests:

All authors declare no competing interest.

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Authors' Contributions:

Wrote manuscript draft (MS,LQ), prepared illustrations (MS), approved final manuscript (MS, DG, TW, CRI, WC, JMG, LQ), conceived project (MS, LQ), analyzed data (MS), formulated research questions (MS, LQ),

interpreted results (MS, TW, DG, CRI, JMG, WC, LQ), led investigation (MS). All authors read and approved the final manuscript.

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Table 1

Due to technical limitations Table 1 is available as a download in the Supplementary Files.

Figures

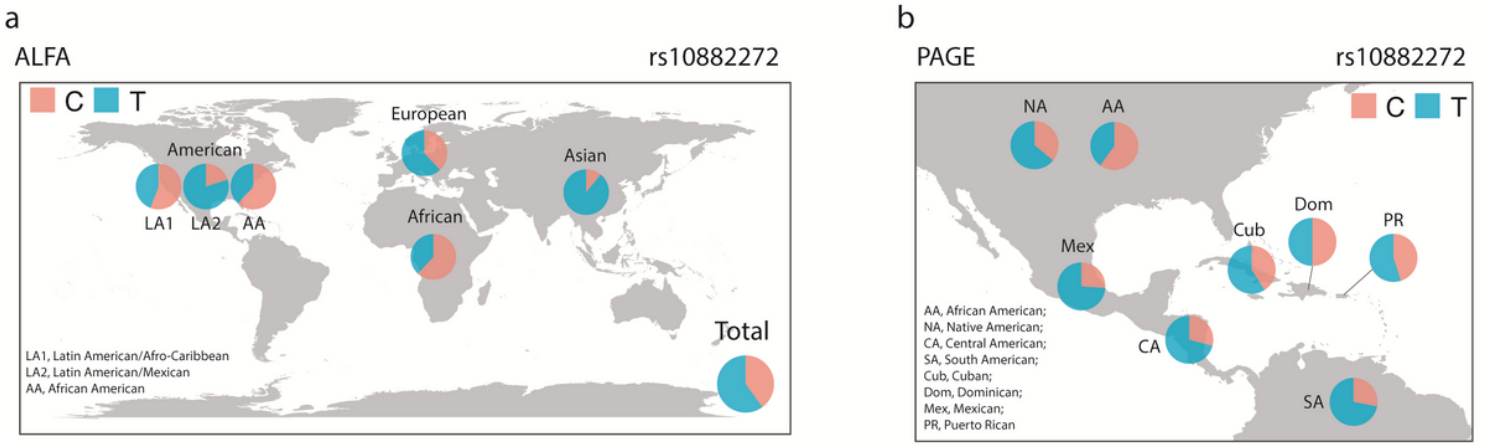

Figure 1

Figure 1

Variations of the allele frequencies of rs10882272 We plotted the allele frequency of each ethnic group (a) Allele Frequency Aggregator (ALFA) and (b) Population Architecture using Genomics and Epidemiology (PAGE). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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