Native American Ancestry and Pigmentation Allele Contributions to Skin Color in a Caribbean Population

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Abstract

Interest in the genetic basis of variation in skin pigmentation in Native American populations led us to seek indigenous populations of the Western Hemisphere with African and minimal European admixture to study the effect of Native American ancestry on skin color. Admixture analysis from DNA collected from 458 individuals in the Kalinago territory of the Commonwealth of Dominica showed shared ancestry with East Asians at K=3 and 55% Native American, 32% African, and 11% European ancestry at K=6, the highest Native American ancestry of Caribbean populations. Skin pigmentation was 20 to 80 melanin units, averaging 46. Three albino individuals were homozygous for multi-nucleotide polymorphism *OCA2*^{NW273KV} of African origin, whose population allele frequency was 0.03 and single allele effect size was -8 melanin units. Hypopigmenting allele frequencies for *SLC24A5*^{A111T} and *SLC45A2*^{L374F} were 0.14 and 0.05, whose single allele effect sizes were -6 and -3, respectively. Skin color plots of individuals lacking known hypopigmenting alleles suggests that Native American Ancestry reduced pigmentation by more than 20 melanin units (low and high estimates 21.8 and 28.5). Shared ancestry with East Asians at K=3 suggests potential sharing of one or more pigmentation alleles.

Introduction

Skin pigmentation is a highly heritable polygenic trait influenced by health and environment (Barsh, 2003). European variants that lighten pigmentation include non-ancestral coding polymorphisms in *SLC24A5* (Basu Mallick et al., 2013; Lamason et al., 2005; Soejima and Koda, 2007) and *SLC45A2* (Lucotte and Yuasa, 2013; Soejima and Koda, 2007; Yuasa et al., 2006) that are nearly fixed. However, the genetic basis for lighter skin pigmentation in Native American and East Asian populations, who carry the same ancestral alleles as Africans at these loci, has yet to be established. Dark skin was the ancestral phenotype for anatomically modern humans (Jablonski and Chaplin, 2000; Lamason et al., 2005), whose evolution towards lighter skin at higher latitudes occurred independently in eastern and western Eurasia (Adhikari et al., 2019; Basu Mallick et al., 2013; Norton et al., 2007; Yang et al., 2016), potentially driven by a UV-dependent photoactivation step in the formation of vitamin D (Engelsen, 2010; Hanel and Carlberg, 2020; Holick, 1981; Loomis, 1967).

Native Americans share common ancestry with East Asians (Derenko et al., 2010; Tamm et al., 2007), diverging before 15 kya (Gravel et al., 2013; Moreno-Mayar et al., 2018; Reich et al., 2012), but the extent to which these populations share pigmentation variants remains to be determined. High European admixture is characteristic of most Native American populations (Brown et al., 2017; Gravel et al., 2013; Klimentidis et al., 2009; Reich et al., 2012), complicating the characterization of pigmentation variants specific to Native Americans.

Prior to European contact, the Caribbean islands were inhabited by populations who migrated from the northern coast of South America (Benn-Torres et al., 2008; HARVEY et al., 1969; Honychurch, 2012; “Island Caribs,” 2016; Torres et al., 2015, 2013). During the Colonial period, large numbers of Africans were introduced into the Caribbean as slave labor (Honychurch, 2012; Torres et al., 2013). As a consequence African and European admixture, and high mortality among the indigenous populations, Native American ancestry now contributes only a minor portion of the ancestry of most Caribbean islanders (1000 Genomes Project Consortium, 2010; The 1000 Genomes Project Consortium, 2015; Torres et al., 2015, 2013). The islands of Dominica and St. Vincent were the last colonized by Europeans, in the late 1700s (Honychurch, 2012, 1998; Rogoziński, 2000). In 1903, the British granted 15 km^2 (3,700 acres) on the eastern coast of Dominica as a reservation for the Kalinago, who were then called “Carib”. When Dominica gained Independence in 1978, legal rights and a degree of protection from assimilation were gained by the inhabitants of the Carib Reserve (redesignated *Kalinago Territory* in 2015) (Honychurch, 2012). The

Kalinago, numbering about 3,000 living within the Territory ("Kalinago Territory," 2021), consider themselves to be of primarily Native American and African ancestry.

Early in our genetic and phenotypic survey of the Kalinago, we noted one individual with albinism, and discovered that two others were known to reside in the Territory. Oculocutaneous albinism (OCA) is a recessive trait characterized by visual system abnormalities and hypopigmentation of skin, hair, and eyes (Gargiulo et al., 2011; Gronskov et al., 2007; Grønskov et al., 2014; Hong et al., 2006; Vogel et al., 2008) that is caused by mutations in any of several autosomal pigmentation genes (Carrasco et al., 2009; Edwards et al., 2010; Gao et al., 2017; Grønskov et al., 2013; Kausar et al., 2013; King et al., 2003; Spritz et al., 1995; Stevens et al., 1997, 1995; Vogel et al., 2008; Woolf, 2005; Yi et al., 2003). Here, we report on ancestry, distribution of measured skin color, identification of an albinism allele, and the hypopigmenting effects of this allele and the European *SLC24A5*^{A111T} and *SLC45A2*^{L374} alleles in a sample representing 15% of the population (Figure S1).

Results & Discussion

Our search for a population admixed for Native American/African ancestries led us to the "Carib" population in the Commonwealth of Dominica. Observations from an initial trip to Dominica suggested wide variation in Kalinago skin color. Pursuit of the genetic studies described here required learning about oral and written histories, detailed discussion with community leadership, and IRB approval from Ross University (until Hurricane Maria in 2017, the largest medical school in Dominica), the Department of Health of the Commonwealth of Dominica, and relationship-building with three administrations the Kalinago Council over 15 years.

Population Sample

Our DNA and skin-color sampling program encompassed 458 individuals, representing 15% of the population of the territory and including the three known albino individuals. Ages ranged from 6 to 93 (Table S1 and Figure S2). We were able to obtain genealogical information for about half of the parents (243 mothers and 194 fathers); community-defined ancestry (described as 'black,' 'Kalinago,' or 'Mixed') for both parents was obtained for 426 individuals (92% of sample), including 221 from which DNA samples were obtained.

Kalinago Ancestry

The earliest western mention of the Kalinago (originally as "Caribs") was in Christopher Columbus's journal dated 26th November 1492 (Honychurch, 2012). Little is known about the detailed cultural and genetic similarities and differences between them and other pre-contact groups such as the Taino in the Caribbean. African admixture in the present Kalinago population derived from the African slave trade, but we were unable to identify written historical record that includes specific regional origin or well-defined contributions from other groups. The population's linguistics is uninformative, as they speak the same French-based Antillean Creole spoken on the neighboring islands of Guadeloupe and Martinique (in addition to English).

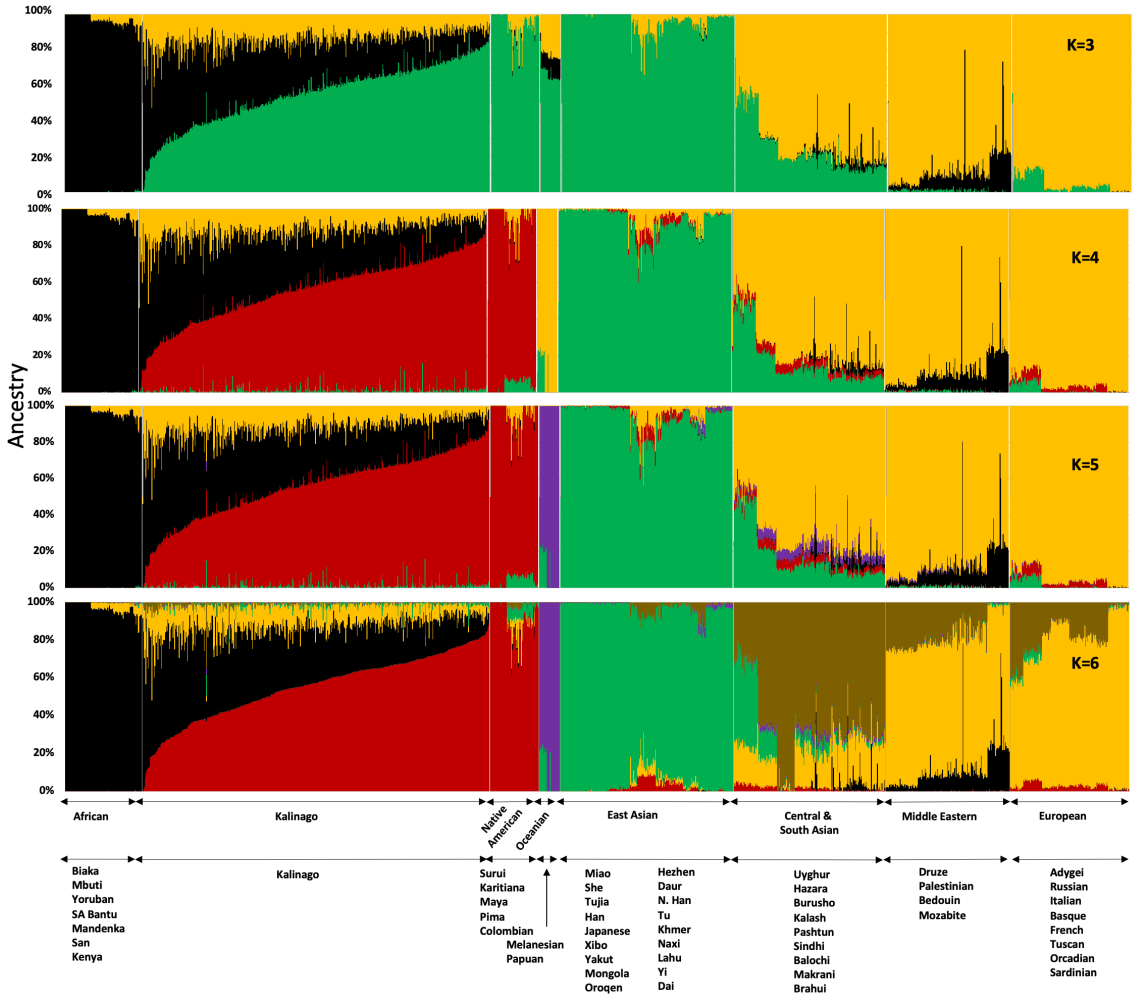


Figure 1: Admixture analysis of Kalinago compared with Human Genome Diversity Project populations. Results are depicted using stacked bar plots, with one column per individual. At K=3, the Kalinago, Native Americans, Oceanians, and East Asians fall into the same cluster. At K=4, the Kalinago and the Native Americans are separated from the East Asians.

To study Kalinago population structure, we combined our Kalinago SNP genotype data with HGDP (Li et al., 2008) data and analyzed using ADMIXTURE (Figures 1 and S3) as described in Methods. Shared ancestry of the Kalinago with East Asians at K=3 suggests the potential sharing of one or more lighter skin alleles between those populations. At K=4 and higher, a Native American component (that predominates in Kalinago) separates from the East Asian component. Consistent with prior work, an Oceanian component appears at K=5, and a Central & South Asian component appears at K=6. These are minor components in our Kalinago sample (average <1%) (Table S3). On average, the Kalinago show 55% Native American, 32% African, and 11% European ancestry. The individual with least admixture has 94% Native American and 6% African. Principal component analysis (Figure S4) provides additional insight into the relationships between Kalinago and potential source populations.

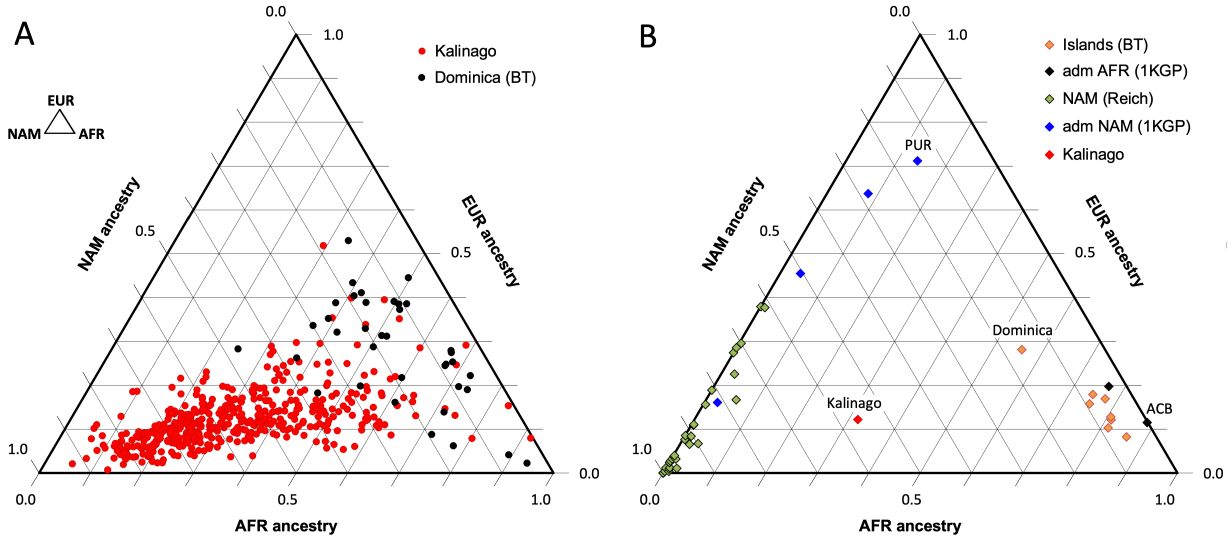


Figure 2. Comparison of Kalinago ancestry with that of other populations in the Western Hemisphere. Ternary plots show estimated proportions of African (AFR), European (EUR) and Native American (NAM) ancestry. **A,** Comparison of individuals (n=452, omitting 6 individuals with EAS > 0.1) genotyped in this study to individuals (n=38) from southern Dominica sampled by Torres et al., 2013, **B,** Comparison of population averages. Kalinago, this study (n=458); Islands (BT) indicates Caribbean islanders reported in Torres et al., 2013, with Dominica labeled; admixed (adm) AFR (1KGP) and admixed NAM (1KGP) represent admixed populations from The 1000 Genomes Project Consortium, 2015, with Caribbean samples PUR (Puerto Rico) and ACB (Barbados) labeled; and AMR (Reich) indicates mainland Native American samples reported in Reich et al., 2012. Inset shows ancestries at vertices.

Our analysis of Kalinago ancestry revealed considerably more Native American and less European ancestry than the Dominican samples of Torres et al. (2013) from outside of the Kalinago Territory (Figure 2A) and

129 those admixed populations from the 1000 Genomes Project (The 1000 Genomes Project Consortium,
130 2015). Some Western Hemisphere Native Americans reported in Reich et al. (2012) have varying
131 proportions of European but very little African admixture (Figure 2B) . Overall, the Kalinago have more
132 Native American and less European ancestry than any other Caribbean population.

133 Specifically, the 55% Native American ancestry observed for the Kalinago is far greater than the reported
134 13% in Puerto Rico (Gravel et al., 2013), 10-15% for Tainos across the Caribbean (Schroeder et al., 2018),
135 and 8% for Cubans (Marcheco-Teruel et al., 2014). Samples from Jamaica and the Lesser Antilles (Torres
136 et al., 2015, 2013) yielded an average of 7.7% Native American ancestry (range 5.6% to 16.2%), with the
137 highest value from a population of Kalinago ancestry outside the reservation in Dominica. Relevant to the
138 potential mapping of Native American light skin color alleles, the Kalinago has the lowest European
139 ancestry compared to other reported Caribbean Native Americans in St. Kitts (8.2%), Barbados (11.5%)
140 and Puerto Rico (71%) (Torres et al., 2013). Potential reasons for the high percentage of Native American
141 ancestry in the Kalinago likely include their segregation within the 3,700-acre Kalinago Territory in
142 Dominica granted by the British in 1903, and the Kalinago tradition of women marring non-Kalinago being
143 required to leave the Territory; non-Kalinago spouses of Kalinago men are allowed to move to the
144 Territory (KCC, KCA, Personal Communication with Kalinago Council, 2014). These factors help explain why
145 Kalinago samples collected outside the Kalinago territory (Torres et al., 2013), show lower fractional
146 Native American ancestry.

147 During our fieldwork, it was noted that members of the Kalinago community characterized themselves
148 and others in terms of perceived ancestry as “black,” “Kalinago,” or “mixed,” based primarily on
149 phenotype. These folk categorizations were broadly supported by differences in admixture (Figures S5,
150 S6). Compared to individuals identified as “Mixed,” those identified as “Kalinago” have on average more
151 Native American ancestry (67% vs 51%), less European ancestry (10% vs 14%), and less African ancestry
152 (23% vs 34%). Individuals described as “Kalinago” were slightly lighter and had a narrower MI distribution
153 (42.5 ± 5.6, mean ± SD) than those described as “Mixed” (45.8 ± 9.6).

154 *Kalinago Skin Color Variation*

155 Melanin index unit (MI) calculated from skin reflectance (see Methods) was used as a quantitative
156 measure of melanin pigmentation (Ang et al., 2012; Diffey et al., 1984). The MI in the Kalinago ranged
157 from 20.7 to 79.7 (Figure S7), averaging 45.7. The three Kalinago albino individuals sampled had the lowest
158 values (20.7, 22.4 and 23.8). Excluding these, the MI ranged between 28.7 to 79.7 and averaged 45.9. For

comparison, the MI averaged 25 and 21 for people of East Asian and European ancestry, respectively, as measured with the same equipment in our laboratory (Ang et al., 2012; Tsetskhladze et al., 2012). This range is similar to that of another indigenous population related to East Asians, the Senoi of Peninsular Malaysia (MI 24 to 78; mean = 45.7) (Ang et al., 2012). The Senoi are believed include admixture from Malaysian Negritos whose pigmentation is darker (mean = 55) (Ang et al., 2012) than that of the average Kalinago. In comparison, the average MI was 53.4 for Africans in Cape Verde (Beleza et al., 2012) and 59 for African-Americans (Shriver et al., 2003).

An OCA2 albinism allele in the Kalinago

Oculocutaneous albinism (OCA) is a genetically determined condition characterized by nystagmus, reduced visual acuity, foveal hypoplasia and strabismus as well as hypopigmentation of the skin, hair and eye (Dessinioti et al., 2009; van Geel et al., 2013). The three sampled albino individuals had pale skin (MI 20.7, 22.4 and 23.8 vs. 29-80 for non-albinos), showed nystagmus, and reported photophobia and high susceptibility to sunburn. In contrast to the brown irides and black hair of most Kalinago, including their parents, the albino individuals had golden blonde hair and grey irides with varying amounts of green and blue.

Whole exome sequencing of one albino individual and one parent (obligate carrier) identified 12 variant alleles in 7 oculocutaneous albinism genes (or genomic regions) that were heterozygous in the parent and homozygous for a non-reference allele in the albino individual (summarized in Table S4A); none was a nonsense or splice site variant. Five of the twelve potential candidate mutations found by this approach were intronic, one was synonymous, one was located in the 5'UTR, and three were in 3'UTR (Table S4B). Two missense variants were found in *OCA2*: SNP rs1800401 (c.913C>T or p.Arg305Trp in exon 9), *R305W*, and multi-nucleotide polymorphism rs797044784 in exon 8 (c.819_822delCTGGinsGGTC; p.Asn273_Trp274delinsLysVal), *NW273KV*.

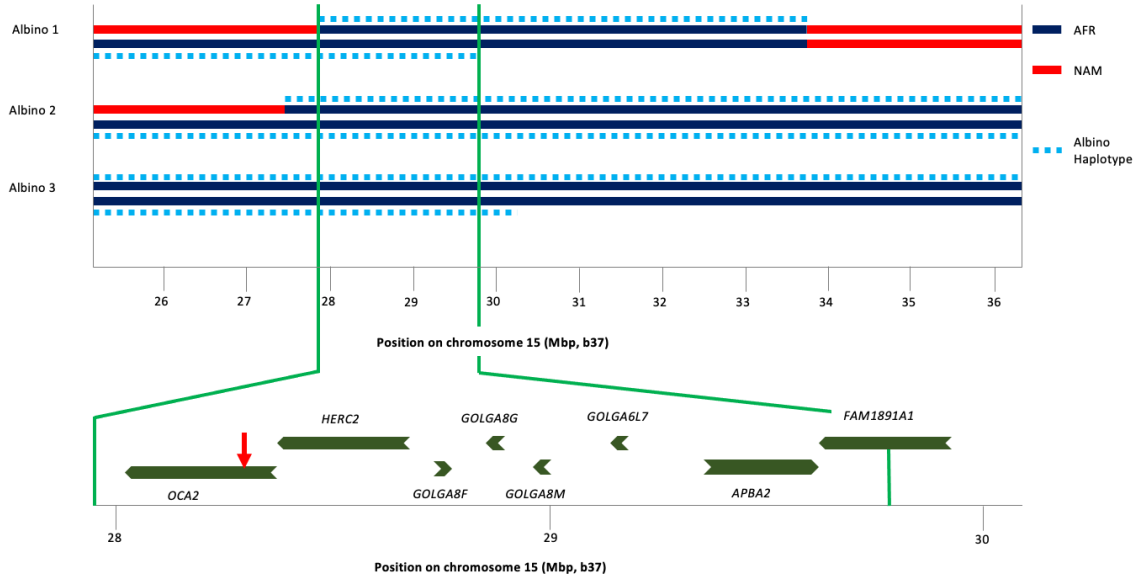
Of 458 Kalinago *OCA2* genotypes, 26 carried *NW273KV* and 60 carried *R305W* (Table 1). Only *NW273KV* homozygotes were albino, and neither of the two *R305W* homozygotes (who were either heterozygous or homozygous ancestral for *NW273KV*) were albino. Notably, one Kalinago individual who is homozygous derived for *R305W* mutation but homozygous ancestral for *NW273* has an MI of 72, among the darkest in the entire population. Therefore, *R305W* is not an albinism allele, as expected from its high population frequencies (> 0.10 in some African, South Asian, and European populations)(The 1000 Genomes Project Consortium, 2015). Notably, the black hair and dark eyes of Kalinago *R305W* homozygotes without the

189 *NW273KV* indicate that the *in silico* predictions by SIFT, Polyphen 2.0 and PANTHER that *R305W* is a likely
190 pathogenic variant (Kamaraj and Purohit, 2013) are incorrect. The observed patterns of zygosity suggest
191 that *NW273KV* arose on the background of a haplotype carrying the widespread *R305W* variant.

192 **Table 1. Albinism among *NW273KV* and *R305W* genotypes.**

Allele/Genotype		***NW273KV* genotype**			
		Homozygous Ancestral[a]	Heterozygous	Homozygous Derived	Total
***R305W* genotype**	Homozygous Ancestral	398	0	0	398
	Heterozygous	33	22	0	55
	Homozygous Derived	1	1	3*	5
	Total	432	23	3*	458

193 [a] Ancestral=reference allele and derived=alternate allele for both variants.
194 * Albino phenotype.
195



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197 **Figure 3. Haplotype analysis for three albino individuals.** Inner two lines indicate NAM (red) or AFR
198 (black) ancestry; no EUR ancestry was found in this genomic region. For this local ancestry analysis, the
199 region shown here consisted of 110 non-overlapping segments with 7 to 346 SNPs each (mean 65). The
200 deduced extent of shared albino haplotype (dotted light blue lines) is indicated on each
201 chromosome. Minimum homozygous region (determined by albino individual 1) shared by all three
202 albino individuals is shown at expanded scale below. Genes in this region are labeled, and the position of
203 the *NW273KV* polymorphism in *OCA2* is indicated by the red arrowhead.

204

The sole prior reported instance of albinism that includes the *NW273KV* variant involves a compound heterozygote of African-American descent (Garrison et al., 2004; Lee et al., 1994). The conservation of the NW sequence among vertebrates and its inclusion in a potential N-linked glycosylation site (Rinchik et al., 1993), that is eliminated by the mutation, supports the pathogenicity of this mutation. The *NW273KV* frequency in our sample (0.03) translates into a Hardy-Weinberg albinism frequency (p^2 = 0.0009) of ~1 per 1000, as observed (3 in a population of about 3000). Examination of publicly available data reveals three *OCA2*^{NW273KV} heterozygotes in the 1000 Genome Project, a pair of siblings from Barbados (ACB) and one individual from Sierra Leone (MSL) (The 1000 Genomes Project Consortium, 2015). These three individuals share a haplotype of 1.5 Mb but no more than 1.04 Mb are shared with the Kalinago albinos.

One of the three albinos was also heterozygous for *SLC24A5*^{A111T}, but his skin and hair color was not lighter than that of the other two albinos, who were homozygous for the ancestral allele at *SLC24A5*^{A111}; this observation is consistent with epistasis of *OCA2* albinism over *SLC24A5*^{A111T}. Eight sampled non-albino individuals had combinations of lighter hair, fair skin, and lighter irides, among these, seven were heterozygous for *SLC24A5*^{A111T}, and four were heterozygous for the albino variant. A precise understanding of the phenotypic effects of the combinations of these hypopigmenting alleles will require further study.

Genetic Contribution of Native American Ancestry to Kalinago Skin Color Variation

Among the primary goals of this work is quantification of the contribution of Native American ancestry to skin pigmentation. Answering this question required identifying the Kalinago as a Native American population admixed for African Ancestry. To minimize interference of pigmentation lightening alleles specific to Europeans, we confirmed the relatively small 15% European ancestry of this population, and now need to identify individuals lacking either of the two known hypopigmenting variants fixed in Europeans, *SLC24A5*^{A111T} and *SLC45A2*^{L374F}. In addition, we needed to identify individuals that are also ancestral for the *OCA2*^{NW273KV} albinism allele in this population.

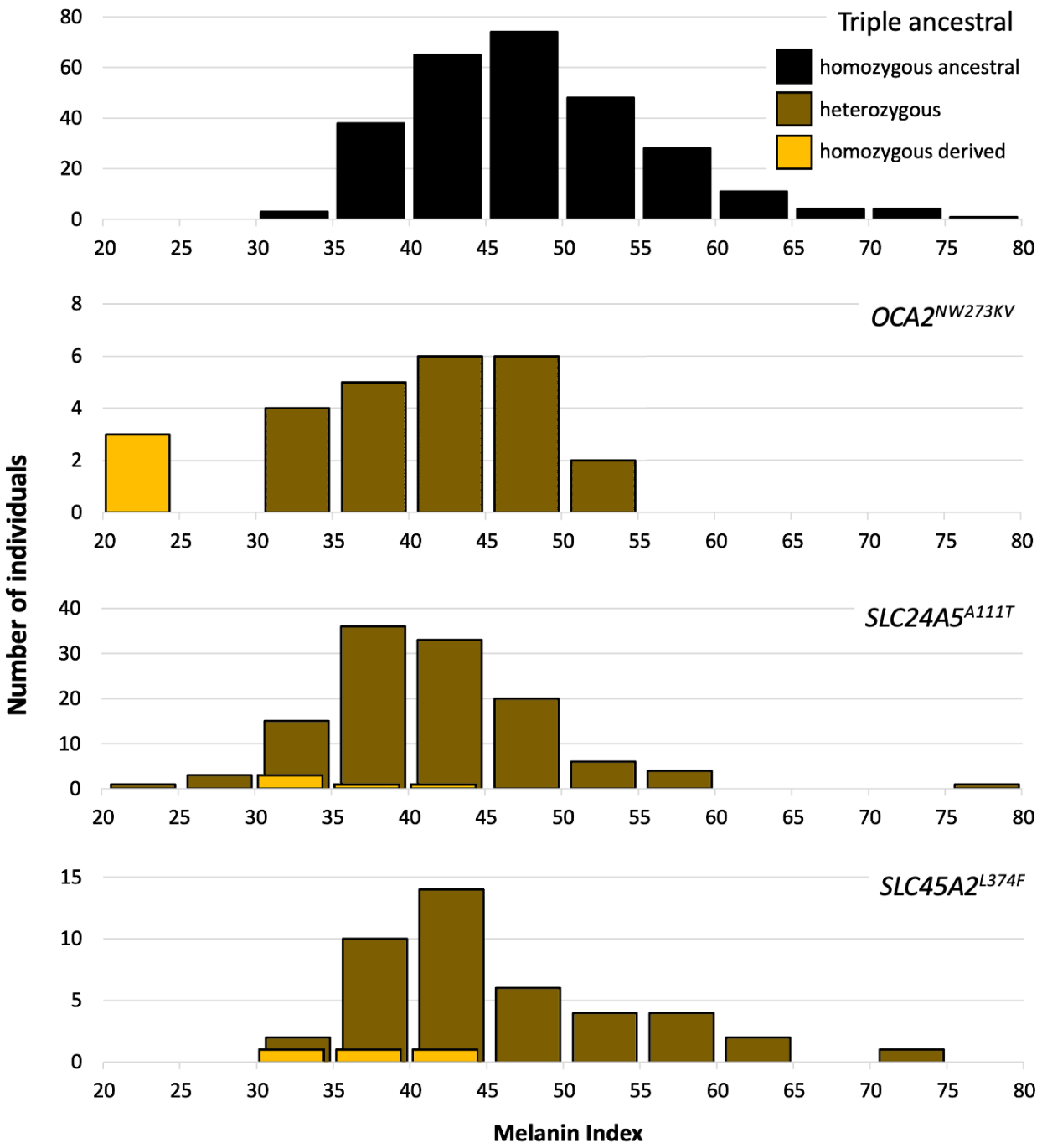

Figure 4. Skin color distribution of Kalinago samples according to genotype. Triple ancestral for three pigmentation alleles (*SLC24A5*^{111A}, *SLC45A2*^{374L} *and* *OCA2*^{273NW}) and derived (heterozygous or homozygous) for the indicated variant: *OCA2*^{NW273KV}; *SLC24A5*^{A111T}; and *SLC45A2*^{L374F}.

To control for the effects of the known European pigmentation loci, all Kalinago samples were genotyped for two known pigmentation polymorphisms of European origin, *SLC24A5*^{A111T} and *SLC45A2*^{L374F}. The

phenotypic effects of these variants and *OCA2*^{NW273KV} are shown in the histograms of Figure 4. Each variant decreases melanin pigmentation, and homozygotes are lighter than heterozygotes. The greatest effect is seen in the *OCA2*^{NW273KV} homozygotes (the albino individuals), as previously noted. The frequencies of the derived alleles of *SLC24A5*^{A111T} and *SLC45A2*^{L374F} in the Kalinago sample are 0.14 and 0.05, respectively.

The higher frequency of *SLC24A5*^{A111T} compared to *SLC45A2*^{L374F} frequencies is not explained solely by European admixture, given that most Europeans are fixed for both alleles. This deviation can, however, be accounted for by the involvement of source populations that have a lower frequency of *SLC45A2*^{L374F} than *SLC24A5*^{A111T}. The 0.03 excess of *SLC24A5*^{A111T} frequency over EUR ancestry indicates a non-negligible frequency of *SLC24A5*^{A111T} in one or more African source populations. At 32% AFR ancestry, this corresponds to an average *SLC24A5*^{A111T} frequency of about 0.09 for the AFR source populations. Although many sub-Saharan West African populations (the likeliest source of AFR ancestry in the Kalinago)(Micheletti et al., 2020) have lower *SLC24A5*^{A111T} frequencies, a similar frequency is observed in the Mende of Sierra Leone (MSL) (Micheletti et al., 2020; The 1000 Genomes Project Consortium, 2015), while some West African populations such as Hausa and Mandinka have frequencies exceeding 0.10 (Cheung et al., 2000; Rajeevan et al., 2012). The 0.06 deficit of *SLC45A2*^{L374F} frequency compared to EUR ancestry (11%) corresponds to an average *SLC45A2*^{L374F} frequency in the European source population close to 0.5. This is far below the frequency of 0.82 observed the 2015 Genomes Project Spanish population sample (IBS) (The 1000 Genomes Project Consortium, 2015). It should be noted that the major component in North African and Middle Eastern populations is not distinguished from Europeans in our analysis; these populations (and also inhabitants of Andalusia in Spain) have a wide range of *SLC45A2*^{L374F} frequencies dropping considerably below that of IBS (Cheung et al., 2000; Rajeevan et al., 2012). We are unable with existing information to definitively account for the higher frequency of *SLC24A5*^{A111T} over that of *SLC45A2*^{L374F}.

Table 2. Effect sizes for covariates in full model with 10 Principal Components

covariate	Effect size[a]	Adjusted *p*-value
rs1426654 (*SLC24A5*^{A111T})	-5.8	1.5E-12
rs16891982 (*SLC45A2*^{L374F})	-2.8	0.015
albino allele (*OCA2*^{NW273KV})	-7.8	2.5E-05
sex (female vs male)	-2.4	0.0013

[a] per allele effect size, in melanin units, for *A111T* and *L374F*; effect of first allele for albino variant

To investigate the relative contributions of genetic variation to skin color, we performed genome wide association analyses using an additive model for Melanin Index, conditioning on sex, ancestry, and

genotypes for *SLC24A5*^{A111T}, *SLC45A2*^{L374F} and *OCA2*^{NW273KV}. These analyses omitted the three albino individuals. We found that sex, all three genotyped polymorphisms, and the first principal component were statistically significant (effect sizes shown in Table 2). Effect sizes were about -6 units (per allele) for *SLC24A5*^{A111T}, -3 units for *SLC45A2*^{L374F} and -8 units for the first *OCA2*^{NW273KV} allele. When controlling for *OCA2*^{NW273KV} status, *OCA2*^{R305W} had no detectable effect on skin color (not shown).

The effect size for *SLC24A5*^{A111T} is consistent with previously reported results of -5 melanin units for African-Americans (Lamason et al., 2005; Norton et al., 2007) and -5.5 for the admixed inhabitants of the Cape Verde islands (Beleza et al., 2013). Reported effect sizes for continental Africans are both higher and lower -7.7 in Crawford et al. (2017) and -3.6 Martin et al. (2017b), while the estimated effect size in the CANDELA study (GWAS of combined admixed populations from Mexico, Brazil, Columbia, Chile and Peru) (Adhikari et al., 2019) is about -3 melanin units. For *SLC45A2*^{L374F}, significance was found in Beleza et al. (2013) and Adhikari et al. (2019) and for African Americans but not the African Caribbean subsample in Norton et al (2007) (Norton et al., 2007)

Our estimate that a single *OCA2*^{NW273KV} allele causes about -8 melanin units of skin lightening is the first reported population-based effect size measurement for any albinism allele. To study the effect of homozygosity, we applied the estimated parameters to the three albinos, who were lighter by an average of 10 units than predicted by the additive model ($p < 0.0033$, 1-tailed t-test). An additive model for skin color in albinos is rejected; the nature of the non-linearity or epistasis remains to be investigated.

The strong dependence of pigmentation on ancestry for individuals lacking hypopigmenting alleles *SLC24A5*^{A111T}, *SLC45A2*^{L374F} and *OCA2*^{NW273KV} is depicted in Figure 5. Positive deviations from the best fit are apparent at both high and low NAM ancestry, but these do not change the conclusions that AFR ancestry contributes to darker skin compared to NAM ancestry, and more importantly, that there are skin-lightening variants of Native American origin.

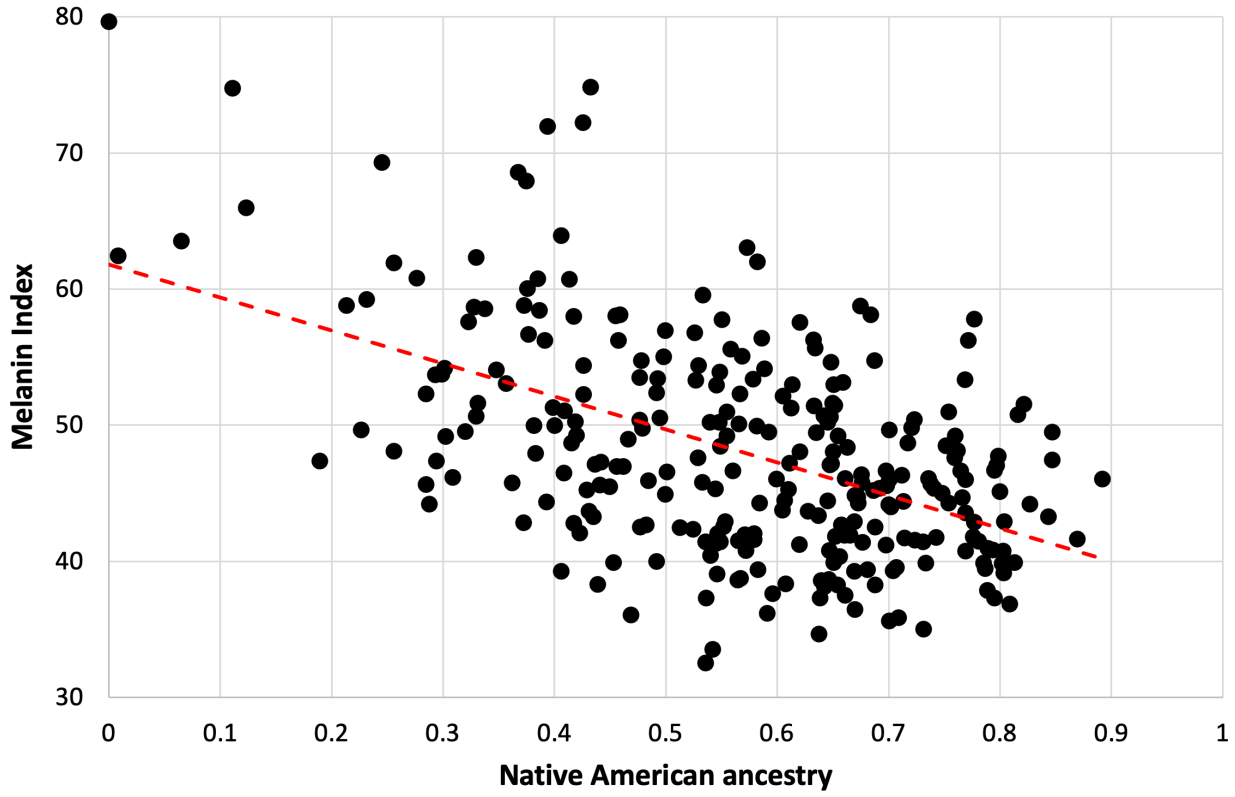

Figure 5. Dependence of Melanin Unit on ancestry for Kalinago. Only individuals who are ancestral for *SLC24A5*^{111A}, *SLC45A2*^{374L}, and *OCA2*^{273NW} alleles are shown (n=276). The dotted red line represents the best fit (linear regression).

To estimate the contribution of Native American ancestry to skin hypopigmenting alleles, we analyzed the 276 samples without the *SLC24A5*^{A111T}, *SLC45A2*^{L374F} and *OCA2*^{NW273KV} polymorphisms plotted in Figure 5. One conservative estimate of the effect of Native American Ancestry on skin color, -21.8 melanin units, is provided by the difference in pigmentation between Kalinago with less than 20% Native American ancestry (MI= 65.6), and Kalinago of more than 80% Native American ancestry (MI= 43.8). An alternative and larger estimate, -28.5 melanin units, derives if we estimate the pigmentation of Kalinago individuals with >80% African ancestry (MI = 72.3). In light of the shared ancestry between Native Americans and East Asians shown by admixture analysis at K=3 (Figure 1), it can be expected that individual hypopigmenting alleles of significant affect size remain to be identified.

Material and Methods

Ethics Statement

The study was reviewed and approved by the Kalinago council and institutional review boards of Penn State University (29269EP), Ross University, and the Dominica Ministry of Health (H125). Informed consent was obtained from each participant enrolled in the study, and in the case of minors, consent was also obtained from a parent or guardian.

Recruitment

Participants from among the Kalinago populations were recruited with the help of nurses from the Kalinago Territory in 2014. Recruitment took place throughout the territory's 8 hamlets. Place and date of birth, reported ancestry of parents and grandparents, number of siblings, and response to sun exposure (tanning ability, burning susceptibility) were obtained by interview. Hair color and texture and eye color (characterized as black, brown, gray, blue, green, hazel, no pigment) were noted visually but not measured quantitatively.

Skin Reflectometry

Skin reflectance was measured using a Datacolor CHECK^{PLUS} spectrophotometer and converted to melanin unit as we have previously described (Ang et al., 2012; Diffey et al., 1984). To minimize the confounding effects of sun exposure and body hair, skin color measurements were measured on each participant's inner arm, and the average of triplicate measurements was generated. Measurements at this location are generally used as an approximation for constitutive skin pigmentation (Choe et al., 2006; Park and Lee, 2005). Before skin color measurements were taken, alcohol wipes were used to minimize the effect of dirt and/or oil. In order to minimize blanching due to occlusion of blood from the region being measured, care was taken not to apply only sufficient pressure to the skin to prevent ambient light from entering the scanned area (Fullerton et al., 1996).

DNA Collection

Saliva samples were collected using the Oragene Saliva kit, and DNA was extracted using the prepIT.L2P kit, both from DNA Genotek (Ottawa, Canada). DNA integrity was checked by agarose gel electrophoresis and quantitated using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Further quantification was done using Qubit Fluorometer (Thermo Fisher Scientific, Waltham, MA) as needed, following manufacturer instructions.

Genotyping

Oculocutaneous albinism variants previously identified in African and Native Americans (Carrasco et al., 2009; King et al., 2003; Stevens et al., 1997; Yi et al., 2003) were amplified by PCR in all albino individuals as well as control samples using published conditions. Selected alleles of *SLC24A5, SLC45A2*, and *OCA2* were amplified in all sampled individuals as described in Table S2. Amplicons generated by 30 cycles of PCR using an Eppendorf thermocycler were sequenced (GeneWiz, South Plainfield, NJ) and the chromatograms viewed using Geneious software.

Illumina SNP genotyping using the Infinium Omni2.5-8 BeadChip was performed for all the individuals sampled. This was performed in three cohorts, using slightly different versions of the array, and the results combined. Due to ascertainment differences between the cohorts, analysis is presented here only for the combined sample. After quality control to eliminate duplicates and monomorphic variants, and to remove variants and individuals with genotype failure rates > 0.05, 358 Kalinago individuals and 1 638 140 unique autosomal SNPs remained.

Whole exome sequencing of albino and obligate carriers

In order to identify the causative variant for albinism in the Kalinago, 2 samples (one albino and one parent) were selected for whole exome sequencing. Following shearing of input DNA (1 microgram) using a Covaris E220 Foucsed-ultrasonicator (Woburn, MA), exome enrichment and library preparation was done using the Agilent SureSelect V5+UTR kit (Santa Clara, CA). The samples were sequenced at 50x coverage using a HiSeq 2500 sequencer (Illumina, San Diego, CA).

The *fastq* files were aligned back to Human Reference Genome GRCh37 (HG19) using BWA(Li and Durbin, 2009) and bowtie (Langmead et al., 2009). Candidate SNP polymorphisms were identified using GATK's UnifiedGenotyper (McKenna et al., 2010), while the IGV browser was used to examine the exons of interest for indels (Thorvaldsdottir et al., 2013). Variants with low sequence depth (< 10) in either sample were excluded from further consideration.

Computational analysis

Association analysis, basic statistics, and merges with other datasets were performed using plink 1.9 (Chang et al., 2015; Purcell et al., 2007). Phasing and analysis of regions of homozygosity by descent and identity by descent were performed with Beagle 4.1 (Browning and Browning, 2013, 2007), using 1000 Genomes Project (1KGP) phased data (The 1000 Genomes Project Consortium, 2015) as reference.

The genotyped individuals were randomly partitioned into nine subsets of 50 or 51 individuals (n=50 subsets) in which no pair exhibited greater than second-order relationship (PI_HAT > 0.25 using --genome command in plink). Using the same criteria, a maximal subset of 184 individuals was also generated (n=184 subset).

Principle components analysis (PCA) was performed using the smartpca program (version 13050) in the eigensoft package (Price et al., 2006). For comparison to HGDP populations, Kalinago samples were projected onto principal components calculated for the HGDP samples alone. For use as covariates in association analyses, the n=184 subset was used to generate the PCA, and the remaining individuals were projected onto the same axes.

Admixture analysis was performed using the ADMIXTURE program (Alexander et al., 2009; Zhou et al., 2011). Each of the nine n=50 subsets was merged with the N=940 subset of HGDP data (Li et al., 2008; Rosenberg, 2006) for analysis and the outputs combined.

For association analysis, we removed the three albino individuals from the analysis. In addition to the entire remaining sample, we also analyzed the n=184 subset and each n=50 subset; the latter results were combined using METAL (Willer et al., 2010). P-values were adjusted for statistic inflation by genomic control (median statistic method).

Statistical analysis of pigmentary effect of albinism involved fitting parameters to an additive model for the sample containing carriers but lacking albinos, applying the same model to the albino individuals, and comparing residuals for the albinos and the other individuals.

Local ancestry analysis of the region containing the albinism allele was performed using the PopPhased version of rfmix (v1.5.4) with the default window size of 0.2 cM (Maples et al., 2013). A subset of 1KGP data served as reference haplotypes for European and African populations, and the Native American ancestry segments of the admixed samples as determined by (Martin et al., 2017a) were combined to generate synthetic Native American reference haplotypes.

Data Availability Statement

The whole exome sequencing and whole genome SNP genotyping data underlying this article cannot be shared publicly due to the privacy of individuals and stipulation by the Kalinago community. The data will be shared on reasonable request to the corresponding author.

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