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Genetic Variation Predicts Serum Lycopene Concentrations in a Multiethnic Population of Postmenopausal Women[1,2]

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Abstract

Background: The consumption and blood concentrations of lycopene are both positively and inversely associated with the risk of several chronic diseases. The inconsistences in lycopene disease association studies may stem from a lack of knowledge about the genetic variation in the synthesis, metabolism, and deposition of transport and binding proteins, which potentially influence serum lycopene concentrations.

Objective: We examined the association between variation across the genome and serum concentrations of lycopene in a multiethnic population.

Methods: Participants included African (n = 914), Hispanic (n = 464), and European (n = 1203) American postmenopausal women from the Women's Health Initiative. We analyzed ~7 million single nucleotide polymorphisms (SNPs). Linear regression models were used to assess associations between each SNP and serum concentrations (log transformed, continuous) of lycopene; we adjusted for age, body mass index, and population substructure. Models were run separately by ethnicity, and results were combined in a transethnic fixed-effects meta-analysis.

Results: In the meta-analysis, the scavenger receptor class B, member 1 (*SCARB1*) gene, which encodes for a cholesterol membrane transporter, was significantly associated with lycopene concentrations (rs1672879; $P < 2.68 \times 10^{-9}$). Each additional G allele resulted in a 12% decrease in lycopene concentrations for African Americans, 20% decrease for Hispanic Americans, and 9% decrease for European Americans. In addition, 2 regions were significantly associated with serum lycopene concentrations in African Americans: the slit homolog 3 gene (*SLIT3*), which serves as a molecular guidance cue in cellular migration, and the dehydrogenase/reductase (SDR family) member 2 (*DHRS2*) gene, which codes for an oxidoreductase that mitigates the breakdown of steroids.

Conclusions: We found 3 novel loci associated with serum lycopene concentrations, 2 of which were specific to African Americans. Future functional studies looking at these specific genes may provide insight into the metabolism and underlying function of lycopene in humans, which may further elucidate lycopene's influence on disease risk and health. This trial was registered at clinicaltrials.gov as NCT00000611. *J Nutr* 2015;145:187–92.

Keywords: lycopene, carotenoid metabolism, genetic variation, scavenger receptor class B type 1 protein, multiethnic, postmenopausal women, nutritional epidemiology

Introduction

Lycopene is 1 of >600 carotenoids. Carotenoids, a diverse group of lipid-soluble phytochemicals, protect plants from oxidative damage, serve as pigments to attract pollinating insects, and act as precursors to key plant hormones (1, 2). In the United States, one of the most widely consumed carotenoids is lycopene. Lycopene is most known for the characteristic red color it imparts to tomatoes and tomato-based products, watermelon, red bell peppers, pink grapefruit, and other red or pink fruits and vegetables (2).

Both the consumption and blood concentrations of lycopene are inversely associated with the risk of several chronic diseases, including cardiovascular disease, metabolic syndrome, and cancer (most notably prostate cancer) (3–13). Recently, however, the presumed role for lycopene in prostate cancer prevention is disputed (14–16). Inconsistencies in lycopene-disease association

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studies may partly stem from a lack of knowledge about mediating factors that influence serum lycopene.

Known predictors of serum lycopene include diet, dietary supplement use, BMI, smoking, and sex (17–20). These characteristics account for, at best, 25% of the variance in serum lycopene concentrations. In addition to dietary and lifestyle predictors, a variety of binding proteins and carrier molecules influence nutrient concentrations in complex ways (1, 10, 17). Lycopene is predominantly transported in LDLs, which also carry the bulk of cholesterol in the plasma; thus, plasma lycopene concentrations and total cholesterol are highly correlated (21). Genetic variation in the synthesis, metabolism, and deposition of these transport and binding proteins may influence serum lycopene (22–25), but this is an understudied area that needs further investigation, especially in ethnically diverse populations.

Accordingly, our objective for this work was to examine the association between variation across the genome and circulating concentrations of lycopene in African American, Hispanic American, and European American postmenopausal women from the Women's Health Initiative (WHI)[6].

Methods

Study population

The WHI is a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancers, and osteoporotic fractures in postmenopausal women (26). Briefly, the WHI was designed as a set of randomized controlled clinical trials (CTs) and an observational study (OS). The CT (n = 68,132) included 3 overlapping components: the hormone therapy trials (n = 27,347), dietary modification trial (n = 48,835), and calcium and vitamin D trial (n = 36,282). Eligible women could be randomly assigned into 1, 2, or all 3 of the CT components. Women who were ineligible or unwilling to join the CT were invited to join the OS (n = 93,676). Twenty core blood analytes (including lycopene and total cholesterol) were measured in a 6% random subsample of CT participants at baseline, years 1, 3, and 6, and in a 1% random subsample of OS participants at baseline. All WHI participants provided written informed consent, and institutional review board approval was obtained at each of the 40 WHI clinical centers and at the clinical coordinating center at the Fred Hutchinson Cancer Research Center.

For this analysis we included participants with baseline serum lycopene and total cholesterol data from 2 WHI genetic studies: *1*) the SNP Health Association Resource (SHARe) cohort and *2*) the Genomics and Randomized Trials Network (GARNET). SHARe is a cohort study of 12,007 minority women (n = 8405 African Americans and n = 3602 Hispanic Americans) who participated either in 1 of the CTs or the OS; 1378 SHARe participants have baseline serum lycopene and total cholesterol measures (914 African Americans and 464 Hispanic Americans). GARNET is a case-control trial of 4416 European Americans who participated in the hormone therapy with myocardial infarction, stroke, venous thrombosis, diabetes, and matching controls; 1203 European Americans have baseline serum lycopene and total cholesterol measures.

Procedures

At WHI baseline clinic visits, participants completed standardized questionnaires for assessment of health history, age, race/ethnicity, and other health and lifestyle characteristics, including diet, dietary supplement use, cigarette smoking, and leisure physical activity. Height, weight, and waist and hip circumferences were measured on all participants with the use of a standard protocol. BMI was calculated as weight (kg)/height (m^2).

Blood lycopene and cholesterol measures

A blood specimen was obtained from all WHI participants after a 12-h, overnight fast at the baseline visit. Serum and buffy coat were processed by a standard protocol and stored at −70°C in a central biorepository (Fisher Bioservices) until analysis (26).

Serum lycopene was measured at Medical Research Laboratories with the use of HPLC on the Hitachi 747 analyzer (27). The assay CV for lycopene with the use of 8% blinded duplicates in each assay batch was 9.4%. Plasma total cholesterol was assayed at the University of Minnesota Medical Center with the use of the cholesterol oxidate method on the Roche Modular P Chemistry analyzer. The assay CV for cholesterol with the use of 19% blinded duplicates in each assay batch was 1.4%.

Genotyping

SHARe. DNA samples plus 2% (n = 188) blinded duplicate pairs were sent to Affymetrix Inc. for genotyping on the Genome-wide Human SNP Array 6.0 (909,622 SNPs); ~1% of samples failed genotyping. Other sample exclusions included call rate < 95%, unexpected duplicates, genotype data on the Y chromosome, and relative pairs (parent-offspring, twins, siblings, and half-siblings; total n = 313). For relative pairs, we excluded the sample with the lowest call rate. Average concordance for 188 pairs of blinded duplicate samples was 99.8%.

SNPs were excluded if they had call rate < 95%, concordance for duplicates < 98%, or Hardy-Weinberg equilibrium $P < 10^{-4}$.

GARNET. DNA samples plus 1% (n = 35) blinded duplicate pairs were sent to the Broad Institute Genetic Analysis Platform for genotyping on the Illumina HumanOmni1-Quad v1–0 B SNP array (1,016,423 SNPs); ~2.7% of samples failed genotyping. Other sample exclusions included call rate < 98%, unexpected duplicates, genotype data on the Y chromosome, and relative pairs (parent-offspring, twins, siblings, and half-siblings; total n = 12). For relative pairs, we excluded the sample with the lowest call rate. Participants with sex chromosome abnormalities were retained, but their X chromosome genotypes were filtered out of the analysis. Average concordance for 35 pairs of blinded duplicate samples was 99.8%.

SNPs were excluded if call rate < 97%, greater than zero discordant call in duplicate genotyping, number of sample trio inheritance errors > 1, BeadStudio metrics GenTrain score < 0.6 or cluster separation values < 0.4, or Hardy-Weinberg equilibrium $P < 10^{-4}$.

Imputation

SHARe and GARNET were both imputed to the 1000 Genomes Project (1kGP). The X chromosome was not imputed. The 1kGP reference panel (version 3.20101123) consisted of 1092 samples (246 Africans, 181 Admixed Americans, 286 Asians, and 379 Europeans). The genome-wide association data were first grouped into sets comprising 2500 SNPs; neighboring SNP sets overlapped by 500 SNPs. Then all SNP sets were phased by using BEAGLE (28). SHARe was imputed to 1kGP by using minimac, a low-memory and computationally efficient implementation of the MaCH algorithm (29), and GARNET was imputed by using BEAGLE. For each participant, genotypes were reported as a dosage value (a continuous number between 0 and 2) that reflects the expected number of copies of an allele at that SNP conditional on the directly observed genotypes in both the subject and the phased haplotype assignments in the 1kGP samples. For this analysis we excluded poorly imputed SNPs (R^2 < 0.5) and those SNPs with minor allele frequencies (MAFs) < 5%. This resulted in the analysis of 8,458,634 SNPs for African Americans, 6,389,009 SNPs for Hispanic Americans, and 6,305,487 SNPs for European Americans.

Genetic ancestry

SHARe. Genetic ancestry was calculated separately for African and Hispanic Americans, using principal components analysis (PCA) as

[6] Abbreviations used: *BCMO1*, 15,15′-monooxygenase 1; CT, controlled clinical trials; *DHRS2*, dehydrogenase/reductase (SDR family) member 2; GARNET, Genomics and Randomized Trials Network; MAF, minor allele frequency; OS, observational study; PCA, principal components analysis; SHARe, SNP Health Association Resource; *SCARB1*, scavenger receptor class B, member 1; *SLIT3*, slit homolog 3; SNP, single nucleotide polymorphism; SR-BI, scavenger receptor class B type 1 protein; WHI, Women's Health Initiative; 1kGP, 1000 Genomes Project.

described by Patterson et al. (31). Here, we used 178,101 independent autosomal SNPs (with missing call rates < 5% and MAFs > 5%) that were common between our samples and the reference panels for the PCA. Our reference included 475 publically available samples from HapMap Yoruba from Ibadan, Nigeria, HapMap Utah residents with Northern and Western European ancestry, the Human Genome Diversity Project East Asian population, and the Human Genome Diversity Project Native American populations. These same samples were used to determine ancestral percentages by using Frappe (30); among African Americans samples (n = 57) with <10% African American ancestry were identified and excluded. We used the top 4 principal components to adjust for genetic ancestry in our analysis of African and Hispanic Americans.

GARNET. Genetic ancestry was calculated by using PCA as described by Patterson et al. (31). Here, we used 112,304 independent autosomal SNPs (with missing call rates < 5% and MAFs > 5%) that were common between our samples and the reference panels for PCA. Our reference included 270 publically available samples from the following HapMap populations: Utah residents with Northern and Western European ancestry, Yoruba from Ibadan, Nigeria, Japanese from Tokyo, Japan, and Han Chinese from Beijing, China. We used the top 4 principal components to adjust for genetic ancestry in our analysis of European Americans.

Statistical analysis

To avoid the possibility of extreme lycopene values affecting our results, we used Winsorized means of lycopene and total cholesterol values. Therefore, instead of dropping outliers that are more extreme than the first and 99th quantile, we replaced these values by the value at the first and 99th quantile, respectively. In addition, we applied the natural logarithmic transformation to improve the normality of the biomarker distributions.

Linear regression models were used to assess associations between each SNP and serum concentrations (log-transformed, continuous) of lycopene. Genotype was modeled as an additive effect, with the genotype dosage values used as the primary predictor of interest. A 1 degree-of-freedom likelihood ratio test was used to assess statistical significance. A significance threshold of $P < 5 \times 10^{-8}$ was used to define a single result as genome-wide significant. The baseline model covariates included the 4 principal components of ancestry, BMI (continuous), and baseline age (continuous). We ran an additional model, which included baseline model covariates and total serum cholesterol (log-transformed, continuous). This model examined the association of genetic variants with serum lycopene independent of serum total cholesterol concentrations. We did not adjust for smoking status because only a small proportion of the population smoked (6–11%). We examined African Americans, Hispanic Americans, and European Americans both separately and combined (using a fixed-effects meta-analysis). Analyses were conducted with R 3.0 and METASOFT (for meta-analysis) (32).

Results

Baseline characteristics of study participants are given in **Table 1**. European American women were on average older than African American and Hispanic American women ($P < 0.001$). African American women had the largest BMI ($P < 0.001$). Among all ethnic groups, Hispanic Americans had the highest serum lycopene concentrations, whereas African Americans had the lowest ($P < 0.01$ and $P < 0.05$, respectively). European Americans had the highest total cholesterol concentrations

TABLE 1 Baseline characteristics of study population[1]

Characteristic	African American (n = 914)	Hispanic American (n = 464)	European American (n = 1203)
Age groups, n (%)			
50–54 y	176 (19.3)	110 (23.7)	84 (8.5)
55–59 y	203 (22.2)	103 (22.2)	188 (19.1)
60–69 y	397 (43.4)	215 (46.3)	456 (46.3)
70–79 y	138 (15.1)	36 (7.8)	257 (26.1)
WHI enrollment, n (%)			
Observational study	74 (8.1)	70 (15.1)	NA
Clinical trials	840 (91.9)	394 (84.9)	985 (100.0)
Hormone trials, n (%)			
Estrogen alone	132 (14.4)	57 (12.3)	199 (20.2)
Estrogen alone placebo	151 (16.5)	69 (14.9)	206 (20.9)
Estrogen + progesterone	107 (11.7)	74 (15.9)	307 (31.2)
Estrogen + progesterone placebo	109 (11.9)	85 (18.3)	273 (27.7)
Dietary modification, n (%)			
Intervention	220 (24.1)	91 (19.6)	NA
Comparison	347 (38.0)	123 (26.5)	NA
Calcium + vitamin D, n (%)			
Intervention	213 (23.3)	118 (25.4)	NA
Placebo	236 (25.8)	112 (24.1)	NA
Case status, n (%)			
Myocardial infarction	NA	NA	30 (3.0)
Stroke	NA	NA	18 (1.8)
Venous thrombosis	NA	NA	25 (2.5)
Diabetes	NA	NA	58 (5.9)
Controls	NA	NA	864 (87.7)
Lifestyle and diet			
Current smoker, n (%)	102 (11.2)	31 (6.7)	107 (10.9)
BMI, kg/m^2	31.8 ± 6.3	29.4 ± 5.2	28.8 ± 6.0
Serum lycopene, μg/mL	0.39 ± 0.2	0.44 ± 0.2	0.41 ± 0.2
Serum cholesterol, mg/dL	220 ± 40.5	220 ± 36.6	228 ± 37.6

[1] Data are presented as means ± SDs unless noted otherwise. NA, not applicable; WHI, Women's Health Initiative.

TABLE 2 SNPs in the *SCARB1* region associated with serum lycopene in transethnic fixed-effects meta-analysis[1]

		Meta-analysis				African American				Hispanic American				European American			
SNP	A1/A2	*P*	β	*P*-het	I^2	*P*	β	CAF	MAF	*P*	β	CAF	MAF	*P*	β	CAF	MAF
rs1672879*	G/T	2.68×10^{-9}	−0.14	0.25	28.3	7.85×10^{-5}	−0.12	0.59	0.41	6.26×10^{-6}	−0.20	0.77	0.23	0.14	−0.09	0.97	0.03
rs701107	A/G	2.43×10^{-8}	−0.13	0.30	17.2	2.59×10^{-4}	−0.12	0.60	0.40	2.04×10^{-5}	−0.19	0.77	0.23	0.15	−0.09	0.97	0.03
rs838861	T/C	2.32×10^{-8}	−0.14	0.19	40.4	7.29×10^{-4}	−0.11	0.67	0.33	4.65×10^{-6}	−0.20	0.78	0.22	0.14	−0.09	0.97	0.03

[1] Baseline model was further adjusted for age, BMI, and first 4 principal components of ancestry. *SNP with the most significant association in the meta-analysis with serum lycopene for this region. A1/A2, coded/noncoded allele; CAF, coded allele (A1) frequency; I^2, index of the degree of heterogeneity; MAF, minor allele frequency; *P*-het, *P* values for heterogeneity, indicating whether effect sizes are homogeneous across ancestry samples; *SCARB1*, scavenger receptor class B member 1; SNP, single nucleotide polymorphism.

compared with all other ethnic groups ($P < 0.001$). No other differences were observed between the 3 subpopulations, except that the proportions of each population enrolled in various parts of the WHI clinical trials varied.

The results of the fixed-effects meta-analysis of the genome-wide associations for serum lycopene in the baseline model are presented in **Table 2**. By combining the 3 subpopulations, 3 SNPs on chromosome 12 located near the scavenger receptor class B member 1 (*SCARB1*) gene met our prespecified criteria for genome-wide significance (Table 2). The strongest signal in this region was rs1672879 ($P < 2.68 \times 10^{-9}$). Here, each additional G allele resulted in a 12% decrease in lycopene concentrations for African Americans (MAF = 0.41), a 20% decrease for Hispanic Americans (MAF = 0.28), and a 9% decrease for European Americans (MAF = 0.03). In the model in which we adjusted for total serum cholesterol, rs1672879 remained significantly associated ($P < 4.09 \times 10^{-8}$) with a similar effect size (β = −0.12); no additional regions were significant in the adjusted model.

The results of the genome-wide associations for serum lycopene in African Americans are presented in **Table 3**. In Hispanic and European Americans no SNPs met the criteria for genome-wide significance in either the baseline or adjusted models; hence, results are not shown. Two regions were significantly associated with serum lycopene concentrations in African Americans: 4 SNPs in the slit homolog 3 (*SLIT3*) gene on chromosome 5 and the 3 SNPs in the dehydrogenase/reductase (SDR family) member 2 (*DHRS2*) gene on chromosome 14 (Table 3). The most statistically significant signal in the *SLIT3* region was rs78219687 ($P < 9.87 \times 10^{-9}$; β = 0.39; MAF = 0.05), and the most statistically significant signal in the *DHRS2* region was rs74036811 ($P < 9.55 \times 10^{-9}$; β = 0.38; MAF = 0.05). In the model adjusted for total cholesterol, the *DHRS2* region remained significantly associated with serum lycopene concentrations in African Americans with a similar effect size (rs74036811; $P < 4.48 \times 10^{-9}$; β = 0.38). The results from the adjusted model also suggested an association between the *SLIT3* region and lycopene with a similar effect size (rs78219687; $P < 1.51 \times 10^{-7}$; β = 0.34).

Discussion

Our genome-wide analysis found 3 novel regions associated with circulating serum lycopene concentrations. Two of these regions were ethnically specific to African Americans. This marks the first time such an analysis was done in a multiethnic study population.

The *SCARB1* region significantly associated with serum lycopene in the meta-analysis. We found similar effect sizes for this variant across the 3 ethnic groups; the smaller MAF in European Americans likely explains the weaker signal observed in this population. The overall consistency for this locus adds support for this finding through built-in replication.

The *SCARB1* gene encodes for a cholesterol membrane transporter called scavenger receptor class B type I (SR-BI). In vitro, SR-BI mediates the absorption of lycopene and cholesterol and other fat-soluble vitamins (33–36). Candidate gene studies have found variants in *SCARB1* to associate with serum concentrations of vitamin E and provitamin A carotenoids but not lycopene (37, 38). To our knowledge this is the first genome-wide association study to observe a significant association between this region and serum lycopene. Variants in this gene likely influence the ability of SR-BI to absorb lycopene at the intestinal level and/or to modify plasma lipid concentrations such as LDLs, which predominately transport lycopene (22, 33). Additional consequences of altered *SCARB1* function include modified platelet function, decreased adrenal steroidogenesis, changes in lipid profiles, and insulin sensitivity to dietary fat (39–41).

Variants in the *SLIT3* and *DHRS2* regions were significantly associated with lycopene concentrations in African Americans in the unadjusted model; after adjustment for total cholesterol only the variants in the *DHRS2* region remained significant.

The variants found significant in these regions were monomorphic in Hispanic and European Americans, which is why we observed an association only in African Americans. Suggestion of African American-specific effects was noted before. In a study by Arab et al. (18) they found, despite stronger validity in reported energy intakes for African Americans than for whites, that the 24-h dietary recall correlated less with serum lycopene in African Americans than in whites. The researchers speculated that one reason for this finding could be racially related genetic

TABLE 3 SNPs in the *SLIT3* and *DHRS2* regions associated with serum lycopene in African Americans[1]

Nearest gene	Chr	SNP	A1/A2	*P*	β	CAF	MAF
SLIT3	5	rs78219687*	G/A	9.87×10^{-9}	0.39	0.95	0.05
		rs114819789	G/A	3.44×10^{-8}	0.41	0.95	0.05
		rs74659379	G/T	3.42×10^{-8}	0.41	0.95	0.05
		rs114731073	A/T	3.40×10^{-8}	0.41	0.95	0.05
DHRS2	14	rs74036811*	C/G	9.54×10^{-9}	0.38	0.95	0.05
		rs17095390	G/C	9.55×10^{-8}	0.38	0.95	0.05
		rs17095435	C/T	2.22×10^{-8}	0.39	0.95	0.05

[1] Baseline model was further adjusted for age, BMI, and first 4 principal components of ancestry. *SNP with the most significant association in African Americans with serum lycopene for this region. A1/A2, coded/non-coded allele; CAF, coded allele (A1) frequency; Chr, chromosome number; *DHRS2*, dehydrogenase/reductase (SCR family) member 2; MAF, minor allele frequency; *SLIT3*, slit homolog 3; SNP, single nucleotide polymorphism.

variants that influence circulating concentrations. Perhaps the African American-specific effects we observed in the *SLIT3* and *DHRS2* regions partially explain the variance in serum lycopene concentrations unaccounted for by diet.

The *SLIT3* gene serves as a molecular guidance cue in cellular migration, and its function may be mediated by interaction with roundabout homolog receptors. This gene is associated with birth defects and multiple types of cancer, including melanoma, thyroid cancer, and lung cancer (42–45). The *DHRS2* region codes for a NAD/NADP-dependent oxidoreductase that mitigates the breakdown of steroids, retinoids, prostaglandins, and xenobiotics; one could hypothesize that this protein also aids in the metabolism of lycopene. In addition, *DHRS2* plays a noncatalytic role in the regulation of the cell cycle and apoptosis (46).

A previous study found the β-carotene 15,15-monooxygenase 1 (*BCMO1*) gene, a key enzyme in provitamin A carotenoid metabolism, to associate with serum lycopene concentrations in European Americans (25). However, our analysis and a more recently conducted study by Hendrickson et al. (24) did not observe an association with this locus and serum lycopene concentrations in European Americans. In addition, we did not observe this association in either African or Hispanic Americans in our study. Earlier research notes that *BCMO1* is not thought to catalyze lycopene or other non-provitamin A carotenoids because of their molecular structure (47, 48); however, a more recent in vitro study surprisingly found that *BCMO1* catalyzed the oxidative cleavage of lycopene with a catalytic efficiency similar to that of β-carotene (49). Follow-up and replication in a larger transethnic study sample should further investigate the association between the *BCMO1* region and lycopene concentrations.

Limitations of our study merit consideration. We had a limited sample size; however, despite this we found significant associations after adjusting for multiple testing. Our study population contained only women; therefore, sex differences in the association between the genetic variant and serum lycopene concentrations could not be examined.

In conclusion, we were able to examine associations between genetic variants and serum lycopene concentrations in an ethnically diverse study sample. This is the first time that this association was studied in an African American or Hispanic American population. Here, we found 3 novel loci associated with serum lycopene concentrations, 2 of which were specific to African Americans. Future studies, with ethnically diverse populations, should attempt to replicate these findings. Given the replication of findings, functional studies looking at these specific genes may help provide insight into the metabolism and underlying function of lycopene in humans, which may help further elucidate lycopene's influence on disease risk and health.

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MLN was responsible for project conception; NZ, JL, and CD analyzed the data; NZ wrote the manuscript; CK, UP, and MLN contributed to the edits of the final manuscript; and NZ had primary responsibility for the final content. All authors read and approved the final manuscript.

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