Dissecting dynamics and differences of selective pressures in the evolution of human pigmentation

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Abstract

Human pigmentation is a highly diverse and complex trait among populations, and has drawn particular attention from both academic and non-academic investigators for thousands of years. Previous studies detected selection signals in several human pigmentation genes, but few studies have integrated contribution from multiple genes to the evolution of human pigmentation. Moreover, none has quantified selective pressures on human pigmentation over epochs and between populations. Here, we dissect dynamics and differences of selective pressures during different periods and between distinct populations with new approaches. We propose a new model with multiple populations to estimate historical selective pressures by summarizing selective pressures on multiple genes. We use genotype data of 19 genes associated with human pigmentation from 17 datasets, and obtain data for 2346 individuals of six representative population groups from worldwide. Our results quantify selective pressures on light pigmentation not only in modern Europeans (0.0249/generation) but also in proto-Eurians (0.00665/generation). Our results also support several derived alleles associated with human dark pigmentation may under directional selection by quantifying differences of selective pressures between populations. Our study provides a first attempt to quantitatively investigate the dynamics of selective pressures during different time periods in the evolution of human pigmentation, and may facilitate studies of the evolution of other complex traits.

41 **Author Summary**

42 The color variation of human skin, hair, and eye is affected by multiple genes with different
 43 roles. This diversity may be shaped by natural selection and adapted for ultraviolet radiation
 44 in different environments around the world. As human populations migrated out from Africa,
 45 the ultraviolet radiation in the environment they encountered also changed. It is possible that
 46 the selective pressures on human pigmentation varied throughout human evolutionary history.
 47 In this study, we develop a new approach and estimate historical selective pressures on light
 48 pigmentation not only in modern Europeans but also in proto-Eurasians. To our best
 49 knowledge, this is the first study that quantifies selective pressures during different time
 50 periods in the evolution of human pigmentation. Besides, we provide statistical evidence to
 51 support several genes associated with human dark pigmentation may be favored by natural
 52 selection. Thus, natural selection may not only affect light pigmentation in Eurasians, but also
 53 influence dark pigmentation in Africans.

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Introduction

Human pigmentation—the color of human skin, hair, and eye—is one of the most diverse traits among populations. Its obvious diversity has attracted attention from both academic and non-academic investigators for thousands of years, as noted by Charles Darwin one century ago [1] and as noticed by ancient Egyptians more than 4000 years ago [2]. Why human pigmentation diverges, however, remains a central puzzle in human biology [3]. Some researchers have proposed that the diversity of human pigmentation is adapted for ultraviolet radiation (UVR) and driven by natural selection [4–6]. Dark skin may prevent sunburn amongst individuals in low latitude areas with high UVR, while light skin may protect infants against rickets in high latitude areas with low UVR [5–9]. A better understanding of how natural selection shapes the diversity of human pigmentation could provide relevant and beneficial information for public health [4–6].

During the last decade, many studies have applied statistical tests to detect signals of natural selection in several human pigmentation genes [10–18]. These genes encode different proteins, including: signal regulators—ASIP, KITLG, MC1R—stimulating the melanogenic pathway; possible enhancers—BNC2, HERC2—regulating pigmentation gene expression; important enzymes—TYR, TYRP1, DCT—converting tyrosine into melanin; putative exchangers—OCA2, SLC24A4, SLC24A5, SLC45A2, TPCN2—controlling the environment within melanosomes; and an exocyst complex unit and molecular motor—EXOC2, MYO5A—conveying vesicles and organelles within the cytoplasm [19–33]. These proteins work at different stages of the melanogenic pathway, illustrating that human pigmentation is a complex trait affected by multiple genes with different roles.

Previous studies applied two groups of methods to detect natural selection. One group of methods detects unusually long extended haplotype homozygosity [10–16, 34, 35]. The other group of methods identifies extremely local population differentiation [10, 12–15, 17]. By applying both groups of methods, previous studies have aimed to interpret the evolution of individual pigmentation genes; however, few studies have integrated contributions from multiple genes to the evolution of human pigmentation. Moreover, none of these studies have quantitatively investigated the historical selective pressures of pigmentation genes during different epochs, and compared the differences of selective pressures between different

populations. Therefore, it is necessary to perform an extensive quantification of selective pressures on human pigmentation using a creative approach.

Results and Discussion

The model

On the basis of a previous study [36], we measure selective pressures by (genic) selection coefficients. For any single nucleotide polymorphism (SNP) L , we can estimate the expectation of the selection (coefficient) difference per generation between populations i and j by

$$d_{ij}(L) = \left[\ln \frac{p_i(L)}{q_i(L)} - \ln \frac{p_j(L)}{q_j(L)} \right] / t_{ij}, \quad (1)$$

where p and q are the frequencies of derived and ancestral alleles in a population, respectively; and t_{ij} is the divergence time of the populations i and j from their most recent common ancestor. Details of the calculations are described elsewhere [36].

We can extend Eq. 1 to summarize selection differences of multiple SNPs, because a complex trait is usually affected by multiple loci. Here, we take two bi-allelic SNPs as an example. We can estimate the selection difference of a trait affected by two SNPs between populations i and j using

$$d_{ij}(L_1L_2) = \left[\ln \frac{p_i(L_1L_2)}{q_i(L_1L_2)} - \ln \frac{p_j(L_1L_2)}{q_j(L_1L_2)} \right] / t_{ij},$$

where $p(L_1L_2)$ is the frequency of the combination carrying two alleles associated with one possible outcome of a trait, such as light pigmentation; $q(L_1L_2)$ is the frequency of the combination carrying two alleles associated with another outcome of the same trait, such as dark pigmentation. With linkage equilibrium between L_1 and L_2 , we have $p(L_1L_2) = p(L_1)p(L_2)$ and $q(L_1L_2) = q(L_1)q(L_2)$. Thus,

$$d_{ij}(L_1L_2) = d_{ij}(L_1) + d_{ij}(L_2).$$

We further assume the distribution of selection difference in each SNP is identical and independent. Therefore, the variance of $d_{ij}(L_1L_2)$ is

$$\text{var}[d_{ij}(L_1L_2)] = \text{var}[d_{ij}(L_1)] + \text{var}[d_{ij}(L_2)].$$

The confidence interval (CI) of $d_{ij}(L_1L_2)$ becomes $d_{ij}(L_1L_2) \pm 1.96 \sqrt{\text{var}[d_{ij}(L_1L_2)]}$.

More generally, for a trait with n SNPs in linkage equilibrium as well as independent and identically distributed selection differences, the expectation and variance of the total selection difference in this trait is

$$\begin{aligned} d_{ij}(L_1 L_2 \cdots L_n) &= \sum_{i=1}^n d_{ij}(L_k) \\ \text{var}[d_{ij}(L_1 L_2 \cdots L_n)] &= \sum_{i=1}^n \text{var}[d_{ij}(L_k)] \end{aligned} \quad (2)$$

Based on Eq. 2, we develop a new approach for dissecting historical selective pressures over epochs of the human evolutionary history. We simplify the evolutionary history of six representative human populations as a binary tree (Fig. 1).

Fig. 1. Time-varied selective pressures on an evolutionary tree. We model the evolutionary history of six representative human populations as a binary tree. Here, s_i ($i = 0, 1, \dots, 10$) denotes the selection coefficient of the i -th epoch and can be obtained by estimating selection differences between paired populations. The numbers on the branches indicate different epochs. Divergence times between populations were based on previous studies [37–40]. We assumed one generation time is ~ 30 years. We obtain an optimal solution deviated least from neutral evolution using a probabilistic approach. The optimal solution (/generation) is $s_1^* = -0.0188, s_2^* = -0.0204, s_3^* = -0.00614, s_4^* = 0.0249, s_5^* = 0.00622, s_6^* = -0.00480, s_7^* = 0.000218, s_8^* = 0.00665, s_9^* = 0.00813, s_{10}^* = 0.00398$. In the solution, numbers larger than

zero suggest natural selection favored light pigmentation, while those less than zero indicate natural selection preferred dark pigmentation.

When k is the most recent common ancestor of i and j , we can divide d_{ij} in Eq. 1 into separate terms:

$$d_{ij}t_{ij} = \left(\ln \frac{p_i}{q_i} - \ln \frac{p_k}{q_k}\right) - \left(\ln \frac{p_j}{q_j} - \ln \frac{p_k}{q_k}\right).$$

We can further divide the selection difference between paired populations into multiple terms, if there are multiple branches between them. For example, using the notations and demographic model in Fig. 1, we can estimate the total selection difference between East and West Africans as

$$d_{21}t_1 = -\left(\ln \frac{p_1}{q_1} - \ln \frac{p_r}{q_r}\right) + \left(\ln \frac{p_2}{q_2} - \ln \frac{p_w}{q_w}\right) + \left(\ln \frac{p_w}{q_w} - \ln \frac{p_r}{q_r}\right).$$

Let $s_1 = \left(\ln \frac{p_1}{q_1} - \ln \frac{p_r}{q_r}\right)/t_1$, $s_2 = \left(\ln \frac{p_2}{q_2} - \ln \frac{p_w}{q_w}\right)/t_2$, $s_{10} = \left(\ln \frac{p_w}{q_w} - \ln \frac{p_r}{q_r}\right)/(t_1 - t_2)$, then we have

$$d_{21}t_1 = -s_1t_1 + s_2t_2 + s_{10}(t_1 - t_2).$$

Therefore, we can represent the selection difference between paired populations as a combination of selection coefficients during different time periods. Using matrix algebra, we can represent the selection differences of all the paired populations in Fig. 1 as

$$\mathbf{d} = \mathbf{T}s, \quad (3)$$

where

$$\mathbf{T} = \begin{bmatrix} -t_1 & t_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & t_1 - t_2 \\ -t_1 & 0 & t_3 & 0 & 0 & 0 & 0 & 0 & t_2 - t_3 & t_1 - t_2 \\ -t_1 & 0 & 0 & t_4 & 0 & 0 & 0 & t_3 - t_4 & t_2 - t_3 & t_1 - t_2 \\ -t_1 & 0 & 0 & 0 & t_5 & 0 & t_4 - t_5 & t_3 - t_4 & t_2 - t_3 & t_1 - t_2 \\ -t_1 & 0 & 0 & 0 & 0 & t_5 & t_4 - t_5 & t_3 - t_4 & t_2 - t_3 & t_1 - t_2 \\ 0 & -t_2 & t_3 & 0 & 0 & 0 & 0 & 0 & t_2 - t_3 & 0 \\ 0 & -t_2 & 0 & t_4 & 0 & 0 & 0 & t_3 - t_4 & t_2 - t_3 & 0 \\ 0 & -t_2 & 0 & 0 & t_5 & 0 & t_4 - t_5 & t_3 - t_4 & t_2 - t_3 & 0 \\ 0 & -t_2 & 0 & 0 & 0 & t_5 & t_4 - t_5 & t_3 - t_4 & t_2 - t_3 & 0 \\ 0 & 0 & -t_3 & t_4 & 0 & 0 & 0 & t_3 - t_4 & 0 & 0 \\ 0 & 0 & -t_3 & 0 & t_5 & 0 & t_4 - t_5 & t_3 - t_4 & 0 & 0 \\ 0 & 0 & -t_3 & 0 & 0 & t_5 & t_4 - t_5 & t_3 - t_4 & 0 & 0 \\ 0 & 0 & 0 & -t_4 & t_5 & 0 & t_4 - t_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & -t_4 & 0 & t_5 & t_4 - t_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -t_5 & t_5 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

To obtain the optimal solution, we propose a probabilistic approach. Under neutral evolution (NE), we consider each estimated s as an independent random variable following a

normal distribution with a mean of zero and a variance of σ^2 . For each solution with ten variables, the summation below follows a chi-square distribution with ten degrees of freedom:

$$\sum_{i=1}^{10} \frac{s_i^2}{\sigma_i^2} \sim \chi^2(10).$$

Therefore, we have $\Pr(|\mathbf{s}|^2 > |\mathbf{s}_a|^2 \mid \text{NE}) \geq \Pr(|\mathbf{s}|^2 > |\mathbf{s}_b|^2 \mid \text{NE})$, if $|\mathbf{s}_a|^2 \leq |\mathbf{s}_b|^2$ for solutions a and b . Here, $|\mathbf{s}|^2$ is the norm of a vector $\mathbf{s}$. In other words, we can choose the most conservative solution with the least deviation from neutral evolution using a probabilistic approach. Thus, the optimal solution $\mathbf{s}^*$ is

$$\mathbf{s}^* = \mathbf{T}^+ \mathbf{d}, \quad (4)$$

where $\mathbf{T}^+$ is the pseudo-inverse of $\mathbf{T}$.

Selective pressures over epochs

We applied our new approach with genotype data of worldwide populations from 17 publicly available datasets (Table S1). After data cleaning (Materials and Methods), we obtained 2346 individuals and grouped them into six population groups based on their geographic locations (Table S2). We also selected 52 SNPs in 19 genes for analysis due to their association with human pigmentation in published genome-wide association studies (GWAS) or phenotype prediction models (Table S3). We then used Eq. 2 with 31 SNPs not in strong linkage disequilibrium ($r^2 < 0.8$) to estimate the total selection differences on human pigmentation (Materials and Methods). The maximum differences were observed between Europeans and the two African populations, while the minimum difference was observed between West and East Africans (Table 1). The estimated 95% confidence intervals (CI) indicate the difference between East and West Africans, as well as between Oceanians and East Asians, is likely due to genetic drift (Table 1). We further assessed the significance levels of the observed selection differences by randomly sampling 10,000 sets of 31 SNPs in the genome and obtained the empirical distributions of population differences (Fig. 1). The differences from random sets of SNPs were close to zero, whereas those from SNPs associated with human pigmentation were significantly departure from zero (Fig. 1). This suggests that most population differences on SNPs associated with human pigmentation are possibly contributed by natural selection and not confounded by genetic drift.

178 **Table 1. Selection differences with 95% CI associated with human pigmentation between**
 179 **populations ($\times 10^{-3}$ /generation).**

	WAF	EAF	OCN	EUR	NAS	EAS
WAF	0	-3.527 ± 3.745	-17.402 ± 6.623	-33.992 ± 5.425	-24.397 ± 6.359	-20.052 ± 6.084
EAF	3.527 ± 3.745	0	-17.614 ± 8.391	-38.668 ± 6.900	-26.484 ± 8.085	-20.976 ± 7.753
OCN	17.402 ± 6.623	17.614 ± 8.391	0	-27.368 ± 8.695	-11.534 ± 9.078	-4.373 ± 8.511
EUR	33.992 ± 5.425	38.668 ± 6.900	27.368 ± 8.695	0	19.793 ± 9.400	28.747 ± 8.907
NAS	24.397 ± 6.359	26.484 ± 8.085	11.534 ± 9.078	-19.793 ± 9.400	0	11.018 ± 8.741
EAS	20.052 ± 6.084	20.976 ± 7.753	4.373 ± 8.511	-28.747 ± 8.907	-11.018 ± 8.741	0

180 Populations are abbreviated as follows: WAF, West Africans; EAF, East Africans; OCN,
 181 Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

Fig. 2. Significance levels of the selection differences associated with human pigmentation between populations. The blue bars are the empirical distributions of population differences using 10,000 random sets of 31 SNPs in the genomes. The red lines are the selection differences between populations using 31 SNPs associated human pigmentation (Materials and Methods). Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

We then solved the linear system (Eq. 4) with the observed selection differences on human pigmentation (Table 1). Our estimate shows that the modern European lineage had the largest selective pressure ($s_4^* = 0.0249/\text{generation}$) on light pigmentation than the other branches (Fig. 1), suggesting that recent natural selection favored light pigmentation in Europeans. Recent studies using ancient DNA could support our observation of recent directional selection in Europeans [18, 41]. Our results also reveal the selective pressure on light pigmentation in the ancestral population of Europeans and East Asians ($s_8^* = 0.00665/\text{generation}$). This shared selection is also supported by other studies, revealing that *ASIP*, *BNC2*, and *KITLG* were under directional selection before the divergence of ancestral Europeans and East Asians [16, 34]. We further applied SLiM 2 [42] to examine whether the optimal solution could reproduce the observed selection differences (Table 1). We set up a human demographic model according to previous studies and used the optimal solution as selection coefficients during different periods (Materials and Methods). The simulated selection differences were close to the data and little affected by the initial frequency of the beneficial allele (Fig. 3). This also illustrates that though we assume genic selection, our model could approximate genotypic selection in diploids (Materials and Methods).

Fig. 3. Comparisons between selection differences from simulation and the data. The

selection differences are: d_{21} , differences between East Africans and West Africans; d_{31} , differences between Oceanians and West Africans; d_{41} , differences between Europeans and West Africans; d_{51} , differences between North Asians and West Africans; d_{61} , differences between East Asians and West Africans; d_{32} , differences between Oceanians and East Africans;

d_{42} , differences between Europeans and East Africans; d_{52} , differences between North Asians and East Africans; d_{62} , differences between East Asians and East Africans; d_{43} , differences between Europeans and Oceanians; d_{53} , differences between North Asians and Oceanians; d_{63} , differences between East Asians and Oceanians; d_{54} , differences between North Asians and Europeans; d_{64} , differences between East Asians and Europeans; d_{65} , differences between East Asians and North Asians.

Selection differences between populations

We also separately quantified selection differences of individual SNPs associated with human pigmentation (Table S4) using Eq. 1. Ten SNPs were removed because of their low derived allele frequencies among populations in our data (Materials and Methods). Statistical tests suggest that selective pressures in many loci differed significantly between populations ($p < 0.05$). The remaining 42 SNPs were categorized into five groups (Fig. 4).

Fig. 4. Selection differences in individual loci between populations. We used Eq. 1 to

quantify the selection differences of 42 SNPs associated with human pigmentation, and

categorized them into five kinds of patterns: (A) Derived alleles affected by Eurasian-shared

selection; (B) Derived alleles affected by African-specific selection; (C) Alleles affected by

European-specific selection; (D) Alleles affected by Asian-specific selection; and (E) Others. Red color (positive numbers) indicates selective pressures of populations in rows are larger than those in columns; blue color (negative numbers) indicates selective pressures of populations in rows are smaller than those in columns. Populations are abbreviated as follows: 1, West Africans; 2, East Africans; 3, Oceanians; 4, Europeans; 5, North Asians; 6, East Asians

In the first group, derived alleles may be affected by Eurasian-shared selection (Fig. 4A). Among these SNPs, rs6119471 (*ASIP*) has large selection difference between Eurasians and Africans (Table S4). The derived allele of rs6119471 (*ASIP*) is almost fixed across Eurasians but maintains a low frequency in Africans (Fig. S2). Recent studies applied this SNP to predict dark/non-dark pigmentation phenotype in humans [43]. This may be explained by different selective pressures on this SNP among populations. Other SNPs, such as rs642742 (*KITLG*) and rs10756819 (*BNC2*), exhibit non-significant differences, suggesting that selection may contribute less to the diversity of these SNPs.

Our results also indicate that two SNPs in *MC1R* (rs2228479 and rs885479) largely differ between Eurasians and Africans (Table S4). Previous studies used variants in *MC1R* to solve a long-standing puzzle, regarding whether light pigmentation in low UVR areas is caused by directional selection or the relaxation of selective pressures [18, 44, 45]. The relaxation of selective pressures would suggest that the diversity of *MC1R* variants increased in Eurasians due to the lack of selective constraints. In this scenario, the genetic diversity of *MC1R* variants could be largely attributed to genetic drift. In contrast, directional selection would suggest that *MC1R* variants were under positive selection in Eurasians. In this scenario, genetic drift cannot explain the genetic divergence of *MC1R* between Africans and Eurasians. Our statistical results show that the divergences of rs2228479 and rs885479 between Eurasians and Africans are highly significant departure from neutral evolution (Table S4), suggesting that directional selection is the more likely explanation. Experimental evidence suggests that the derived allele of rs2228479 could cause lower affinity for alpha-melanocyte stimulating hormone than the ancestral allele [46]. Another study showed that the derived allele of rs885479 carries a lower risk of developing freckles and severe solar lentigines than

the ancestral allele in East Asians [47]. These studies revealed the potential roles of these *MC1R* variants in pigmentation phenotypes.

In the second group, derived alleles may be affected by African-specific selection (Fig. 4B). All these derived alleles are in/near two genes (*DDB1* and *MFSD12*) and were recently associated with human dark pigmentation [48]. The previous study [48] did not find signals of positive selection at *MFSD12* using Tajima's D or iHS. Our method [36] show that these SNPs in *MFSD12* differ significantly between Africans and Eurasians—possible signals of directional selection (Table S4). From the first and second groups, we can observe that directional selection not only affects derived alleles associated with light pigmentation in Eurasians, but also influences derived alleles associated with dark pigmentation in Africans. This observation suggests that human pigmentation is under directional selection with diversifying orientations among different populations. Thus, the previous view that the dark pigmentation in Africans is the result of purifying selection on ancestral alleles is incomplete [45]. Moreover, these new loci illustrate that we still have little understanding of the genetic diversity within African populations, and more research in this area is needed [49].

The third and fourth groups display European- and Asian-specific selection, respectively (Fig. 4C and 4D). One notable SNP is rs1426654 (*SLC24A5*), which had the largest selection difference between Europeans and East Asians in our study (0.005774/generation). Previous studies reported that this SNP is under strong directional selection in Europeans [10–15]. Another notable SNP is rs1800414 (*OCA2*), which had a large selection difference between East Asians and other populations. This reveals a potential role of rs1800414 (*OCA2*) on light pigmentation in East Asians. Several studies have suggested directional selection on this SNP in East Asians [50, 51]. These large selection differences indicate the significant contributions of these SNPs to light pigmentation in Europeans and East Asians, respectively. Other SNPs in these groups also support the hypothesis that recent natural selection for light pigmentation independently occurred in Europeans and Asians since they diverged [14, 50, 51]. Interestingly, Oceanians comprise both African-specific (*DDB1*) and Asian-specific (*OCA2*) selection. However, due to limited sample size of Oceanians in our data from publicly available resources (Table S2), it should be cautious to interpret these results. Thus, it would be helpful to analyze larger datasets of Oceanians to confirm our observation.

The last group includes the five remaining SNPs (Fig. 4E), which exhibit specific selection differences between limited population pairs. Among them, the derived allele of rs1800401 (*OCA2*) and the ancestral allele of rs12896399 (*SLC24A4*) are both associated with dark pigmentation (Table S2). Only rs12896399 (*SLC24A4*) differs significantly between West Africans and Eurasians (Table S4). This may be a selection signal associated with dark pigmentation in West Africans, again indicating possible genetic diversity within African populations. We note that rs35264875 (*TPCN2*) and rs12821256 (*KITLG*) might be affected by selection in both East Africans and Europeans. A recent study showed that rs12821256 might have large effect on the skin pigmentation in South Africans [52]. The other two SNPs, rs3829241 (*TPCN2*) and rs642742 (*KITLG*), also differ between Eurasians and Africans (Fig. 4A). These similar patterns of *TPCN2* and *KITLG* might suggest some connection between them.

Compared with previous studies [10–18], our study has three advantages. First, our approach considers the fluctuation of selective pressures that was ignored by previous studies. Our results provide more information about the dynamics of selective pressures during human evolution. Second, we summarize selective pressures based on multiple human pigmentation genes (Eq. 2), while previous studies usually tested selection signals in individual human pigmentation genes. Moreover, we simultaneously interpret selective pressures in multiple populations, whereas previous studies separately investigated selection signals in single population. Third, we do not need to assume population continuity as in those ancient DNA studies [18, 41], because our study is based on genetic data from only present-day populations.

We note that our investigation has several limitations. First, our model is based on the infinite population size model. The limited sample size would affect our results, therefore, we grouped populations into a large population group based on their geographic locations to mitigate the effect of sample size. Analysis of data with larger sample size could improve our estimate, as more and more genomic datasets become available. Second, although we chose the solution that deviates least from neutral evolution as the optimal solution, we cannot exclude the possibility of other solutions. This reflects the difficulty of analyzing historical selective pressures, which is a well-recognized challenge in population genetics [53]. Our

solution provides a first step toward resolving the dynamics of selection in the evolution of human pigmentation. This solution may be improved by combining both ancient and modern human genetic data, as well as by using a Bayesian framework with varied selection coefficients among loci for inference. Adding more population groups would also possibly improve the solution, because this would provide more constraints in the linear system (Eq. 4). Third, our results may be affected by a severe bottleneck. A recent study [53] suggests a more severe Out-of-Africa bottleneck in human evolutionary history than in the model used in our simulation. This would probably reduce the selection differences between Eurasians and Africans, leading to an underestimation of selective pressures. Fourth, our results may also be affected by population migration and sub-structure. We used knowledge from previous studies, principle component analysis and F_3 test to rigorously prune potential admixed populations, including South Asians, Central Asians, the Middle East People and Americans. Removing these populations would lose information of selective pressures on human pigmentation in these lineages; however, as a first step to explore the historical selective pressures in the evolution of human pigmentation, we focused more on reducing the bias induced by population admixture. New methods explicitly accounting for population admixture would be helpful to provide more comprehensive view on the dynamics of selective pressures during the evolution of human pigmentation. Besides, we demonstrate that our estimate provides lower bounds of selection differences on human pigmentation when migration or sub-structure exists (Text S1). Finally, our candidate SNPs may be biased. For example, our results indicate small genetic differences on human pigmentation between these two populations (Table 1), while recent studies [52] suggest Oceanians are darker than East Asians in skin pigmentation using melanin index. One possible reason is that some Oceanian-specific or East-Asian-specific SNPs are missing. This is because we selected candidates based on results from published GWAS or phenotype prediction models, and most of these studies used samples with European ancestry [55]. More studies on non-European populations could resolve this missing diversity and enhance our knowledge on the evolution of human pigmentation.

To summarize, we extended an established method [36] to dissect dynamics of selective pressures over epochs. Our study provides the first attempt to resolve time-varied selective

pressures in the evolution of human pigmentation. The fluctuation of selective pressures is an important factor in evolution [53], but few studies have revealed time-varied selective pressures in human populations. Our study also provides information on differences of selective pressures between distinct population groups. Further studies are in progress to verify our present views on the evolution of human pigmentation.

Materials and Methods

Data preparation

Seventeen datasets [40, 56–71] containing genotype data from worldwide human populations were obtained from the listed resources (Table S1). After downloading, all the genotype data were lifted over to genomic coordinates using the Human Reference Genome hg19. A merged dataset containing 6531 individuals was obtained after removing duplicated and related individuals. After merging, SNPs with call rate less than 0.99 or individuals with call rate less than 0.95 were removed. SNPs in strong linkage disequilibrium were further removed by applying a window of 200 SNPs advanced by 25 SNPs and an r^2 threshold of 0.8 (--indep-pairwise 200 25 0.8) in PLINK 1.7 [72]. The remaining 61,597 SNPs were used for further analysis. In order to mitigate the bias induced by population migration, potential admixed populations, such as the Middle East People and South Asians, were excluded according to previous studies [40, 56–71], principal component analysis (PCA) using SMARTPCA (version: 13050) from EIGENSOFT (version: 6.0.1) [73, 74], and F_3 test using ADMIXTOOLS (version: 3.0) [75]. Finally, 2346 individuals were obtained and divided into six groups according to their geographic regions for further analysis. These groups are West Africans, East Africans, Oceanians, Europeans, North Asians and East Asians. The PCA plot (Fig. S1) shows that these 2346 individuals were properly separated into six population groups.

Fig. S1. PCA plots of 2346 samples.

Data imputation

Genotypes of 19 human pigmentation genes with 500-kb flanking sequences on both sides were obtained from the genotype datasets. Haplotype inference and genotype imputation were performed on the selected genotypes using BEAGLE 4.1 [76, 77] with 1000 Genomes phase 3 haplotypes as the reference panel. During phasing and imputation, the effective population size was assumed to be 10,000 ($N_e = 10000$), and the other parameters were set to the default values. Ten SNPs (rs1110400, rs11547464, rs12203592, rs1800407, rs1805005, rs1805006, rs1805007, rs1805008, rs1805009, rs74653330) were removed because of their low derived allele frequencies in our datasets after imputation (Fig. S2). Because rs12203592 (*IRF4*) was removed, 18 genes with the remaining 42 SNPs were used for further analysis.

Fig. S2. Derived allele frequencies of candidate SNPs from imputation and the 1000 Genomes project. Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

Estimating selection differences between populations and selective pressures over epochs

We used Eq. 1 to estimate the selection differences of the remaining 42 SNPs. We then used Eq. 2 and selected 31 SNPs not in strong linkage disequilibrium ($r^2 < 0.8$) as well as known phenotypes to estimate the total selection differences on human pigmentation between populations. These SNPs were: rs3829241, rs56203814, rs916977, rs1800414, rs10424065, rs6119471, rs1408799, rs11230664, rs1407995, rs4959270, rs1800401, rs2378249, rs1042602, rs12350739, rs6058017, rs12821256, rs1393350, rs1426654, rs642742, rs6510760, rs1129038, rs2228479, rs35264875, rs12896399, rs26722, rs16891982, rs885479, rs28777, rs1800404, rs10756819, rs2402130. To dissect selective pressures over epochs, we applied Eq. 4 with the total selection differences from the selected 31 SNPs and the divergence times shown in Fig. 1.

Reproducing the observed selection differences from the optimal solution

We used SLiM 2 (version: 2.6) [42] to simulate a demographic model of human evolution (Fig. S3) to examine whether the optimal solution could reproduce the observed selection differences. We varied the initial frequency of the beneficial allele with 0.001 and 0.01. We divided the optimal solution by 31 to obtain the average selection coefficient for each SNP, because we used 31 SNPs to estimate the total selection differences on human pigmentation (Text S2). We used the effective population size of each population estimated by previous studies [78, 79]. We set both the mutation rate and the recombination rate to 1×10^{-8} /generation/site. In each run, we simulated a fragment with 10^6 base pairs, and set the 50,000th site under selection. We repeated each set of parameters more than 10,000 times, and analyzed those results in which beneficial alleles were not fixed or lost in all the populations. We compared the average selection differences from simulation with the observed selection differences.

All the simulations were performed in Digital Ocean (<https://cloud.digitalocean.com/>) Optimized Droplets. The information of these droplets is as follows: CPU, Intel® Xeon® Platinum 8168 Processor; Random-access memory, 64 GB; Operating system, Ubuntu 16.04.4 x64.

Fig. S3. The demography model for simulation. The italic numbers indicate population sizes at different time periods. Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

We noticed that the selection coefficient in SLiM 2 measures differences in fitness between genotypes instead of alleles. We can transform the selection coefficient of genotypes into that of alleles as follows. Let the fitness of the ancestral allele A be 1, and the relative fitness of the derived allele a is e^s . When s is close to 0, we can approximate e^s as $1 + s$ using

the Taylor series. The fitness of genotype aa becomes $(1+s)^2 = 1+2s+s^2 \approx 1+2s$, and the fitness of genotype Aa is $1+s = 1+0.5s'$. If s' is the selection coefficient in SLiM 2, then $s' = 2s$; and the dominance coefficient becomes 0.5.

Supporting Information

S1 Table. Data resources.

S2 Table. Population information.

S3 Table. Candidate SNPs.

S4 Table. Selection differences on the selected 42 SNPs.

S1 Fig. PCA plots of 2346 samples.

S2 Fig. Derived allele frequencies of candidate SNPs from imputation and the 1000 Genomes project. Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

S3 Fig. The demography model for simulation. The italic numbers indicate population sizes at different time periods. Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

S1 Text. The effects of migration and substructure.

S2 Text. A sample script for simulation with SLiM 2.

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Author Contribution

X.H. and Y.H. designed the study. X.H. collected and simulated the data. X.H. and Y.H. developed the model, analyzed the data and wrote the manuscript. S.W. and L.J. revised the manuscript.

References

1. Darwin C. 1889. *The descent of man, and selection in relation to sex*. New York: D. Appleton and Company.
2. Norton HL. 2005. *Human skin pigmentation variation: a phenotypic, genotypic and evolutionary perspective*. Ph.D. Dissertation, Pennsylvania State University. Available from <https://etda.libraries.psu.edu/catalog/6658>
3. Rees JL, Harding RM. Understanding the evolution of human pigmentation: Recent contributions from population genetics. *J Invest Dermatol*. 2012; 132: 846–853.
4. Barsh GS. What controls variation in human skin color? *PLoS Biol*. 2003; 1: 19–22.
5. Jablonski NG, Chaplin G. The evolution of human skin coloration. *J Hum Evol*. 2000; 39: 57–106.
6. Parra EJ. Human pigmentation variation: evolution, genetic basis, and implications for public health. *Am J Phys Anthropol*. 2007; Suppl 45: 85–105.
7. Jablonski NG, Chaplin G. The colours of humanity: the evolution of pigmentation in the human lineage. *Phil Trans R Soc B* 2017; 372: 20160349.
8. Cuthill IC, Allen WL, Arbuckle K, Caspers B, Chaplin G, Hauber ME, et al. The biology of color. *Science* 2017; 357: eaan0221.
9. Hochberg Z, Hochberg I. Evolutionary perspective in rickets and vitamin D. *Front Endocrinol*. 2019; 10: 306. doi: 10.3389/fendo.2019.00306
10. Izagirre N, García I, Junquera C, de la Rúa C, Alonso S. A scan for signatures of positive selection in candidate loci for skin pigmentation in humans. *Mol Biol Evol*. 2006; 23: 1697–1706.
11. Voight BF, Kudaravalli S, Wen X, Pritchard JK. A map of recent positive selection in the human genome. *PLoS Biol*. 2006; 5: e147.

- 479 12. Lao O, de Gruijter JM, van Duijin K, Navarro A, Kayser M. Signatures of positive
480 selection in genes associated with human skin pigmentation as revealed from analyses of
481 single nucleotide polymorphisms. *Ann Hum Genet.* 2007; 71: 354–369.
- 482 13. Myles S, Somel M, Tang K, Kelso J, Stoneking M. Identifying genes underlying skin
483 pigmentation differences among human populations. *Hum Genet.* 2007; 120: 613–621.
- 484 14. Norton HL, Kittles RA, Parra E, McKeigue P, Mao X, Cheng K, et al. Genetic evidence
485 for the convergent evolution of light skin in Europeans and East Asians. *Mol Biol Evol.*
486 2007; 24: 710–722.
- 487 15. Pickrell J, Coop G, Novermbre J, Kudaravalli S, Li JZ, Absher D, et al. Signals of recent
488 positive selection in a worldwide sample of human populations. *Genome Res.* 2009; 19:
489 826–837.
- 490 16. Beleza S, Santos AM, McEvoy B, Alves I, Martinho C, Cameron E, et al. The timing of
491 pigmentation lightening in Europeans. *Mol Biol Evol.* 2013; 30: 24–35.
- 492 17. Hider JL, Gittelman RM, Shah T, Edwards M, Rosenbloom A, Akey JM, et al. Exploring
493 signatures of positive selection in pigmentation candidate genes in populations of East
494 Asian ancestry. *BMC Evol Biol.* 2013; 13: 150.
- 495 18. Wilde S, Timpson A, Kirsanow K, Kaiser E, Kayser M, Unterländer M, et al. Direct
496 evidence for positive selection of skin, hair, and eye pigmentation in Europeans during
497 the last 5,000 y. *Proc Natl Acad Sci USA* 2014; 111: 4832–4837.
- 498 19. Abdel-Malek ZA, Scott MC, Furumura M, Lamoreux ML, Ollmann M, Barsh GS, et al.
499 The melanocortin 1 receptor is the principal mediator of the effects of agouti signaling
500 protein on mammalian melanocytes. *J Cell Biol.* 2010; 114: 1019–1024.
- 501 20. Rebbeck TR, Kanetsky PA, Walker AH, Holmes R, Halpern AC, Schuchter LM, et al. *P*
502 gene as an inherited biomarker of human eye color. *Cancer Epidem Biomar.* 2002; 11:
503 782–784.
- 504 21. Duffy DL, Box NF, Chen W, Palmer JS, Montgomery GW, James MR, et al. Interactive
505 effects of MC1R and OCA2 on melanoma risk phenotypes. *Hum Mol Genet.* 2004; 13:
506 447–461.

- 507 22. Duffy DL, Montgomery GW, Chen W, Zhao ZZ, Le L, James MR, et al. A
508 three-single-nucleotide polymorphism haplotype in intron 1 of *OCA2* explains most
509 human eye-color variation. *Am J Hum Genet.* 2007; 80: 241–252.
- 510 23. Graf J, Hodgson R, van Daal A. Single nucleotide polymorphisms in the *MATP* gene are
511 associated with normal human pigmentation variation. *Hum Mutat.* 2005; 25: 278–284.
- 512 24. Sulem P, Gudbjartsson DF, Stacey SN, Helgason A, Rafnar T, Magnusson KP, et al.
513 Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nat Genet.* 2007;
514 39: 1443–1452.
- 515 25. Sulem P, Gudbjartsson DF, Stacey SN, Helgason A, Rafnar T, Jakobsdottir M, et al. Two
516 newly identified genetic determinants of pigmentation in Europeans. *Nat Genet.* 2008; 40:
517 835–837.
- 518 26. Anno S, Abe T, Yamamoto T. Interactions between SNP alleles at multiple loci contribute
519 to skin color differences between Caucasoid and Mongoloid subjects. *Int J Biol Sci.* 2008;
520 4: 81–86.
- 521 27. Han J, Kraft P, Nan H, Guo Q, Chen C, Qureshi A, et al. A genome-wide association
522 study identifies novel alleles associated with hair color and skin pigmentation. *PLoS*
523 *Genet.* 2008; 4: e1000074.
- 524 28. Ito S, Wakamatsu K. Chemistry of mixed melanogenesis - pivotal roles of dopaquinone.
525 *Photochem Photobiol.* 2008; 84: 582–592.
- 526 29. Kayser M, Liu F, Janssens AC, Rivadeneira F, Lao O, van Duijn K, et al. Three
527 genome-wide association studies and a linkage analysis identify *HERC2* as a human iris
528 color gene. *Am J Hum Genet.* 2008; 82: 411–423.
- 529 30. Sturm RA, Duffy DL. Human pigmentation genes under environmental selection.
530 *Genome Biol.* 2012; 13: 248.
- 531 31. Visser M, Kayser M, Palstra R. *HERC2* rs12913832 modulates human pigmentation by
532 attenuating chromatin-loop formation between a long-range enhance and the *OCA2*
533 promoter. *Genome Res.* 2012; 22: 446–455.
- 534 32. Visser M, Palstra R, Kayser M. Human skin color is influenced by an intergenic DNA
535 polymorphism regulating transcription of the nearby *BNC2* pigmentation gene. *Hum Mol*
536 *Genet.* 2014; 23: 5750–5762.

- 537 33. Guenther CA, Tasic B, Luo L, Bedell MA, Kingsley DM. A molecular basis for classic
538 blond hair color in Europeans. *Nat Genet.* 2014; 46: 748–754.
- 539 34. McEvoy B, Beleza S, Shriver MD. The genetic architecture of normal variation in human
540 pigmentation: an evolutionary perspective and model. *Hum Mol Genet.* 2006; 15:
541 R176–R181.
- 542 35. Donnelly MP, Paschou P, Grigorenko E, Gurwitz D, Barta C, Lu RB, et al. A global view
543 of the *OCA2-HERC2* region and pigmentation. *Hum Genet.* 2012; 131: 683–696.
- 544 36. He Y, Wang M, Huang X, Li R, Xu H, Xu S, et al. A probabilistic method for testing and
545 estimating selection differences between populations. *Genome Res.* 2015; 25: 1903–1909.
- 546 37. Schaffner SF, Foo C, Gabriel S, Reich D, Daly MJ, Altshuler D. Calibrating a coalescent
547 simulation of human genome sequence variation. *Genome Res.* 2005; 15: 1576–1583.
- 548 38. Oppenheimer S. 2012. Out-of-Africa, the peopling of continents and islands: tracing
549 uniparental gene trees across the map. *Phil Trans R Soc B.* 367: 770–784.
- 550 39. Schiffel S, Durbin R. Inferring human population size and separation history from
551 multiple genome sequences. *Nat Genet.* 2014; 46: 919–925.
- 552 40. Modal M, Casals F, Xu T, Dall’Olio GM, Pybus M, Netea MG, et al. Genomic analysis of
553 Andamanese provides insights into ancient human migration into Asia and adaptation.
554 *Nat Genet.* 2016; 48: 1066–1070.
- 555 41. Mathieson I, Lazaridis I, Rohland N, Mallick S, Patterson N, Roodenberg SA, et al.
556 Genome-wide patterns of selection in 230 ancient Eurasians. *Nature* 2015; 528: 499–503.
- 557 42. Haller BC, Messer PW. SLiM 2: Flexible, interactive forward genetic simulations. *Mol*
558 *Biol Evol.* 2017; 34: 230–240.
- 559 43. Spichenok O, Budimljia ZM, Mitchell AA, Jenny A, Kovacevic L, Marjanovic D, et al.
560 Prediction of eye and skin color in diverse populations using seven SNPs. *Forensic Sci Int*
561 *Gen.* 2011; 5: 472–478.
- 562 44. Rana BK, Hewett-Emmett D, Jin L, Chang BH, Sambuughin N, Lin M, et al. High
563 polymorphism at the human melanocortin 1 receptor locus. *Genetics* 1999; 151:
564 1547–1557.
- 565 45. Harding RM, Healy E, Ray AJ, Ellis NS, Flanagan N, Todd C, et al. Evidence for variable
566 selective pressures at MC1R. *Am J Hum Genet.* 2000; 66: 1351–1361.

567 46. Xu X, Thörnwall M, Lundin L, Chhajlani V. Val92Met variant of the melanocyte
568 stimulating hormone receptor gene. *Nat Genet.* 1996; 14: 384.

569 47. Motokawa T, Kato T, Hashimoto Y, Katagiri T. Effect of Val92Met and Arg163Gln
570 variants of the *MC1R* gene on freckles and solar lentigines in Japanese. *Pigment Cell Res.*
571 2007; 20: 140–143.

572 48. Crawford NG, Kelly DE, Hansen MEB, Beltrame MH, Fan S, Bowman BL, et al. Loci
573 associated with skin pigmentation identified in African populations. *Science* 2017; 358:
574 eaa8433.

575 49. Lasisi T, Shriver MD. Focus on African diversity confirms complexity of skin
576 pigmentation genetics. *Genome Biol.* 2018; 19: 13.

577 50. Edwards M, Bigham A, Tan J, Li S, Gozdzik A, Ross K, et al. Association of the *OCA2*
578 polymorphism His615Arg with melanin content in East Asian Populations: further
579 evidence of convergent evolution of skin pigmentation. *PLoS Genet.* 2010; 6: e1000867.

580 51. Yang Z, Zhong H, Chen J, Zhang X, Zhang H, Luo X, et al. A genetic mechanism for
581 convergent skin lightening during recent human evolution. *Mol Biol Evol.* 2016; 33:
582 1177–1187.

583 52. Martin AR, Lin M, Granka JM, Myrick JW, Liu X, Sockell A, et al. An unexpectedly
584 complex architecture for skin pigmentation in Africans. *Cell* 2017; 171: 1340–1353.

585 53. Crow JF, Kimura M. 2009. *An introduction to population genetics theory*. Caldwell: The
586 Blackburn Press.

587 54. Terhorst J, Kamm JA, Song YS. Robust and scalable inference of population history from
588 hundreds of unphased whole genomes. *Nat Genet.* 2017; 49: 303–309.

589 55. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies.
590 *Cell* 2019; 177: 26–31.

591 56. Li JZ, Absher DM, Tang H, Southwick AM, Casto AM, Ramachandran S, et al.
592 Worldwide human relationships inferred from genome-wide patterns of variation. *Science*
593 2008; 319: 1100–1104.

594 57. Behar DM, Yunusbayev B, Metsplau M, Metsplau E, Rosset S, Parik J, et al. The
595 genome-wide structure of the Jewish people. *Nature* 2010; 466: 238–242.

58. Cristofaro JD, Pennarun E, Mazières S, Myres NM, Lin AA, Temori SA, et al. Afghan Hindu Kush: where Eurasian sub-continent gene flows converge. *PLoS One* 2013; 8: e76748.
59. Fedorova SA, Reidla M, Metspalu E, Metspalu M, Rootsi S, Tambets K, et al. 2013. Autosomal and uniparental portraits of the native populations of Sakha (Yakutia): implications for the peopling of Northeast Eurasia. *BMC Evol Biol.* 2013; 13: 127.
60. Kovacevic L, Tambets K, Ilumäe AM, Kushniarevich A, Yunusbayev B, Solnik A, et al. Standing at the gateway to Europe - the genetic structure of Western Balkan populations based on autosomal and haploid markers. *PLoS One* 2014; 9: e105090.
61. Metspalu M, Romero IG, Yunusbayev B, Chaubey G, Mallick CB, Hudjashov G, et al. Shared and unique components of human population structure and genome-wide signals of positive selection in South Asia. *Am J Hum Genet.* 2011; 89: 731–744.
62. Pagani L, Kivisild T, Tarekegn A, Ekong R, Plaster C, Gallego Romero I, et al. Ethiopian genetic diversity reveals linguistic stratification and complex influences on the Ethiopian gene pool. *Am J Hum Genet.* 2012; 91: 83–96.
63. Raghavan M, Skoglund P, Graf KE, Metspalu M, Albrechtsen A, Moltke I, et al. 2014. Upper Paleolithic Siberian genome reveals dual ancestry of Native Americans. *Nature* 2014; 505: 87–91.
64. Rasmussen M, Li Y, Lindgreen S, Pedersen JS, Albrechtsen A, Moltke I, et al. Ancient human genome sequence of an extinct Palaeo-Eskimo. *Nature* 2010; 463: 757–762.
65. Teo YY, Sim X, Ong RTH, Tan AKS, Chen J, Tantoso E, et al. Singapore genome variation project: a haplotype map of three Southeast Asian populations. *Genome Res.* 2009; 19: 2154–2162.
66. The 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* 2010; 467: 1061–1073.
67. The International HapMap 3 Consortium. Integrating common and rare genetic variation in diverse human populations. *Nature* 2010; 467: 52–58.
68. Xing J, Wuren T, Simonson TS, Watkins WS, Witherspoon D, Wu W, et al. Genomic analysis of natural selection and phenotypic variation in high-altitude Mongolians. *PLoS Genet.* 2013; 9: e1003634.

- 626 69. Yunusbayev B, Metspalu M, Järve M, Kutuev I, Rootsi S, Metspalu E, et al. The
627 Caucasus as an asymmetric semipermeable barrier to ancient human migrations. *Mol Biol*
628 *Evol.* 2012; 29: 359–365.
- 629 70. Yunusbayev B, Metspalu M, Metspalu E, Valeev, A., Litvinov S, Valiev R, et al. The
630 genetic legacy of the expansion of Turkic-speaking nomads across Eurasia. *PLoS Genet.*
631 2015; 11: e1005068.
- 632 71. Pagani L, Lawson DJ, Jagoda E, Morseburg A, Eriksson A, Mitt M, et al. Genomic
633 analyses inform on migration events during the peopling of Eurasia. *Nature* 2016; 538:
634 238–242.
- 635 72. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. 2007.
636 PLINK: a toolset for whole-genome association and population-based linkage analysis.
637 *Am J Hum Genet.* 2007; 81: 559–575.
- 638 73. Patterson N, Price AL, Reich D. 2006. Population structure and eigenanalysis. *PLoS*
639 *Genet.* 2006; 2: e190.
- 640 74. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal
641 components analysis corrects for stratification in genome-wide association studies. *Nat*
642 *Genet.* 2006; 38: 904–909.
- 643 75. Patterson N, Moorjani P, Luo Y, Mallick S, Rohland N, Zhang Y, et al. 2012. Ancient
644 admixture in human history. *Genetics* 2012; 192: 1065–1093.
- 645 76. Browning BL, Browning SR. Genotype imputation with millions of reference samples.
646 *Am J Hum Genet.* 2016; 98: 116–126.
- 647 77. Browning SR, Browning BL. Rapid and accurate haplotype phasing and missing data
648 inference for whole genome association studies by use of localized haplotype clustering.
649 *Am J Hum Genet.* 2007; 81: 1084–1097.
- 650 78. McEvoy BP, Powell JE, Goddard ME, Visscher PM. Human population dispersal "Out of
651 Africa" estimated from linkage disequilibrium and allele frequencies of SNPs. *Genome*
652 *Res.* 2011; 21: 821–829.
- 653 79. Mezzavilla M, Ghirotto S. Neon: An R package to estimate human effective population
654 size and divergence time from patterns of linkage disequilibrium between SNPs. *J*
655 *Comput Sci Syst Biol.* 2015; 8: 37–44.

80. Walsh S, Liu F, Wollstein A, Kovatsi L, Ralf A, Kosiniak-Kamysz A, et al. The HRisPlex system for simultaneous prediction of hair and eye colour from DNA. *Forensic Sci Int Genet* 2013; 7: 98–115.
81. Praetorius C, Grill C, Stacey SN, Metcalf AM, Gorkin DU, Robinson KC, et al. A polymorphism in IRF4 affects human pigmentation through a tyrosinase-dependent MITF/TFAP2A pathway. *Cell* 2013; 155: 1022–1033.
82. Jacobs LC, Wollstein A, Lao O, Hofman A, Klaver CC, Uitterlinden AG, et al. Comprehensive candidate gene study highlights UGT1A and BNC2 as new genes determining continuous skin color variation in Europeans. *Hum Genet.* 2013; 132: 147–158.
83. Stokowki RP, Pant PV, Dadd T, Fereday A, Hinds DA, Jarman C, et al. A genomewide association study of skin pigmentation in a South Asian population. *Am J Hum Genet.* 2007; 81: 1119–1132.
84. Miller CT, Beleza S, Pollen AA, Schluter D, Kittles RA, Shriver MD, et al. *cis*-Regulatory changes in *Kit ligand* expression and parallel evolution of pigmentation in sticklebacks and humans. *Cell* 2007; 131: 1179–1189.
85. Murray N, Norton HL, Parra EJ. Distribution of two OCA2 polymorphisms associated with pigmentation in East-Asian populations. *Hum Genome Var* 2015; 2: 15058.
86. Branicki W, Brudnik U, Wojas-Pelc A. Interactions between *HERC2*, *OCA2* and *MC1R* may influence human pigmentation phenotype. *Ann Hum Genet.* 2009; 73: 160–170.
87. Branicki W, Liu F, van Duijin K, Draus-Barini J, Pośpiech E, Walsh S, et al. Model-based prediction of human hair color using DNA variants. *Hum Genet.* 2011; 129: 443–454.
88. Eiberg H, Troelsen J, Nielsen M, Mikkelsen A, Mengel-From J, Kjaer KW, et al. Blue eye color in humans may be caused by a perfectly associated founder mutation in a regulatory element located within the *HERC2* gene inhibiting *OCA2* expression. *Hum Genet.* 2008; 123: 177–187.
89. Sturm RA, Duffy DL, Zhao ZZ, Leite FP, Stark MS, Hayward NK, et al. A single SNP in an evolutionary conserved region within intron 86 of the *HERC2* gene determines human blue-brown eye color. *Am J Hum Genet.* 2008; 82: 424–431.

- 686 90. Lamason RL, Mohideen MA, Mest JR, Wong AC, Norton HL, Aros MC, et al. SLC24A5,
687 a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science* 2005;
688 310: 1782–1786.
- 689 91. Hart KL, Kimura SL, Mushailov V, Budimlijia ZM, Prinz M, Wurmbach E. Improved
690 eye- and skin-color prediction based on 8 SNPs. *Croat Med J.* 2013; 54: 248–256.
- 691 92. Bonilla C, Boxill LA, Donald SA, Williams T, Sylvester N, Parra EJ, et al. The 8818G
692 allele of the agouti signaling protein (ASIP) gene is ancestral and is associated with
693 darker skin color in African Americans. *Hum Genet.* 2005; 116: 402–406.

Table S1 Data resources

Dataset	Sample	Resource	Reference
1KG	2504	http://www.1000genomes.org/	66
HapMap3	1397	http://www.sanger.ac.uk/resources/downloads/human/hapmap3.html	67
Jew	466	http://evolbio.ut.ee/jew/	57
Afghan	24	http://evolbio.ut.ee/afghan/	58
Sakha	40	http://evolbio.ut.ee/sakha/	59
Balkan	70	http://evolbio.ut.ee/balkan/	60
HGDP	1043	ftp://ftp.cephb.fr/hgdp_supp1/	56
India	142	http://evolbio.ut.ee/india/	61
Ethiopian	235	http://mega.bioanth.cam.ac.uk/data/Ethiopia	62
Malta	85	http://evolbio.ut.ee/malta/	63
Saqqaq	197	http://evolbio.ut.ee/saqqaq/	64
SGVP	268	http://phg.nus.edu.sg/StatGen/public_html/SGVP/download.html	65
NorthernEurasian	369	Request from the authors	68
Caucasus	204	http://evolbio.ut.ee/caucasus/	69
Turkic	322	http://evolbio.ut.ee/turkic/	70
Andamanese	10	https://www.ebi.ac.uk/ena/data/view/PRJEB11455	40
EGDP	483	http://evolbio.ut.ee/CGgenomes.html	71

Table S2 Population information

Data resource	Population group	Population abbreviation	Sample size
Ethiopian	East Africans	ANU	21
Ethiopian	East Africans	GUM	15
Ethiopian	East Africans	SUD	23
1KG	East Asians	CHN	208
1KG	East Asians	DAI	93
1KG	East Asians	JAP	104
1KG	East Asians	KHV	96
EGDP	East Asians	BUM	1
EGDP	East Asians	DSN	8
EGDP	East Asians	IGO	8
EGDP	East Asians	LBO	4
EGDP	East Asians	LUZ	2
EGDP	East Asians	MUR	8
EGDP	East Asians	VIZ	2
EGDP	East Asians	VTN	10
HapMap3	East Asians	CHN	152
HapMap3	East Asians	JAP	16
HGDP	East Asians	CHN	44
HGDP	East Asians	DAI	10
HGDP	East Asians	JAP	28
HGDP	East Asians	LAH	8
HGDP	East Asians	MIA	10
HGDP	East Asians	NAX	9
HGDP	East Asians	SHE	10
HGDP	East Asians	TUJ	10
HGDP	East Asians	YIZ	10
SGVP	East Asians	CHN	96
1KG	Europeans	CEU	99
1KG	Europeans	FIN	99
1KG	Europeans	GBR	91
Jew	Europeans	BEL	9
Jew	Europeans	HNG	20
Jew	Europeans	LIT	10
Jew	Europeans	RMN	14
Jew	Europeans	RUS	2
EGDP	Europeans	ALB	3
EGDP	Europeans	BEL	4
EGDP	Europeans	COS	4
EGDP	Europeans	CRO	4
EGDP	Europeans	EST	6

EGDP	Europeans	FIN	3
EGDP	Europeans	GER	3
EGDP	Europeans	HNG	2
EGDP	Europeans	ING	3
EGDP	Europeans	KAR	3
EGDP	Europeans	KOM	2
EGDP	Europeans	LAT	3
EGDP	Europeans	LIT	3
EGDP	Europeans	MOL	2
EGDP	Europeans	MRD	3
EGDP	Europeans	POL	4
EGDP	Europeans	RUS	7
EGDP	Europeans	SWE	2
EGDP	Europeans	UKR	7
EGDP	Europeans	VEP	4
HapMap3	Europeans	CEU	24
Balkan	Europeans	BOS	14
Balkan	Europeans	KSV	9
Balkan	Europeans	MAC	14
Balkan	Europeans	MNT	14
Balkan	Europeans	SER	18
HGDP	Europeans	FRE	28
HGDP	Europeans	ORC	15
HGDP	Europeans	RUS	25
Malta	Europeans	EST	14
Malta	Europeans	RUS	1
NorthernEurasian	Europeans	SLV	25
Turkic	Europeans	GAG	12
Turkic	Europeans	GER	13
Turkic	Europeans	KAR	15
Turkic	Europeans	RUS	33
Turkic	Europeans	VEP	11
EGDP	North Asians	EVK	13
EGDP	North Asians	EVN	8
EGDP	North Asians	NGA	2
EGDP	North Asians	SAK	7
EGDP	North Asians	YAK	1
Sakha	North Asians	DOL	3
Sakha	North Asians	EVN	8
Sakha	North Asians	YAK	1
HGDP	North Asians	YAK	22
Malta	North Asians	DOL	1

Malta	North Asians	EVE	2
Saqqaq	North Asians	DOL	4
Saqqaq	North Asians	EVE	15
Saqqaq	North Asians	NGA	13
Saqqaq	North Asians	YUK	3
Turkic	North Asians	EVE	3
Turkic	North Asians	EVN	3
Turkic	North Asians	NGA	2
Turkic	North Asians	YAK	3
EGDP	Oceanians	KOI	3
EGDP	Oceanians	KOS	3
HGDP	Oceanians	PAP	16
Andamanese	Oceanians	AND	10
1KG	West Africans	ESN	99
1KG	West Africans	GWD	112
1KG	West Africans	MSL	85
1KG	West Africans	YOR	108
HapMap3	West Africans	YOR	46
HGDP	West Africans	MND	22
HGDP	West Africans	YOR	21

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Table S3 Candidate SNP information

Gene	Chromosome	Position (Hg19)	SNP	Ancestral allele	Derived allele	Pigmentation associated with the derived allele	Reference
<i>SLC45A2</i>	5	33951693	rs16891982	C	G	light	23, 80
<i>SLC45A2</i>	5	33958959	rs28777	C	A	light	80
<i>SLC45A2</i>	5	33963870	rs26722	C	T	dark	23
<i>IRF4</i>	6	396321	rs12203592	C	T	light	27, 81
<i>EXOC2</i>	6	457748	rs4959270	C	A	light	80
<i>TYRP1</i>	9	12672097	rs1408799	T	C	light	25
<i>TYRP1</i>	9	12709305	rs683	A	C	dark	80
<i>BNC2</i>	9	16858084	rs10756819	G	A	light	32, 82
<i>BNC2</i>	9	16885017	rs12350739	G	A	light	32
<i>DDB1</i>	11	61076372	rs11230664	C	T	light	48
<i>DDB1</i>	11	61080557	rs7120594	T	C	light	48
<i>DDB1</i>	11	61137147	rs7948623	A	T	dark	48
<i>DDB1</i>	11	61144652	rs1377457	C	A	light	48
<i>TPCN2</i>	11	68846399	rs35264875	A	T	light	25
<i>TPCN2</i>	11	68855363	rs3829241	G	A	light	25
<i>TYR</i>	11	88911696	rs1042602	C	A	light	83
<i>TYR</i>	11	89011046	rs1393350	G	A	light	24
<i>TYR</i>	11	89017961	rs1126809	G	A	light	25
<i>KITLG</i>	12	89299746	rs642742	A	G	light	84
<i>KITLG</i>	12	89328335	rs12821256	T	C	light	24
<i>DCT</i>	13	95096013	rs1407995	T	C	dark	50
<i>DCT</i>	13	95100841	rs2031526	G	A	light	50

<i>SLC24A4</i>	14	92773663	rs12896399	G	T	light	24
<i>SLC24A4</i>	14	92801203	rs2402130	G	A	light	80
<i>OCA2</i>	15	28183354	rs2311843	C	T	Unknown	26
<i>OCA2</i>	15	28197037	rs1800414	A	G	light	50, 51, 85
<i>OCA2</i>	15	28228553	rs74653330	G	A	light	85
<i>OCA2</i>	15	28230318	rs1800407	G	A	light	86, 87
<i>OCA2</i>	15	28235773	rs1800404	G	A	light	48
<i>OCA2</i>	15	28260053	rs1800401	C	T	dark	20
<i>HERC2</i>	15	28356859	rs1129038	G	A	light	35, 88
<i>HERC2</i>	15	28365618	rs12913832	A	G	light	25, 89
<i>HERC2</i>	15	28513364	rs916977	A	G	light	29, 35
<i>HERC2</i>	15	28530182	rs1667394	G	A	light	24, 35
<i>SLC24A5</i>	15	48426484	rs1426654	G	A	light	90
<i>MYO5A</i>	15	52816195	rs4776053	C	T	Unknown	26
<i>MC1R</i>	16	89985844	rs1805005	G	T	light	80
<i>MC1R</i>	16	89985918	rs1805006	C	A	light	80
<i>MC1R</i>	16	89985940	rs2228479	G	A	light	80
<i>MC1R</i>	16	89986091	rs11547464	G	A	light	80
<i>MC1R</i>	16	89986117	rs1805007	C	T	light	80
<i>MC1R</i>	16	89986130	rs1110400	T	C	light	80
<i>MC1R</i>	16	89986144	rs1805008	C	T	light	80
<i>MC1R</i>	16	89986154	rs885479	G	A	light	80
<i>MC1R</i>	16	89986546	rs1805009	G	C	light	80
<i>MFSD12</i>	19	3544892	rs56203814	C	T	dark	48
<i>MFSD12</i>	19	3545022	rs10424065	C	T	dark	48

<i>MFSD12</i>	19	3565253	rs6510760	G	A	dark	48
<i>MFSD12</i>	19	3565599	rs112332856	T	C	dark	48
<i>ASIP</i>	20	32785212	rs6119471	G	C	light	91
<i>ASIP</i>	20	32856998	rs6058017	G	A	light	92
<i>PIGU</i>	20	33218090	rs2378249	A	G	light	87

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Table S4 Selection differences on the 42 selected SNPs

Gene	SNP ID	Ancestral allele	Derived allele	Population1	Population2	Selection difference (Population1 - Population2)	Std	p-value
<i>SLC45A2</i>	rs16891982	C	G	Europeans	NorthAsians	0.003181	7.47E-04	2.10E-05
<i>SLC45A2</i>	rs28777	C	A	Europeans	NorthAsians	0.003107	7.46E-04	3.10E-05
<i>SLC45A2</i>	rs26722	C	T	Europeans	NorthAsians	-0.001767	7.47E-04	0.017939
<i>EXOC2</i>	rs4959270	C	A	Europeans	NorthAsians	4.12E-04	7.38E-04	0.576675
<i>TYRP1</i>	rs1408799	T	C	Europeans	NorthAsians	0.00287	7.90E-04	2.82E-04
<i>TYRP1</i>	rs683	A	C	Europeans	NorthAsians	-0.002354	7.60E-04	0.001943
<i>BNC2</i>	rs10756819	G	A	Europeans	NorthAsians	2.33E-04	7.37E-04	0.752243
<i>BNC2</i>	rs12350739	G	A	Europeans	NorthAsians	0.002475	7.85E-04	0.00161
<i>DDB1</i>	rs11230664	C	T	Europeans	NorthAsians	-8.56E-04	0.001162	0.461178
<i>DDB1</i>	rs7120594	T	C	Europeans	NorthAsians	-5.17E-04	0.001172	0.658962
<i>DDB1</i>	rs7948623	A	T	Europeans	NorthAsians	4.21E-04	0.001176	0.720668
<i>DDB1</i>	rs1377457	C	A	Europeans	NorthAsians	-7.42E-04	0.001165	0.524412
<i>TPCN2</i>	rs35264875	A	T	Europeans	NorthAsians	0.00152	7.85E-04	0.052919
<i>TPCN2</i>	rs3829241	G	A	Europeans	NorthAsians	1.79E-04	7.38E-04	0.808351
<i>TYR</i>	rs1042602	C	A	Europeans	NorthAsians	0.002002	7.90E-04	0.011305
<i>TYR</i>	rs1393350	G	A	Europeans	NorthAsians	0.0023	8.94E-04	0.010076
<i>TYR</i>	rs1126809	G	A	Europeans	NorthAsians	0.002329	8.94E-04	0.009156
<i>KITLG</i>	rs642742	A	G	Europeans	NorthAsians	-1.94E-04	7.43E-04	0.794378
<i>KITLG</i>	rs12821256	T	C	Europeans	NorthAsians	0.002653	0.001149	0.020951
<i>DCT</i>	rs1407995	T	C	Europeans	NorthAsians	0.001528	7.38E-04	0.038476
<i>DCT</i>	rs2031526	G	A	Europeans	NorthAsians	-0.001525	7.38E-04	0.038867
<i>SLC24A4</i>	rs12896399	G	T	Europeans	NorthAsians	3.51E-04	7.38E-04	0.634377
<i>SLC24A4</i>	rs2402130	G	A	Europeans	NorthAsians	-2.25E-04	7.43E-04	0.761965

<i>OCA2</i>	rs2311843	C	T	Europeans	NorthAsians	-0.001944	7.40E-04	0.008596
<i>OCA2</i>	rs1800414	A	G	Europeans	NorthAsians	-0.002739	9.05E-04	0.002475
<i>OCA2</i>	rs1800404	C	T	Europeans	NorthAsians	-2.52E-04	7.43E-04	0.73489
<i>OCA2</i>	rs1800401	C	A	Europeans	NorthAsians	2.58E-04	7.81E-04	0.741106
<i>HERC2</i>	rs1129038	G	A	Europeans	NorthAsians	0.003579	8.33E-04	1.80E-05
<i>HERC2</i>	rs12913832	A	G	Europeans	NorthAsians	0.003566	8.33E-04	1.90E-05
<i>HERC2</i>	rs916977	A	G	Europeans	NorthAsians	0.001695	7.39E-04	0.02177
<i>HERC2</i>	rs1667394	G	A	Europeans	NorthAsians	0.001684	7.39E-04	0.022651
<i>SLC24A5</i>	rs1426654	G	A	Europeans	NorthAsians	0.004135	7.65E-04	0
<i>MYO5A</i>	rs4776053	C	T	Europeans	NorthAsians	-7.63E-04	7.38E-04	0.301197
<i>MC1R</i>	rs2228479	G	A	Europeans	NorthAsians	-9.75E-04	7.40E-04	0.187511
<i>MC1R</i>	rs885479	G	A	Europeans	NorthAsians	-0.001829	7.39E-04	0.013324
<i>MFSD12</i>	rs56203814	C	T	Europeans	NorthAsians	2.40E-04	0.001185	0.839641
<i>MFSD12</i>	rs10424065	C	T	Europeans	NorthAsians	2.40E-04	0.001185	0.839641
<i>MFSD12</i>	rs6510760	G	A	Europeans	NorthAsians	1.39E-04	7.58E-04	0.85424
<i>MFSD12</i>	rs112332856	T	C	Europeans	NorthAsians	9.48E-04	8.98E-04	0.291189
<i>ASIP</i>	rs6119471	G	C	Europeans	NorthAsians	0.001135	0.001449	0.433361
<i>ASIP</i>	rs6058017	G	A	Europeans	NorthAsians	-0.001192	7.91E-04	0.132079
<i>PIGU</i>	rs2378249	A	G	Europeans	NorthAsians	-5.74E-04	7.39E-04	0.437671
<i>SLC45A2</i>	rs16891982	C	G	Europeans	Oceanians	0.002754	6.98E-04	8.00E-05
<i>SLC45A2</i>	rs28777	C	A	Europeans	Oceanians	0.001774	6.71E-04	0.008209
<i>SLC45A2</i>	rs26722	C	T	Europeans	Oceanians	-0.001337	6.78E-04	0.048735
<i>EXOC2</i>	rs4959270	C	A	Europeans	Oceanians	-0.001082	6.83E-04	0.113007
<i>TYRP1</i>	rs1408799	T	C	Europeans	Oceanians	0.002211	7.75E-04	0.00434
<i>TYRP1</i>	rs683	A	C	Europeans	Oceanians	-0.002211	7.75E-04	0.00434
<i>BNC2</i>	rs10756819	G	A	Europeans	Oceanians	3.18E-04	6.68E-04	0.633414

<i>BNC2</i>	rs12350739	G	A	Europeans	Oceanians	0.002508	9.67E-04	0.009475
<i>DDB1</i>	rs11230664	C	T	Europeans	Oceanians	0.002313	6.83E-04	7.03E-04
<i>DDB1</i>	rs7120594	T	C	Europeans	Oceanians	0.002585	6.94E-04	1.94E-04
<i>DDB1</i>	rs7948623	A	T	Europeans	Oceanians	-0.002567	6.98E-04	2.36E-04
<i>DDB1</i>	rs1377457	C	A	Europeans	Oceanians	0.002405	6.86E-04	4.53E-04
<i>TPCN2</i>	rs35264875	A	T	Europeans	Oceanians	-5.25E-04	6.68E-04	0.431752
<i>TPCN2</i>	rs3829241	G	A	Europeans	Oceanians	0.001206	7.11E-04	0.090003
<i>TYR</i>	rs1042602	C	A	Europeans	Oceanians	0.002074	9.67E-04	0.031884
<i>TYR</i>	rs1393350	G	A	Europeans	Oceanians	0.001756	9.67E-04	0.069267
<i>TYR</i>	rs1126809	G	A	Europeans	Oceanians	0.00178	9.67E-04	0.065616
<i>KITLG</i>	rs642742	A	G	Europeans	Oceanians	1.05E-04	6.74E-04	0.876062
<i>KITLG</i>	rs12821256	T	C	Europeans	Oceanians	0.001487	9.67E-04	0.124028
<i>DCT</i>	rs1407995	T	C	Europeans	Oceanians	6.48E-04	6.68E-04	0.332199
<i>DCT</i>	rs2031526	G	A	Europeans	Oceanians	-6.46E-04	6.68E-04	0.334037
<i>SLC24A4</i>	rs12896399	G	T	Europeans	Oceanians	-2.53E-04	6.68E-04	0.704428
<i>SLC24A4</i>	rs2402130	G	A	Europeans	Oceanians	-9.90E-05	6.78E-04	0.884527
<i>OCA2</i>	rs2311843	C	T	Europeans	Oceanians	-0.001052	6.68E-04	0.115666
<i>OCA2</i>	rs1800414	A	G	Europeans	Oceanians	-0.002783	7.87E-04	4.05E-04
<i>OCA2</i>	rs1800404	C	T	Europeans	Oceanians	0.001137	6.70E-04	0.08982
<i>OCA2</i>	rs1800401	C	T	Europeans	Oceanians	8.27E-04	9.69E-04	0.393278
<i>HERC2</i>	rs1129038	G	A	Europeans	Oceanians	0.003037	9.67E-04	0.001678
<i>HERC2</i>	rs12913832	A	G	Europeans	Oceanians	0.003027	9.67E-04	0.001739
<i>HERC2</i>	rs916977	A	G	Europeans	Oceanians	9.80E-04	6.68E-04	0.142565
<i>HERC2</i>	rs1667394	G	A	Europeans	Oceanians	9.71E-04	6.68E-04	0.14624
<i>SLC24A5</i>	rs1426654	G	A	Europeans	Oceanians	0.004289	7.89E-04	0
<i>MYO5A</i>	rs4776053	C	T	Europeans	Oceanians	9.60E-04	7.76E-04	0.215663

<i>MC1R</i>	rs2228479	G	A	Europeans	Oceanians	-1.59E-04	6.87E-04	0.816976
<i>MC1R</i>	rs885479	G	A	Europeans	Oceanians	4.12E-04	7.32E-04	0.57365
<i>MFSD12</i>	rs56203814	C	T	Europeans	Oceanians	-4.43E-04	9.95E-04	0.655763
<i>MFSD12</i>	rs10424065	C	T	Europeans	Oceanians	-4.43E-04	9.95E-04	0.655763
<i>MFSD12</i>	rs6510760	G	A	Europeans	Oceanians	-0.001365	6.69E-04	0.041418
<i>MFSD12</i>	rs112332856	T	C	Europeans	Oceanians	-0.001282	6.75E-04	0.057377
<i>ASIP</i>	rs6119471	G	C	Europeans	Oceanians	0.001543	0.001197	0.197389
<i>ASIP</i>	rs6058017	G	A	Europeans	Oceanians	1.57E-04	6.79E-04	0.816854
<i>PIGU</i>	rs2378249	A	G	Europeans	Oceanians	-6.90E-05	6.81E-04	0.9196
<i>SLC45A2</i>	rs16891982	C	G	Europeans	EastAsians	0.004804	7.53E-04	0
<i>SLC45A2</i>	rs28777	C	A	Europeans	EastAsians	0.003301	7.40E-04	8.00E-06
<i>SLC45A2</i>	rs26722	C	T	Europeans	EastAsians	-0.002147	7.43E-04	0.00388
<i>EXOC2</i>	rs4959270	C	A	Europeans	EastAsians	2.80E-04	7.35E-04	0.70332
<i>TYRP1</i>	rs1408799	T	C	Europeans	EastAsians	0.002875	7.42E-04	1.06E-04
<i>TYRP1</i>	rs683	A	C	Europeans	EastAsians	-0.003298	7.48E-04	1.10E-05
<i>BNC2</i>	rs10756819	G	A	Europeans	EastAsians	2.60E-04	7.35E-04	0.723261
<i>BNC2</i>	rs12350739	G	A	Europeans	EastAsians	0.003316	7.58E-04	1.20E-05
<i>DDB1</i>	rs11230664	C	T	Europeans	EastAsians	8.84E-04	7.60E-04	0.244405
<i>DDB1</i>	rs7120594	T	C	Europeans	EastAsians	0.001224	7.75E-04	0.114356
<i>DDB1</i>	rs7948623	A	T	Europeans	EastAsians	5.27E-04	8.46E-04	0.533572
<i>DDB1</i>	rs1377457	C	A	Europeans	EastAsians	-2.40E-05	7.80E-04	0.97525
<i>TPCN2</i>	rs35264875	A	T	Europeans	EastAsians	0.002125	7.51E-04	0.004686
<i>TPCN2</i>	rs3829241	G	A	Europeans	EastAsians	5.75E-04	7.35E-04	0.43454
<i>TYR</i>	rs1042602	C	A	Europeans	EastAsians	0.003703	8.34E-04	9.00E-06
<i>TYR</i>	rs1393350	G	A	Europeans	EastAsians	0.003095	8.07E-04	1.26E-04
<i>TYR</i>	rs1126809	G	A	Europeans	EastAsians	0.003655	8.95E-04	4.40E-05

<i>KITLG</i>	rs642742	A	G	Europeans	EastAsians	1.58E-04	7.36E-04	0.829732
<i>KITLG</i>	rs12821256	T	C	Europeans	EastAsians	0.003289	8.95E-04	2.38E-04
<i>DCT</i>	rs1407995	T	C	Europeans	EastAsians	0.001625	7.36E-04	0.027173
<i>DCT</i>	rs2031526	G	A	Europeans	EastAsians	-0.001627	7.36E-04	0.026976
<i>SLC24A4</i>	rs12896399	G	T	Europeans	EastAsians	3.12E-04	7.35E-04	0.67082
<i>SLC24A4</i>	rs2402130	G	A	Europeans	EastAsians	-7.69E-04	7.37E-04	0.296629
<i>OCA2</i>	rs2311843	C	T	Europeans	EastAsians	-0.00198	7.36E-04	0.007154
<i>OCA2</i>	rs1800414	A	G	Europeans	EastAsians	-0.004515	8.94E-04	0
<i>OCA2</i>	rs1800404	C	T	Europeans	EastAsians	0.001211	7.35E-04	0.099601
<i>OCA2</i>	rs1800401	C	T	Europeans	EastAsians	0.001064	7.57E-04	0.160263
<i>HERC2</i>	rs1129038	G	A	Europeans	EastAsians	0.004539	7.92E-04	0
<i>HERC2</i>	rs12913832	A	G	Europeans	EastAsians	0.004684	8.07E-04	0
<i>HERC2</i>	rs916977	A	G	Europeans	EastAsians	0.001788	7.36E-04	0.015136
<i>HERC2</i>	rs1667394	G	A	Europeans	EastAsians	0.001778	7.36E-04	0.015681
<i>SLC24A5</i>	rs1426654	G	A	Europeans	EastAsians	0.005774	7.69E-04	0
<i>MYO5A</i>	rs4776053	C	T	Europeans	EastAsians	-1.45E-04	7.36E-04	0.844254
<i>MC1R</i>	rs2228479	G	A	Europeans	EastAsians	-9.51E-04	7.37E-04	0.196783
<i>MC1R</i>	rs885479	G	A	Europeans	EastAsians	-0.001785	7.37E-04	0.015392
<i>MFSD12</i>	rs56203814	C	T	Europeans	EastAsians	0.001563	0.001186	0.18755
<i>MFSD12</i>	rs10424065	C	T	Europeans	EastAsians	8.76E-04	9.41E-04	0.351953
<i>MFSD12</i>	rs6510760	G	A	Europeans	EastAsians	1.37E-04	7.40E-04	0.85293
<i>MFSD12</i>	rs112332856	T	C	Europeans	EastAsians	0.001151	7.69E-04	0.134437
<i>ASIP</i>	rs6119471	G	C	Europeans	EastAsians	-1.88E-04	0.00145	0.896809
<i>ASIP</i>	rs6058017	G	A	Europeans	EastAsians	4.96E-04	7.36E-04	0.500451
<i>PIGU</i>	rs2378249	A	G	Europeans	EastAsians	-2.14E-04	7.36E-04	0.770841
<i>SLC45A2</i>	rs16891982	C	G	Europeans	EastAfricans	0.002845	6.31E-04	6.00E-06

<i>SLC45A2</i>	rs28777	C	A	Europeans	EastAfricans	0.001699	5.53E-04	0.002098
<i>SLC45A2</i>	rs26722	C	T	Europeans	EastAfricans	-4.21E-04	5.68E-04	0.459218
<i>EXOC2</i>	rs4959270	C	A	Europeans	EastAfricans	9.79E-04	5.64E-04	0.08264
<i>TYRP1</i>	rs1408799	T	C	Europeans	EastAfricans	7.12E-04	5.50E-04	0.195475
<i>TYRP1</i>	rs683	A	C	Europeans	EastAfricans	-8.09E-04	5.51E-04	0.142307
<i>BNC2</i>	rs10756819	G	A	Europeans	EastAfricans	0.001721	5.97E-04	0.003941
<i>BNC2</i>	rs12350739	G	A	Europeans	EastAfricans	0.002164	7.70E-04	0.004947
<i>DDB1</i>	rs11230664	C	T	Europeans	EastAfricans	0.002891	5.75E-04	0
<i>DDB1</i>	rs7120594	T	C	Europeans	EastAfricans	0.002582	5.70E-04	6.00E-06
<i>DDB1</i>	rs7948623	A	T	Europeans	EastAfricans	-0.002338	5.71E-04	4.20E-05
<i>DDB1</i>	rs1377457	C	A	Europeans	EastAfricans	0.003024	5.80E-04	0
<i>TPCN2</i>	rs35264875	A	T	Europeans	EastAfricans	8.60E-05	5.52E-04	0.876402
<i>TPCN2</i>	rs3829241	G	A	Europeans	EastAfricans	0.001304	5.97E-04	0.028911
<i>TYR</i>	rs1042602	C	A	Europeans	EastAfricans	0.001831	7.70E-04	0.017436
<i>TYR</i>	rs1393350	G	A	Europeans	EastAfricans	0.001586	7.70E-04	0.039444
<i>TYR</i>	rs1126809	G	A	Europeans	EastAfricans	0.001604	7.70E-04	0.037246
<i>KITLG</i>	rs642742	A	G	Europeans	EastAfricans	0.001378	5.55E-04	0.013057
<i>KITLG</i>	rs12821256	T	C	Europeans	EastAfricans	2.86E-04	5.62E-04	0.611079
<i>DCT</i>	rs1407995	T	C	Europeans	EastAfricans	-4.00E-05	5.53E-04	0.942694
<i>DCT</i>	rs2031526	G	A	Europeans	EastAfricans	6.06E-04	5.72E-04	0.289335
<i>SLC24A4</i>	rs12896399	G	T	Europeans	EastAfricans	9.89E-04	5.64E-04	0.079557
<i>SLC24A4</i>	rs2402130	G	A	Europeans	EastAfricans	5.86E-04	5.49E-04	0.285706
<i>OCA2</i>	rs2311843	C	T	Europeans	EastAfricans	9.39E-04	6.29E-04	0.135776
<i>OCA2</i>	rs1800414	A	G	Europeans	EastAfricans	-5.29E-04	8.31E-04	0.524534
<i>OCA2</i>	rs1800404	C	T	Europeans	EastAfricans	0.001814	5.75E-04	0.001596
<i>OCA2</i>	rs1800401	C	T	Europeans	EastAfricans	1.30E-05	5.77E-04	0.982

<i>HERC2</i>	rs1129038	G	A	Europeans	EastAfricans	0.002572	7.70E-04	8.41E-04
<i>HERC2</i>	rs12913832	A	G	Europeans	EastAfricans	0.002564	7.70E-04	8.72E-04
<i>HERC2</i>	rs916977	A	G	Europeans	EastAfricans	0.002182	5.97E-04	2.60E-04
<i>HERC2</i>	rs1667394	G	A	Europeans	EastAfricans	0.002175	5.97E-04	2.72E-04
<i>SLC24A5</i>	rs1426654	G	A	Europeans	EastAfricans	0.003205	5.94E-04	0
<i>MYO5A</i>	rs4776053	C	T	Europeans	EastAfricans	3.64E-04	5.65E-04	0.518997
<i>MC1R</i>	rs2228479	G	A	Europeans	EastAfricans	0.001173	7.71E-04	0.128136
<i>MC1R</i>	rs885479	G	A	Europeans	EastAfricans	0.001183	7.71E-04	0.124649
<i>MFSD12</i>	rs56203814	C	T	Europeans	EastAfricans	-0.001548	5.81E-04	0.007776
<i>MFSD12</i>	rs10424065	C	T	Europeans	EastAfricans	-0.002352	5.78E-04	4.60E-05
<i>MFSD12</i>	rs6510760	G	A	Europeans	EastAfricans	-0.002269	5.76E-04	8.10E-05
<i>MFSD12</i>	rs112332856	T	C	Europeans	EastAfricans	-0.00259	5.77E-04	7.00E-06
<i>ASIP</i>	rs6119471	G	C	Europeans	EastAfricans	0.002737	7.73E-04	3.98E-04
<i>ASIP</i>	rs6058017	G	A	Europeans	EastAfricans	0.001219	5.51E-04	0.026928
<i>PIGU</i>	rs2378249	A	G	Europeans	EastAfricans	3.14E-04	5.65E-04	0.578311
<i>SLC45A2</i>	rs16891982	C	G	Europeans	WestAfricans	0.00263	4.79E-04	0
<i>SLC45A2</i>	rs28777	C	A	Europeans	WestAfricans	0.001508	4.52E-04	8.40E-04
<i>SLC45A2</i>	rs26722	C	T	Europeans	WestAfricans	-2.48E-04	4.55E-04	0.585986
<i>EXOC2</i>	rs4959270	C	A	Europeans	WestAfricans	3.28E-04	4.50E-04	0.465309
<i>TYRP1</i>	rs1408799	T	C	Europeans	WestAfricans	6.83E-04	4.50E-04	0.128978
<i>TYRP1</i>	rs683	A	C	Europeans	WestAfricans	-8.97E-04	4.50E-04	0.046465
<i>BNC2</i>	rs10756819	G	A	Europeans	WestAfricans	9.96E-04	4.51E-04	0.027057
<i>BNC2</i>	rs12350739	G	A	Europeans	WestAfricans	0.00186	4.88E-04	1.39E-04
<i>DDB1</i>	rs11230664	C	T	Europeans	WestAfricans	0.001682	4.58E-04	2.38E-04
<i>DDB1</i>	rs7120594	T	C	Europeans	WestAfricans	0.001719	4.64E-04	2.09E-04
<i>DDB1</i>	rs7948623	A	T	Europeans	WestAfricans	-0.001286	4.66E-04	0.005809

<i>DDB1</i>	rs1377457	C	A	Europeans	WestAfricans	0.001757	4.59E-04	1.31E-04
<i>TPCN2</i>	rs35264875	A	T	Europeans	WestAfricans	0.001083	4.64E-04	0.019467
<i>TPCN2</i>	rs3829241	G	A	Europeans	WestAfricans	9.58E-04	4.53E-04	0.034415
<i>TYR</i>	rs1042602	C	A	Europeans	WestAfricans	0.001495	4.77E-04	0.001739
<i>TYR</i>	rs1393350	G	A	Europeans	WestAfricans	0.001893	6.21E-04	0.002296
<i>TYR</i>	rs1126809	G	A	Europeans	WestAfricans	0.001317	4.78E-04	0.005828
<i>KITLG</i>	rs642742	A	G	Europeans	WestAfricans	0.001239	4.51E-04	0.005976
<i>KITLG</i>	rs12821256	T	C	Europeans	WestAfricans	0.00173	6.21E-04	0.005338
<i>DCT</i>	rs1407995	T	C	Europeans	WestAfricans	6.70E-05	4.50E-04	0.881067
<i>DCT</i>	rs2031526	G	A	Europeans	WestAfricans	3.96E-04	4.51E-04	0.380466
<i>SLC24A4</i>	rs12896399	G	T	Europeans	WestAfricans	0.001753	4.88E-04	3.32E-04
<i>SLC24A4</i>	rs2402130	G	A	Europeans	WestAfricans	5.91E-04	4.50E-04	0.188372
<i>OCA2</i>	rs2311843	C	T	Europeans	WestAfricans	5.25E-04	4.54E-04	0.246673
<i>OCA2</i>	rs1800414	A	G	Europeans	WestAfricans	2.26E-04	6.68E-04	0.734638
<i>OCA2</i>	rs1800404	C	T	Europeans	WestAfricans	0.001079	4.50E-04	0.016588
<i>OCA2</i>	rs1800401	C	T	Europeans	WestAfricans	-4.49E-04	4.51E-04	0.320382
<i>HERC2</i>	rs1129038	G	A	Europeans	WestAfricans	0.00197	4.69E-04	2.70E-05
<i>HERC2</i>	rs12913832	A	G	Europeans	WestAfricans	0.001964	4.69E-04	2.80E-05
<i>HERC2</i>	rs916977	A	G	Europeans	WestAfricans	0.001317	4.51E-04	0.003482
<i>HERC2</i>	rs1667394	G	A	Europeans	WestAfricans	0.001354	4.51E-04	0.002681
<i>SLC24A5</i>	rs1426654	G	A	Europeans	WestAfricans	0.002367	4.60E-04	0
<i>MYO5A</i>	rs4776053	C	T	Europeans	WestAfricans	1.97E-04	4.51E-04	0.661346
<i>MC1R</i>	rs2228479	G	A	Europeans	WestAfricans	0.001567	6.21E-04	0.011649
<i>MC1R</i>	rs885479	G	A	Europeans	WestAfricans	0.001576	6.21E-04	0.011201
<i>MFSD12</i>	rs56203814	C	T	Europeans	WestAfricans	-0.001347	4.72E-04	0.004295
<i>MFSD12</i>	rs10424065	C	T	Europeans	WestAfricans	-0.001503	4.71E-04	0.001434

<i>MFSD12</i>	rs6510760	G	A	Europeans	WestAfricans	-0.001407	4.51E-04	0.001801
<i>MFSD12</i>	rs112332856	T	C	Europeans	WestAfricans	-0.001501	4.52E-04	8.93E-04
<i>ASIP</i>	rs6119471	G	C	Europeans	WestAfricans	0.002735	6.21E-04	1.10E-05
<i>ASIP</i>	rs6058017	G	A	Europeans	WestAfricans	0.001095	4.50E-04	0.015015
<i>PIGU</i>	rs2378249	A	G	Europeans	WestAfricans	-8.40E-05	4.50E-04	0.852618
<i>SLC45A2</i>	rs16891982	C	G	NorthAsians	Oceanians	2.09E-04	6.90E-04	0.761863
<i>SLC45A2</i>	rs28777	C	A	NorthAsians	Oceanians	-7.11E-04	6.59E-04	0.280548
<i>SLC45A2</i>	rs26722	C	T	NorthAsians	Oceanians	7.70E-05	6.62E-04	0.907271
<i>EXOC2</i>	rs4959270	C	A	NorthAsians	Oceanians	-0.001411	6.72E-04	0.03568
<i>TYRP1</i>	rs1408799	T	C	NorthAsians	Oceanians	-8.50E-05	7.99E-04	0.915284
<i>TYRP1</i>	rs683	A	C	NorthAsians	Oceanians	-3.28E-04	7.79E-04	0.67392
<i>BNC2</i>	rs10756819	G	A	NorthAsians	Oceanians	1.32E-04	6.56E-04	0.840146
<i>BNC2</i>	rs12350739	G	A	NorthAsians	Oceanians	5.27E-04	9.83E-04	0.591614
<i>DDB1</i>	rs11230664	C	T	NorthAsians	Oceanians	0.002999	9.63E-04	0.001845
<i>DDB1</i>	rs7120594	T	C	NorthAsians	Oceanians	0.002999	9.63E-04	0.001845
<i>DDB1</i>	rs7948623	A	T	NorthAsians	Oceanians	-0.002904	9.63E-04	0.00257
<i>DDB1</i>	rs1377457	C	A	NorthAsians	Oceanians	0.002999	9.63E-04	0.001845
<i>TPCN2</i>	rs35264875	A	T	NorthAsians	Oceanians	-0.001741	6.91E-04	0.011742
<i>TPCN2</i>	rs3829241	G	A	NorthAsians	Oceanians	0.001063	7.01E-04	0.12938
<i>TYR</i>	rs1042602	C	A	NorthAsians	Oceanians	4.72E-04	9.85E-04	0.631774
<i>TYR</i>	rs1393350	G	A	NorthAsians	Oceanians	-8.40E-05	0.00104	0.935849
<i>TYR</i>	rs1126809	G	A	NorthAsians	Oceanians	-8.40E-05	0.00104	0.935849
<i>KITLG</i>	rs642742	A	G	NorthAsians	Oceanians	2.60E-04	6.66E-04	0.696333
<i>KITLG</i>	rs12821256	T	C	NorthAsians	Oceanians	-6.35E-04	0.00119	0.593386
<i>DCT</i>	rs1407995	T	C	NorthAsians	Oceanians	-5.75E-04	6.57E-04	0.381764
<i>DCT</i>	rs2031526	G	A	NorthAsians	Oceanians	5.75E-04	6.57E-04	0.381764

<i>SLC24A4</i>	rs12896399	G	T	NorthAsians	Oceanians	-5.34E-04	6.57E-04	0.416225
<i>SLC24A4</i>	rs2402130	G	A	NorthAsians	Oceanians	8.10E-05	6.70E-04	0.903342
<i>OCA2</i>	rs2311843	C	T	NorthAsians	Oceanians	5.03E-04	6.58E-04	0.444072
<i>OCA2</i>	rs1800414	A	G	NorthAsians	Oceanians	-5.92E-04	6.70E-04	0.376725
<i>OCA2</i>	rs1800404	C	T	NorthAsians	Oceanians	0.001338	6.62E-04	0.04329
<i>OCA2</i>	rs1800401	C	T	NorthAsians	Oceanians	6.21E-04	9.78E-04	0.525882
<i>HERC2</i>	rs1129038	G	A	NorthAsians	Oceanians	1.74E-04	0.001008	0.862992
<i>HERC2</i>	rs12913832	A	G	NorthAsians	Oceanians	1.74E-04	0.001008	0.862992
<i>HERC2</i>	rs916977	A	G	NorthAsians	Oceanians	-3.76E-04	6.57E-04	0.567236
<i>HERC2</i>	rs1667394	G	A	NorthAsians	Oceanians	-3.76E-04	6.57E-04	0.567236
<i>SLC24A5</i>	rs1426654	G	A	NorthAsians	Oceanians	9.81E-04	7.68E-04	0.201703
<i>MYO5A</i>	rs4776053	C	T	NorthAsians	Oceanians	0.001571	7.65E-04	0.04014
<i>MC1R</i>	rs2228479	G	A	NorthAsians	Oceanians	6.21E-04	6.75E-04	0.357846
<i>MC1R</i>	rs885479	G	A	NorthAsians	Oceanians	0.001875	7.21E-04	0.009264
<i>MFSD12</i>	rs56203814	C	T	NorthAsians	Oceanians	-6.35E-04	0.00119	0.593386
<i>MFSD12</i>	rs10424065	C	T	NorthAsians	Oceanians	-6.35E-04	0.00119	0.593386
<i>MFSD12</i>	rs6510760	G	A	NorthAsians	Oceanians	-0.001476	6.69E-04	0.027402
<i>MFSD12</i>	rs112332856	T	C	NorthAsians	Oceanians	-0.002041	7.73E-04	0.008293
<i>ASIP</i>	rs6119471	G	C	NorthAsians	Oceanians	6.35E-04	0.00119	0.593386
<i>ASIP</i>	rs6058017	G	A	NorthAsians	Oceanians	0.001111	7.05E-04	0.115076
<i>PIGU</i>	rs2378249	A	G	NorthAsians	Oceanians	3.90E-04	6.70E-04	0.560041
<i>SLC45A2</i>	rs16891982	C	G	NorthAsians	EastAsians	0.001997	5.71E-04	4.71E-04
<i>SLC45A2</i>	rs28777	C	A	NorthAsians	EastAsians	2.38E-04	5.38E-04	0.657895
<i>SLC45A2</i>	rs26722	C	T	NorthAsians	EastAsians	-4.67E-04	5.31E-04	0.378937
<i>EXOC2</i>	rs4959270	C	A	NorthAsians	EastAsians	-1.62E-04	5.30E-04	0.759375
<i>TYRP1</i>	rs1408799	T	C	NorthAsians	EastAsians	6.00E-06	6.46E-04	0.992184

<i>TYRP1</i>	rs683	A	C	NorthAsians	EastAsians	-0.001162	6.01E-04	0.053093
<i>BNC2</i>	rs10756819	G	A	NorthAsians	EastAsians	3.40E-05	5.28E-04	0.948733
<i>BNC2</i>	rs12350739	G	A	NorthAsians	EastAsians	0.001035	6.65E-04	0.119833
<i>DDB1</i>	rs11230664	C	T	NorthAsians	EastAsians	0.002143	0.001209	0.076471
<i>DDB1</i>	rs7120594	T	C	NorthAsians	EastAsians	0.002143	0.001209	0.076471
<i>DDB1</i>	rs7948623	A	T	NorthAsians	EastAsians	1.30E-04	0.001274	0.918425
<i>DDB1</i>	rs1377457	C	A	NorthAsians	EastAsians	8.83E-04	0.001224	0.470813
<i>TPCN2</i>	rs35264875	A	T	NorthAsians	EastAsians	7.44E-04	6.52E-04	0.253889
<i>TPCN2</i>	rs3829241	G	A	NorthAsians	EastAsians	4.87E-04	5.30E-04	0.358337
<i>TYR</i>	rs1042602	C	A	NorthAsians	EastAsians	0.002093	7.99E-04	0.008792
<i>TYR</i>	rs1393350	G	A	NorthAsians	EastAsians	9.79E-04	9.13E-04	0.28368
<i>TYR</i>	rs1126809	G	A	NorthAsians	EastAsians	0.001632	0.001029	0.112903
<i>KITLG</i>	rs642742	A	G	NorthAsians	EastAsians	4.33E-04	5.40E-04	0.422821
<i>KITLG</i>	rs12821256	T	C	NorthAsians	EastAsians	7.83E-04	0.001359	0.564616
<i>DCT</i>	rs1407995	T	C	NorthAsians	EastAsians	1.19E-04	5.31E-04	0.822512
<i>DCT</i>	rs2031526	G	A	NorthAsians	EastAsians	-1.25E-04	5.31E-04	0.813192
<i>SLC24A4</i>	rs12896399	G	T	NorthAsians	EastAsians	-4.70E-05	5.30E-04	0.928955
<i>SLC24A4</i>	rs2402130	G	A	NorthAsians	EastAsians	-6.70E-04	5.43E-04	0.217046
<i>OCA2</i>	rs2311843	C	T	NorthAsians	EastAsians	-4.50E-05	5.33E-04	0.933321
<i>OCA2</i>	rs1800414	A	G	NorthAsians	EastAsians	-0.002186	5.52E-04	7.40E-05
<i>OCA2</i>	rs1800404	C	T	NorthAsians	EastAsians	0.0018	5.40E-04	8.52E-04
<i>OCA2</i>	rs1800401	C	T	NorthAsians	EastAsians	9.92E-04	6.41E-04	0.122014
<i>HERC2</i>	rs1129038	G	A	NorthAsians	EastAsians	0.001182	7.99E-04	0.139204
<i>HERC2</i>	rs12913832	A	G	NorthAsians	EastAsians	0.001375	8.22E-04	0.094386
<i>HERC2</i>	rs916977	A	G	NorthAsians	EastAsians	1.14E-04	5.30E-04	0.829383
<i>HERC2</i>	rs1667394	G	A	NorthAsians	EastAsians	1.16E-04	5.30E-04	0.826312

<i>SLC24A5</i>	rs1426654	G	A	NorthAsians	EastAsians	0.002017	5.61E-04	3.21E-04
<i>MYO5A</i>	rs4776053	C	T	NorthAsians	EastAsians	7.61E-04	5.30E-04	0.1509
<i>MC1R</i>	rs2228479	G	A	NorthAsians	EastAsians	2.90E-05	5.30E-04	0.956249
<i>MC1R</i>	rs885479	G	A	NorthAsians	EastAsians	5.40E-05	5.29E-04	0.918692
<i>MFSD12</i>	rs56203814	C	T	NorthAsians	EastAsians	0.001629	0.001624	0.315933
<i>MFSD12</i>	rs10424065	C	T	NorthAsians	EastAsians	7.83E-04	0.001359	0.564616
<i>MFSD12</i>	rs6510760	G	A	NorthAsians	EastAsians	-3.00E-06	5.71E-04	0.996409
<i>MFSD12</i>	rs112332856	T	C	NorthAsians	EastAsians	2.50E-04	8.55E-04	0.769913
<i>ASIP</i>	rs6119471	G	C	NorthAsians	EastAsians	-0.001629	0.001624	0.315933
<i>ASIP</i>	rs6058017	G	A	NorthAsians	EastAsians	0.002077	6.35E-04	0.001071
<i>PIGU</i>	rs2378249	A	G	NorthAsians	EastAsians	4.42E-04	5.32E-04	0.405868
<i>SLC45A2</i>	rs16891982	C	G	NorthAsians	EastAfricans	8.87E-04	7.11E-04	0.21234
<i>SLC45A2</i>	rs28777	C	A	NorthAsians	EastAfricans	-2.13E-04	6.41E-04	0.740327
<i>SLC45A2</i>	rs26722	C	T	NorthAsians	EastAfricans	6.67E-04	6.52E-04	0.306577
<i>EXOC2</i>	rs4959270	C	A	NorthAsians	EastAfricans	7.26E-04	6.52E-04	0.26576
<i>TYRP1</i>	rs1408799	T	C	NorthAsians	EastAfricans	-0.001054	6.63E-04	0.11218
<i>TYRP1</i>	rs683	A	C	NorthAsians	EastAfricans	6.40E-04	6.50E-04	0.325313
<i>BNC2</i>	rs10756819	G	A	NorthAsians	EastAfricans	0.001578	6.80E-04	0.020383
<i>BNC2</i>	rs12350739	G	A	NorthAsians	EastAfricans	6.41E-04	8.53E-04	0.45233
<i>DDB1</i>	rs11230664	C	T	NorthAsians	EastAfricans	0.003418	8.48E-04	5.50E-05
<i>DDB1</i>	rs7120594	T	C	NorthAsians	EastAfricans	0.0029	8.39E-04	5.48E-04
<i>DDB1</i>	rs7948623	A	T	NorthAsians	EastAfricans	-0.002597	8.38E-04	0.001932
<i>DDB1</i>	rs1377457	C	A	NorthAsians	EastAfricans	0.00348	8.50E-04	4.20E-05
<i>TPCN2</i>	rs35264875	A	T	NorthAsians	EastAfricans	-8.49E-04	6.62E-04	0.199751
<i>TPCN2</i>	rs3829241	G	A	NorthAsians	EastAfricans	0.001194	6.80E-04	0.079327
<i>TYR</i>	rs1042602	C	A	NorthAsians	EastAfricans	5.99E-04	8.55E-04	0.48367

<i>TYR</i>	rs1393350	G	A	NorthAsians	EastAfricans	1.71E-04	8.92E-04	0.848096
<i>TYR</i>	rs1126809	G	A	NorthAsians	EastAfricans	1.71E-04	8.92E-04	0.848096
<i>KITLG</i>	rs642742	A	G	NorthAsians	EastAfricans	0.001497	6.46E-04	0.020482
<i>KITLG</i>	rs12821256	T	C	NorthAsians	EastAfricans	-0.001347	8.46E-04	0.111491
<i>DCT</i>	rs1407995	T	C	NorthAsians	EastAfricans	-9.80E-04	6.42E-04	0.126771
<i>DCT</i>	rs2031526	G	A	NorthAsians	EastAfricans	0.001545	6.59E-04	0.019011
<i>SLC24A4</i>	rs12896399	G	T	NorthAsians	EastAfricans	7.73E-04	6.52E-04	0.235596
<i>SLC24A4</i>	rs2402130	G	A	NorthAsians	EastAfricans	7.24E-04	6.40E-04	0.258123
<i>OCA2</i>	rs2311843	C	T	NorthAsians	EastAfricans	0.002135	7.09E-04	0.002614
<i>OCA2</i>	rs1800414	A	G	NorthAsians	EastAfricans	0.001157	8.40E-04	0.168583
<i>OCA2</i>	rs1800404	C	T	NorthAsians	EastAfricans	0.001969	6.63E-04	0.002979
<i>OCA2</i>	rs1800401	C	T	NorthAsians	EastAfricans	-1.46E-04	6.78E-04	0.829763
<i>HERC2</i>	rs1129038	G	A	NorthAsians	EastAfricans	3.69E-04	8.70E-04	0.671346
<i>HERC2</i>	rs12913832	A	G	NorthAsians	EastAfricans	3.69E-04	8.70E-04	0.671346
<i>HERC2</i>	rs916977	A	G	NorthAsians	EastAfricans	0.001139	6.81E-04	0.094325
<i>HERC2</i>	rs1667394	G	A	NorthAsians	EastAfricans	0.001139	6.81E-04	0.094325
<i>SLC24A5</i>	rs1426654	G	A	NorthAsians	EastAfricans	6.60E-04	6.70E-04	0.324444
<i>MYO5A</i>	rs4776053	C	T	NorthAsians	EastAfricans	8.34E-04	6.52E-04	0.200935
<i>MC1R</i>	rs2228479	G	A	NorthAsians	EastAfricans	0.001772	8.37E-04	0.034127
<i>MC1R</i>	rs885479	G	A	NorthAsians	EastAfricans	0.002309	8.36E-04	0.005774
<i>MFSD12</i>	rs56203814	C	T	NorthAsians	EastAfricans	-0.001695	8.40E-04	0.043614
<i>MFSD12</i>	rs10424065	C	T	NorthAsians	EastAfricans	-0.0025	8.37E-04	0.002835
<i>MFSD12</i>	rs6510760	G	A	NorthAsians	EastAfricans	-0.002355	6.68E-04	4.27E-04
<i>MFSD12</i>	rs112332856	T	C	NorthAsians	EastAfricans	-0.003174	7.30E-04	1.40E-05
<i>ASIP</i>	rs6119471	G	C	NorthAsians	EastAfricans	0.002038	8.38E-04	0.014996
<i>ASIP</i>	rs6058017	G	A	NorthAsians	EastAfricans	0.001952	6.63E-04	0.003258

<i>PIGU</i>	rs2378249	A	G	NorthAsians	EastAfricans	6.67E-04	6.52E-04	0.306577
<i>SLC45A2</i>	rs16891982	C	G	NorthAsians	WestAfricans	0.001087	5.44E-04	0.045692
<i>SLC45A2</i>	rs28777	C	A	NorthAsians	WestAfricans	2.00E-06	5.19E-04	0.997565
<i>SLC45A2</i>	rs26722	C	T	NorthAsians	WestAfricans	6.09E-04	5.20E-04	0.240886
<i>EXOC2</i>	rs4959270	C	A	NorthAsians	WestAfricans	1.29E-04	5.18E-04	0.803923
<i>TYRP1</i>	rs1408799	T	C	NorthAsians	WestAfricans	-7.09E-04	5.36E-04	0.185954
<i>TYRP1</i>	rs683	A	C	NorthAsians	WestAfricans	2.45E-04	5.26E-04	0.641416
<i>BNC2</i>	rs10756819	G	A	NorthAsians	WestAfricans	8.84E-04	5.19E-04	0.088369
<i>BNC2</i>	rs12350739	G	A	NorthAsians	WestAfricans	6.60E-04	5.67E-04	0.244361
<i>DDB1</i>	rs11230664	C	T	NorthAsians	WestAfricans	0.002097	6.71E-04	0.001773
<i>DDB1</i>	rs7120594	T	C	NorthAsians	WestAfricans	0.00197	6.71E-04	0.003326
<i>DDB1</i>	rs7948623	A	T	NorthAsians	WestAfricans	-0.00149	6.71E-04	0.026434
<i>DDB1</i>	rs1377457	C	A	NorthAsians	WestAfricans	0.002116	6.71E-04	0.001611
<i>TPCN2</i>	rs35264875	A	T	NorthAsians	WestAfricans	3.46E-04	5.46E-04	0.525583
<i>TPCN2</i>	rs3829241	G	A	NorthAsians	WestAfricans	8.71E-04	5.21E-04	0.094207
<i>TYR</i>	rs1042602	C	A	NorthAsians	WestAfricans	5.24E-04	5.59E-04	0.348536
<i>TYR</i>	rs1393350	G	A	NorthAsians	WestAfricans	7.78E-04	7.15E-04	0.276486
<i>TYR</i>	rs1126809	G	A	NorthAsians	WestAfricans	1.87E-04	5.95E-04	0.752689
<i>KITLG</i>	rs642742	A	G	NorthAsians	WestAfricans	0.001333	5.20E-04	0.010391
<i>KITLG</i>	rs12821256	T	C	NorthAsians	WestAfricans	4.44E-04	7.96E-04	0.577185
<i>DCT</i>	rs1407995	T	C	NorthAsians	WestAfricans	-6.74E-04	5.18E-04	0.193307
<i>DCT</i>	rs2031526	G	A	NorthAsians	WestAfricans	0.001135	5.19E-04	0.028743
<i>SLC24A4</i>	rs12896399	G	T	NorthAsians	WestAfricans	0.001583	5.52E-04	0.004124
<i>SLC24A4</i>	rs2402130	G	A	NorthAsians	WestAfricans	7.00E-04	5.19E-04	0.177234
<i>OCA2</i>	rs2311843	C	T	NorthAsians	WestAfricans	0.001468	5.21E-04	0.004867
<i>OCA2</i>	rs1800414	A	G	NorthAsians	WestAfricans	0.001555	6.75E-04	0.021184

<i>OCA2</i>	rs1800404	C	T	NorthAsians	WestAfricans	0.001201	5.20E-04	0.020896
<i>OCA2</i>	rs1800401	C	T	NorthAsians	WestAfricans	-5.74E-04	5.31E-04	0.280179
<i>HERC2</i>	rs1129038	G	A	NorthAsians	WestAfricans	2.35E-04	5.67E-04	0.678681
<i>HERC2</i>	rs12913832	A	G	NorthAsians	WestAfricans	2.35E-04	5.67E-04	0.678681
<i>HERC2</i>	rs916977	A	G	NorthAsians	WestAfricans	4.95E-04	5.19E-04	0.33946
<i>HERC2</i>	rs1667394	G	A	NorthAsians	WestAfricans	5.38E-04	5.19E-04	0.30001
<i>SLC24A5</i>	rs1426654	G	A	NorthAsians	WestAfricans	3.62E-04	5.21E-04	0.486252
<i>MYO5A</i>	rs4776053	C	T	NorthAsians	WestAfricans	5.67E-04	5.18E-04	0.273699
<i>MC1R</i>	rs2228479	G	A	NorthAsians	WestAfricans	0.00204	6.72E-04	0.002397
<i>MC1R</i>	rs885479	G	A	NorthAsians	WestAfricans	0.002462	6.72E-04	2.46E-04
<i>MFSD12</i>	rs56203814	C	T	NorthAsians	WestAfricans	-0.001463	6.71E-04	0.029258
<i>MFSD12</i>	rs10424065	C	T	NorthAsians	WestAfricans	-0.001619	6.71E-04	0.01582
<i>MFSD12</i>	rs6510760	G	A	NorthAsians	WestAfricans	-0.001475	5.24E-04	0.004891
<i>MFSD12</i>	rs112332856	T	C	NorthAsians	WestAfricans	-0.001961	5.73E-04	6.16E-04
<i>ASIP</i>	rs6119471	G	C	NorthAsians	WestAfricans	0.002184	6.71E-04	0.001134
<i>ASIP</i>	rs6058017	G	A	NorthAsians	WestAfricans	0.001673	5.36E-04	0.001802
<i>PIGU</i>	rs2378249	A	G	NorthAsians	WestAfricans	1.95E-04	5.18E-04	0.707335
<i>SLC45A2</i>	rs16891982	C	G	Oceanians	EastAsians	0.001089	6.67E-04	0.102701
<i>SLC45A2</i>	rs28777	C	A	Oceanians	EastAsians	8.66E-04	6.28E-04	0.167747
<i>SLC45A2</i>	rs26722	C	T	Oceanians	EastAsians	-3.81E-04	6.32E-04	0.546907
<i>EXOC2</i>	rs4959270	C	A	Oceanians	EastAsians	0.001306	6.43E-04	0.042308
<i>TYRP1</i>	rs1408799	T	C	Oceanians	EastAsians	8.90E-05	7.45E-04	0.904817
<i>TYRP1</i>	rs683	A	C	Oceanians	EastAsians	-4.27E-04	7.49E-04	0.568553
<i>BNC2</i>	rs10756819	G	A	Oceanians	EastAsians	-1.10E-04	6.27E-04	0.860449
<i>BNC2</i>	rs12350739	G	A	Oceanians	EastAsians	1.45E-04	9.51E-04	0.8785
<i>DDB1</i>	rs11230664	C	T	Oceanians	EastAsians	-0.001606	6.30E-04	0.010798

<i>DDB1</i>	rs7120594	T	C	Oceanians	EastAsians	-0.001606	6.30E-04	0.010798
<i>DDB1</i>	rs7948623	A	T	Oceanians	EastAsians	0.002989	6.82E-04	1.20E-05
<i>DDB1</i>	rs1377457	C	A	Oceanians	EastAsians	-0.002425	6.42E-04	1.59E-04
<i>TPCN2</i>	rs35264875	A	T	Oceanians	EastAsians	0.002225	6.40E-04	5.03E-04
<i>TPCN2</i>	rs3829241	G	A	Oceanians	EastAsians	-7.46E-04	6.73E-04	0.267951
<i>TYR</i>	rs1042602	C	A	Oceanians	EastAsians	8.89E-04	9.91E-04	0.369733
<i>TYR</i>	rs1393350	G	A	Oceanians	EastAsians	7.20E-04	9.76E-04	0.460701
<i>TYR</i>	rs1126809	G	A	Oceanians	EastAsians	0.001144	0.001024	0.26368
<i>KITLG</i>	rs642742	A	G	Oceanians	EastAsians	2.10E-05	6.34E-04	0.973094
<i>KITLG</i>	rs12821256	T	C	Oceanians	EastAsians	0.001144	0.001024	0.26368
<i>DCT</i>	rs1407995	T	C	Oceanians	EastAsians	6.52E-04	6.28E-04	0.298811
<i>DCT</i>	rs2031526	G	A	Oceanians	EastAsians	-6.56E-04	6.28E-04	0.295756
<i>SLC24A4</i>	rs12896399	G	T	Oceanians	EastAsians	5.03E-04	6.28E-04	0.422541
<i>SLC24A4</i>	rs2402130	G	A	Oceanians	EastAsians	-5.17E-04	6.40E-04	0.418887
<i>OCA2</i>	rs2311843	C	T	Oceanians	EastAsians	-5.32E-04	6.28E-04	0.396381
<i>OCA2</i>	rs1800414	A	G	Oceanians	EastAsians	-8.29E-04	6.33E-04	0.190345
<i>OCA2</i>	rs1800404	C	T	Oceanians	EastAsians	-1.68E-04	6.29E-04	0.789951
<i>OCA2</i>	rs1800401	C	T	Oceanians	EastAsians	2.40E-05	9.48E-04	0.979833
<i>HERC2</i>	rs1129038	G	A	Oceanians	EastAsians	5.94E-04	9.68E-04	0.539336
<i>HERC2</i>	rs12913832	A	G	Oceanians	EastAsians	7.20E-04	9.76E-04	0.460701
<i>HERC2</i>	rs916977	A	G	Oceanians	EastAsians	4.50E-04	6.27E-04	0.473124
<i>HERC2</i>	rs1667394	G	A	Oceanians	EastAsians	4.51E-04	6.27E-04	0.471789
<i>SLC24A5</i>	rs1426654	G	A	Oceanians	EastAsians	3.31E-04	7.48E-04	0.658389
<i>MYO5A</i>	rs4776053	C	T	Oceanians	EastAsians	-0.001076	7.41E-04	0.146351
<i>MC1R</i>	rs2228479	G	A	Oceanians	EastAsians	-6.02E-04	6.47E-04	0.351911
<i>MC1R</i>	rs885479	G	A	Oceanians	EastAsians	-0.00184	6.94E-04	0.008036

<i>MFSD12</i>	rs56203814	C	T	Oceanians	EastAsians	0.001694	0.001175	0.149534
<i>MFSD12</i>	rs10424065	C	T	Oceanians	EastAsians	0.001144	0.001024	0.26368
<i>MFSD12</i>	rs6510760	G	A	Oceanians	EastAsians	0.001475	6.29E-04	0.019026
<i>MFSD12</i>	rs112332856	T	C	Oceanians	EastAsians	0.002203	6.52E-04	7.21E-04
<i>ASIP</i>	rs6119471	G	C	Oceanians	EastAsians	-0.001694	0.001175	0.149534
<i>ASIP</i>	rs6058017	G	A	Oceanians	EastAsians	2.40E-04	6.38E-04	0.707433
<i>PIGU</i>	rs2378249	A	G	Oceanians	EastAsians	-1.03E-04	6.41E-04	0.872447
<i>SLC45A2</i>	rs16891982	C	G	Oceanians	EastAfricans	7.26E-04	7.29E-04	0.318758
<i>SLC45A2</i>	rs28777	C	A	Oceanians	EastAfricans	3.35E-04	6.44E-04	0.603448
<i>SLC45A2</i>	rs26722	C	T	Oceanians	EastAfricans	6.08E-04	6.59E-04	0.356442
<i>EXOC2</i>	rs4959270	C	A	Oceanians	EastAfricans	0.001811	6.65E-04	0.006465
<i>TYRP1</i>	rs1408799	T	C	Oceanians	EastAfricans	-9.88E-04	7.12E-04	0.164947
<i>TYRP1</i>	rs683	A	C	Oceanians	EastAfricans	8.92E-04	7.13E-04	0.210637
<i>BNC2</i>	rs10756819	G	A	Oceanians	EastAfricans	0.001476	6.84E-04	0.031069
<i>BNC2</i>	rs12350739	G	A	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>DDB1</i>	rs11230664	C	T	Oceanians	EastAfricans	0.001111	6.56E-04	0.090412
<i>DDB1</i>	rs7120594	T	C	Oceanians	EastAfricans	5.94E-04	6.45E-04	0.357396
<i>DDB1</i>	rs7948623	A	T	Oceanians	EastAfricans	-3.64E-04	6.43E-04	0.57195
<i>DDB1</i>	rs1377457	C	A	Oceanians	EastAfricans	0.001174	6.59E-04	0.074815
<i>TPCN2</i>	rs35264875	A	T	Oceanians	EastAfricans	4.90E-04	6.46E-04	0.448032
<i>TPCN2</i>	rs3829241	G	A	Oceanians	EastAfricans	3.77E-04	7.10E-04	0.59576
<i>TYR</i>	rs1042602	C	A	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>TYR</i>	rs1393350	G	A	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>TYR</i>	rs1126809	G	A	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>KITLG</i>	rs642742	A	G	Oceanians	EastAfricans	0.001297	6.52E-04	0.04667
<i>KITLG</i>	rs12821256	T	C	Oceanians	EastAfricans	-8.58E-04	8.47E-04	0.310831

<i>DCT</i>	rs1407995	T	C	Oceanians	EastAfricans	-5.38E-04	6.46E-04	0.404862
<i>DCT</i>	rs2031526	G	A	Oceanians	EastAfricans	0.001103	6.63E-04	0.096146
<i>SLC24A4</i>	rs12896399	G	T	Oceanians	EastAfricans	0.001184	6.56E-04	0.071209
<i>SLC24A4</i>	rs2402130	G	A	Oceanians	EastAfricans	6.62E-04	6.49E-04	0.308068
<i>OCA2</i>	rs2311843	C	T	Oceanians	EastAfricans	0.001748	7.13E-04	0.014191
<i>OCA2</i>	rs1800414	A	G	Oceanians	EastAfricans	0.001612	8.42E-04	0.055664
<i>OCA2</i>	rs1800404	C	T	Oceanians	EastAfricans	9.40E-04	6.66E-04	0.158276
<i>OCA2</i>	rs1800401	C	T	Oceanians	EastAfricans	-6.23E-04	8.55E-04	0.466227
<i>HERC2</i>	rs1129038	G	A	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>HERC2</i>	rs12913832	A	G	Oceanians	EastAfricans	2.35E-04	9.97E-04	0.813429
<i>HERC2</i>	rs916977	A	G	Oceanians	EastAfricans	0.001428	6.85E-04	0.036998
<i>HERC2</i>	rs1667394	G	A	Oceanians	EastAfricans	0.001428	6.85E-04	0.036998
<i>SLC24A5</i>	rs1426654	G	A	Oceanians	EastAfricans	-9.40E-05	7.37E-04	0.898072
<i>MYO5A</i>	rs4776053	C	T	Oceanians	EastAfricans	-3.75E-04	7.23E-04	0.604181
<i>MC1R</i>	rs2228479	G	A	Oceanians	EastAfricans	0.001295	8.48E-04	0.126915
<i>MC1R</i>	rs885479	G	A	Oceanians	EastAfricans	8.67E-04	8.70E-04	0.319434
<i>MFSD12</i>	rs56203814	C	T	Oceanians	EastAfricans	-0.001207	8.41E-04	0.151188
<i>MFSD12</i>	rs10424065	C	T	Oceanians	EastAfricans	-0.002011	8.38E-04	0.016387
<i>MFSD12</i>	rs6510760	G	A	Oceanians	EastAfricans	-0.001219	6.65E-04	0.066782
<i>MFSD12</i>	rs112332856	T	C	Oceanians	EastAfricans	-0.001604	6.67E-04	0.016127
<i>ASIP</i>	rs6119471	G	C	Oceanians	EastAfricans	0.00155	8.38E-04	0.06457
<i>ASIP</i>	rs6058017	G	A	Oceanians	EastAfricans	0.001098	6.51E-04	0.091568
<i>PIGU</i>	rs2378249	A	G	Oceanians	EastAfricans	3.67E-04	6.64E-04	0.580531
<i>SLC45A2</i>	rs16891982	C	G	Oceanians	WestAfricans	9.61E-04	5.60E-04	0.086576
<i>SLC45A2</i>	rs28777	C	A	Oceanians	WestAfricans	4.33E-04	5.24E-04	0.408818
<i>SLC45A2</i>	rs26722	C	T	Oceanians	WestAfricans	5.63E-04	5.27E-04	0.286

<i>EXOC2</i>	rs4959270	C	A	Oceanians	WestAfricans	9.84E-04	5.31E-04	0.063704
<i>TYRP1</i>	rs1408799	T	C	Oceanians	WestAfricans	-6.57E-04	5.76E-04	0.253421
<i>TYRP1</i>	rs683	A	C	Oceanians	WestAfricans	4.44E-04	5.76E-04	0.441185
<i>BNC2</i>	rs10756819	G	A	Oceanians	WestAfricans	8.03E-04	5.25E-04	0.125638
<i>BNC2</i>	rs12350739	G	A	Oceanians	WestAfricans	3.40E-04	7.00E-04	0.626702
<i>DDB1</i>	rs11230664	C	T	Oceanians	WestAfricans	2.80E-04	5.24E-04	0.592903
<i>DDB1</i>	rs7120594	T	C	Oceanians	WestAfricans	1.52E-04	5.23E-04	0.771004
<i>DDB1</i>	rs7948623	A	T	Oceanians	WestAfricans	2.70E-04	5.24E-04	0.605794
<i>DDB1</i>	rs1377457	C	A	Oceanians	WestAfricans	2.99E-04	5.24E-04	0.568196
<i>TPCN2</i>	rs35264875	A	T	Oceanians	WestAfricans	0.001402	5.36E-04	0.008884
<i>TPCN2</i>	rs3829241	G	A	Oceanians	WestAfricans	2.27E-04	5.47E-04	0.677517
<i>TYR</i>	rs1042602	C	A	Oceanians	WestAfricans	2.38E-04	6.92E-04	0.730883
<i>TYR</i>	rs1393350	G	A	Oceanians	WestAfricans	8.29E-04	7.98E-04	0.299012
<i>TYR</i>	rs1126809	G	A	Oceanians	WestAfricans	2.38E-04	6.92E-04	0.730883
<i>KITLG</i>	rs642742	A	G	Oceanians	WestAfricans	0.001175	5.27E-04	0.025836
<i>KITLG</i>	rs12821256	T	C	Oceanians	WestAfricans	8.29E-04	7.98E-04	0.299012
<i>DCT</i>	rs1407995	T	C	Oceanians	WestAfricans	-3.25E-04	5.24E-04	0.534328
<i>DCT</i>	rs2031526	G	A	Oceanians	WestAfricans	7.87E-04	5.25E-04	0.133799
<i>SLC24A4</i>	rs12896399	G	T	Oceanians	WestAfricans	0.001906	5.57E-04	6.26E-04
<i>SLC24A4</i>	rs2402130	G	A	Oceanians	WestAfricans	6.51E-04	5.28E-04	0.217798
<i>OCA2</i>	rs2311843	C	T	Oceanians	WestAfricans	0.001163	5.27E-04	0.027279
<i>OCA2</i>	rs1800414	A	G	Oceanians	WestAfricans	0.001913	6.78E-04	0.004789
<i>OCA2</i>	rs1800404	C	T	Oceanians	WestAfricans	3.90E-04	5.25E-04	0.457676
<i>OCA2</i>	rs1800401	C	T	Oceanians	WestAfricans	-9.50E-04	6.74E-04	0.158555
<i>HERC2</i>	rs1129038	G	A	Oceanians	WestAfricans	1.29E-04	6.87E-04	0.850487
<i>HERC2</i>	rs12913832	A	G	Oceanians	WestAfricans	1.29E-04	6.87E-04	0.850487

<i>HERC2</i>	rs916977	A	G	Oceanians	WestAfricans	7.23E-04	5.24E-04	0.167892
<i>HERC2</i>	rs1667394	G	A	Oceanians	WestAfricans	7.65E-04	5.25E-04	0.144519
<i>SLC24A5</i>	rs1426654	G	A	Oceanians	WestAfricans	-2.32E-04	5.77E-04	0.687656
<i>MYO5A</i>	rs4776053	C	T	Oceanians	WestAfricans	-3.85E-04	5.76E-04	0.504393
<i>MC1R</i>	rs2228479	G	A	Oceanians	WestAfricans	0.001664	6.83E-04	0.014853
<i>MC1R</i>	rs885479	G	A	Oceanians	WestAfricans	0.001326	7.00E-04	0.05814
<i>MFSD12</i>	rs56203814	C	T	Oceanians	WestAfricans	-0.001078	6.73E-04	0.109476
<i>MFSD12</i>	rs10424065	C	T	Oceanians	WestAfricans	-0.001234	6.73E-04	0.066848
<i>MFSD12</i>	rs6510760	G	A	Oceanians	WestAfricans	-5.80E-04	5.24E-04	0.268324
<i>MFSD12</i>	rs112332856	T	C	Oceanians	WestAfricans	-7.24E-04	5.25E-04	0.167624
<i>ASIP</i>	rs6119471	G	C	Oceanians	WestAfricans	0.001799	6.73E-04	0.007547
<i>ASIP</i>	rs6058017	G	A	Oceanians	WestAfricans	9.99E-04	5.29E-04	0.058665
<i>PIGU</i>	rs2378249	A	G	Oceanians	WestAfricans	-4.20E-05	5.30E-04	0.936817
<i>SLC45A2</i>	rs16891982	C	G	EastAsians	EastAfricans	-1.11E-04	7.02E-04	0.873917
<i>SLC45A2</i>	rs28777	C	A	EastAsians	EastAfricans	-3.32E-04	6.27E-04	0.596567
<i>SLC45A2</i>	rs26722	C	T	EastAsians	EastAfricans	9.01E-04	6.39E-04	0.158605
<i>EXOC2</i>	rs4959270	C	A	EastAsians	EastAfricans	8.07E-04	6.39E-04	0.206507
<i>TYRP1</i>	rs1408799	T	C	EastAsians	EastAfricans	-0.001057	6.29E-04	0.093125
<i>TYRP1</i>	rs683	A	C	EastAsians	EastAfricans	0.001221	6.33E-04	0.053946
<i>BNC2</i>	rs10756819	G	A	EastAsians	EastAfricans	0.001561	6.68E-04	0.019443
<i>BNC2</i>	rs12350739	G	A	EastAsians	EastAfricans	1.24E-04	8.34E-04	0.882304
<i>DDB1</i>	rs11230664	C	T	EastAsians	EastAfricans	0.002346	6.40E-04	2.48E-04
<i>DDB1</i>	rs7120594	T	C	EastAsians	EastAfricans	0.001829	6.29E-04	0.003637
<i>DDB1</i>	rs7948623	A	T	EastAsians	EastAfricans	-0.002662	6.58E-04	5.20E-05
<i>DDB1</i>	rs1377457	C	A	EastAsians	EastAfricans	0.003039	6.50E-04	3.00E-06
<i>TPCN2</i>	rs35264875	A	T	EastAsians	EastAfricans	-0.001222	6.35E-04	0.05446

<i>TPCN2</i>	rs3829241	G	A	EastAsians	EastAfricans	9.51E-04	6.68E-04	0.154736
<i>TYR</i>	rs1042602	C	A	EastAsians	EastAfricans	-4.48E-04	8.61E-04	0.602762
<i>TYR</i>	rs1393350	G	A	EastAsians	EastAfricans	-3.19E-04	8.51E-04	0.708248
<i>TYR</i>	rs1126809	G	A	EastAsians	EastAfricans	-6.45E-04	8.84E-04	0.465599
<i>KITLG</i>	rs642742	A	G	EastAsians	EastAfricans	0.001281	6.31E-04	0.0423
<i>KITLG</i>	rs12821256	T	C	EastAsians	EastAfricans	-0.001738	7.10E-04	0.014326
<i>DCT</i>	rs1407995	T	C	EastAsians	EastAfricans	-0.00104	6.28E-04	0.098027
<i>DCT</i>	rs2031526	G	A	EastAsians	EastAfricans	0.001607	6.45E-04	0.012763
<i>SLC24A4</i>	rs12896399	G	T	EastAsians	EastAfricans	7.97E-04	6.39E-04	0.212191
<i>SLC24A4</i>	rs2402130	G	A	EastAsians	EastAfricans	0.001059	6.26E-04	0.090478
<i>OCA2</i>	rs2311843	C	T	EastAsians	EastAfricans	0.002157	6.97E-04	0.001962
<i>OCA2</i>	rs1800414	A	G	EastAsians	EastAfricans	0.002249	8.26E-04	0.006478
<i>OCA2</i>	rs1800404	C	T	EastAsians	EastAfricans	0.001069	6.48E-04	0.099004
<i>OCA2</i>	rs1800401	C	T	EastAsians	EastAfricans	-6.41E-04	6.56E-04	0.327988
<i>HERC2</i>	rs1129038	G	A	EastAsians	EastAfricans	-2.22E-04	8.46E-04	0.79322
<i>HERC2</i>	rs12913832	A	G	EastAsians	EastAfricans	-3.19E-04	8.51E-04	0.708248
<i>HERC2</i>	rs916977	A	G	EastAsians	EastAfricans	0.001082	6.68E-04	0.105386
<i>HERC2</i>	rs1667394	G	A	EastAsians	EastAfricans	0.00108	6.68E-04	0.105724
<i>SLC24A5</i>	rs1426654	G	A	EastAsians	EastAfricans	-3.49E-04	6.60E-04	0.597169
<i>MYO5A</i>	rs4776053	C	T	EastAsians	EastAfricans	4.53E-04	6.39E-04	0.478246
<i>MC1R</i>	rs2228479	G	A	EastAsians	EastAfricans	0.001758	8.26E-04	0.033387
<i>MC1R</i>	rs885479	G	A	EastAsians	EastAfricans	0.002282	8.26E-04	0.005752
<i>MFSD12</i>	rs56203814	C	T	EastAsians	EastAfricans	-0.00251	8.31E-04	0.002534
<i>MFSD12</i>	rs10424065	C	T	EastAsians	EastAfricans	-0.002891	6.99E-04	3.60E-05
<i>MFSD12</i>	rs6510760	G	A	EastAsians	EastAfricans	-0.002354	6.49E-04	2.86E-04
<i>MFSD12</i>	rs112332856	T	C	EastAsians	EastAfricans	-0.003299	6.60E-04	1.00E-06

<i>ASIP</i>	rs6119471	G	C	EastAsians	EastAfricans	0.002852	8.29E-04	5.79E-04
<i>ASIP</i>	rs6058017	G	A	EastAsians	EastAfricans	9.13E-04	6.27E-04	0.144925
<i>PIGU</i>	rs2378249	A	G	EastAsians	EastAfricans	4.46E-04	6.39E-04	0.485309
<i>SLC45A2</i>	rs16891982	C	G	EastAsians	WestAfricans	3.00E-04	5.36E-04	0.575049
<i>SLC45A2</i>	rs28777	C	A	EastAsians	WestAfricans	-9.20E-05	5.07E-04	0.85544
<i>SLC45A2</i>	rs26722	C	T	EastAsians	WestAfricans	7.93E-04	5.08E-04	0.118286
<i>EXOC2</i>	rs4959270	C	A	EastAsians	WestAfricans	1.93E-04	5.06E-04	0.703733
<i>TYRP1</i>	rs1408799	T	C	EastAsians	WestAfricans	-7.11E-04	5.09E-04	0.16208
<i>TYRP1</i>	rs683	A	C	EastAsians	WestAfricans	7.02E-04	5.11E-04	0.169651
<i>BNC2</i>	rs10756819	G	A	EastAsians	WestAfricans	8.70E-04	5.07E-04	0.086276
<i>BNC2</i>	rs12350739	G	A	EastAsians	WestAfricans	2.52E-04	5.48E-04	0.64552
<i>DDB1</i>	rs11230664	C	T	EastAsians	WestAfricans	0.001253	5.07E-04	0.013528
<i>DDB1</i>	rs7120594	T	C	EastAsians	WestAfricans	0.001126	5.07E-04	0.026524
<i>DDB1</i>	rs7948623	A	T	EastAsians	WestAfricans	-0.001541	5.31E-04	0.003738
<i>DDB1</i>	rs1377457	C	A	EastAsians	WestAfricans	0.001768	5.13E-04	5.67E-04
<i>TPCN2</i>	rs35264875	A	T	EastAsians	WestAfricans	5.30E-05	5.24E-04	0.919283
<i>TPCN2</i>	rs3829241	G	A	EastAsians	WestAfricans	6.80E-04	5.09E-04	0.182182
<i>TYR</i>	rs1042602	C	A	EastAsians	WestAfricans	-3.00E-04	5.65E-04	0.59469
<i>TYR</i>	rs1393350	G	A	EastAsians	WestAfricans	3.92E-04	6.82E-04	0.565332
<i>TYR</i>	rs1126809	G	A	EastAsians	WestAfricans	-4.55E-04	5.86E-04	0.437031
<i>KITLG</i>	rs642742	A	G	EastAsians	WestAfricans	0.001162	5.07E-04	0.021928
<i>KITLG</i>	rs12821256	T	C	EastAsians	WestAfricans	1.35E-04	7.08E-04	0.8484
<i>DCT</i>	rs1407995	T	C	EastAsians	WestAfricans	-7.21E-04	5.06E-04	0.154743
<i>DCT</i>	rs2031526	G	A	EastAsians	WestAfricans	0.001185	5.08E-04	0.019612
<i>SLC24A4</i>	rs12896399	G	T	EastAsians	WestAfricans	0.001601	5.41E-04	0.00308
<i>SLC24A4</i>	rs2402130	G	A	EastAsians	WestAfricans	9.65E-04	5.07E-04	0.057024

<i>OCA2</i>	rs2311843	C	T	EastAsians	WestAfricans	0.001485	5.10E-04	0.00356
<i>OCA2</i>	rs1800414	A	G	EastAsians	WestAfricans	0.002416	6.63E-04	2.69E-04
<i>OCA2</i>	rs1800404	C	T	EastAsians	WestAfricans	4.91E-04	5.07E-04	0.332155
<i>OCA2</i>	rs1800401	C	T	EastAsians	WestAfricans	-9.64E-04	5.13E-04	0.06006
<i>HERC2</i>	rs1129038	G	A	EastAsians	WestAfricans	-2.31E-04	5.43E-04	0.670853
<i>HERC2</i>	rs12913832	A	G	EastAsians	WestAfricans	-3.07E-04	5.48E-04	0.575425
<i>HERC2</i>	rs916977	A	G	EastAsians	WestAfricans	4.50E-04	5.07E-04	0.374526
<i>HERC2</i>	rs1667394	G	A	EastAsians	WestAfricans	4.92E-04	5.07E-04	0.332331
<i>SLC24A5</i>	rs1426654	G	A	EastAsians	WestAfricans	-4.32E-04	5.12E-04	0.398198
<i>MYO5A</i>	rs4776053	C	T	EastAsians	WestAfricans	2.68E-04	5.07E-04	0.597823
<i>MC1R</i>	rs2228479	G	A	EastAsians	WestAfricans	0.002028	6.63E-04	0.00222
<i>MC1R</i>	rs885479	G	A	EastAsians	WestAfricans	0.002441	6.63E-04	2.32E-04
<i>MFSD12</i>	rs56203814	C	T	EastAsians	WestAfricans	-0.002104	6.63E-04	0.001509
<i>MFSD12</i>	rs10424065	C	T	EastAsians	WestAfricans	-0.001928	5.63E-04	6.22E-04
<i>MFSD12</i>	rs6510760	G	A	EastAsians	WestAfricans	-0.001474	5.07E-04	0.003679
<i>MFSD12</i>	rs112332856	T	C	EastAsians	WestAfricans	-0.00206	5.16E-04	6.60E-05
<i>ASIP</i>	rs6119471	G	C	EastAsians	WestAfricans	0.002826	6.63E-04	2.00E-05
<i>ASIP</i>	rs6058017	G	A	EastAsians	WestAfricans	8.54E-04	5.07E-04	0.091702
<i>PIGU</i>	rs2378249	A	G	EastAsians	WestAfricans	2.00E-05	5.07E-04	0.967942
<i>SLC45A2</i>	rs16891982	C	G	EastAfricans	WestAfricans	3.88E-04	3.41E-04	0.255086
<i>SLC45A2</i>	rs28777	C	A	EastAfricans	WestAfricans	1.69E-04	1.81E-04	0.351565
<i>SLC45A2</i>	rs26722	C	T	EastAfricans	WestAfricans	8.40E-05	2.10E-04	0.689776
<i>EXOC2</i>	rs4959270	C	A	EastAfricans	WestAfricans	-4.43E-04	2.06E-04	0.03162
<i>TYRP1</i>	rs1408799	T	C	EastAfricans	WestAfricans	1.22E-04	1.82E-04	0.503424
<i>TYRP1</i>	rs683	A	C	EastAfricans	WestAfricans	-2.59E-04	1.85E-04	0.160278
<i>BNC2</i>	rs10756819	G	A	EastAfricans	WestAfricans	-3.59E-04	2.59E-04	0.165122

<i>BNC2</i>	rs12350739	G	A	EastAfricans	WestAfricans	1.55E-04	4.99E-04	0.756223
<i>DDB1</i>	rs11230664	C	T	EastAfricans	WestAfricans	-5.95E-04	2.06E-04	0.003833
<i>DDB1</i>	rs7120594	T	C	EastAfricans	WestAfricans	-3.15E-04	1.83E-04	0.084296
<i>DDB1</i>	rs7948623	A	T	EastAfricans	WestAfricans	5.57E-04	1.79E-04	0.001852
<i>DDB1</i>	rs1377457	C	A	EastAfricans	WestAfricans	-6.26E-04	2.11E-04	0.003034
<i>TPCN2</i>	rs35264875	A	T	EastAfricans	WestAfricans	0.001016	2.16E-04	3.00E-06
<i>TPCN2</i>	rs3829241	G	A	EastAfricans	WestAfricans	-6.90E-05	2.63E-04	0.792385
<i>TYR</i>	rs1042602	C	A	EastAfricans	WestAfricans	5.30E-05	4.89E-04	0.914067
<i>TYR</i>	rs1393350	G	A	EastAfricans	WestAfricans	6.43E-04	6.29E-04	0.306763
<i>TYR</i>	rs1126809	G	A	EastAfricans	WestAfricans	5.30E-05	4.89E-04	0.914067
<i>KITLG</i>	rs642742	A	G	EastAfricans	WestAfricans	1.53E-04	1.92E-04	0.423979
<i>KITLG</i>	rs12821256	T	C	EastAfricans	WestAfricans	0.001505	4.73E-04	0.001479
<i>DCT</i>	rs1407995	T	C	EastAfricans	WestAfricans	9.90E-05	1.85E-04	0.594727
<i>DCT</i>	rs2031526	G	A	EastAfricans	WestAfricans	-8.20E-05	2.21E-04	0.712095
<i>SLC24A4</i>	rs12896399	G	T	EastAfricans	WestAfricans	9.73E-04	2.81E-04	5.26E-04
<i>SLC24A4</i>	rs2402130	G	A	EastAfricans	WestAfricans	1.30E-04	1.78E-04	0.464636
<i>OCA2</i>	rs2311843	C	T	EastAfricans	WestAfricans	-2.14E-04	3.06E-04	0.483851
<i>OCA2</i>	rs1800414	A	G	EastAfricans	WestAfricans	6.43E-04	6.29E-04	0.306763
<i>OCA2</i>	rs1800404	C	T	EastAfricans	WestAfricans	-3.51E-04	2.24E-04	0.11748
<i>OCA2</i>	rs1800401	C	T	EastAfricans	WestAfricans	-4.59E-04	2.24E-04	0.040104
<i>HERC2</i>	rs1129038	G	A	EastAfricans	WestAfricans	-5.60E-05	4.81E-04	0.90728
<i>HERC2</i>	rs12913832	A	G	EastAfricans	WestAfricans	-5.60E-05	4.81E-04	0.90728
<i>HERC2</i>	rs916977	A	G	EastAfricans	WestAfricans	-4.02E-04	2.59E-04	0.120361
<i>HERC2</i>	rs1667394	G	A	EastAfricans	WestAfricans	-3.59E-04	2.59E-04	0.165122
<i>SLC24A5</i>	rs1426654	G	A	EastAfricans	WestAfricans	-1.57E-04	2.39E-04	0.509837
<i>MYO5A</i>	rs4776053	C	T	EastAfricans	WestAfricans	-8.90E-05	2.08E-04	0.66729

<i>MC1R</i>	rs2228479	G	A	EastAfricans	WestAfricans	6.43E-04	6.29E-04	0.306763
<i>MC1R</i>	rs885479	G	A	EastAfricans	WestAfricans	6.43E-04	6.29E-04	0.306763
<i>MFSD12</i>	rs56203814	C	T	EastAfricans	WestAfricans	-1.27E-04	1.86E-04	0.494038
<i>MFSD12</i>	rs10424065	C	T	EastAfricans	WestAfricans	3.51E-04	1.78E-04	0.048901
<i>MFSD12</i>	rs6510760	G	A	EastAfricans	WestAfricans	3.81E-04	2.24E-04	0.089162
<i>MFSD12</i>	rs112332856	T	C	EastAfricans	WestAfricans	5.39E-04	2.23E-04	0.015703
<i>ASIP</i>	rs6119471	G	C	EastAfricans	WestAfricans	5.78E-04	1.79E-04	0.001269
<i>ASIP</i>	rs6058017	G	A	EastAfricans	WestAfricans	1.35E-04	1.82E-04	0.458646
<i>PIGU</i>	rs2378249	A	G	EastAfricans	WestAfricans	-3.31E-04	2.07E-04	0.109172

700 **Text S1. The effects of migration and substructure.**

701 In this section, we examined how the estimated selection difference $\hat{d}_{ij} = \left(\ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\hat{p}_j}{\hat{q}_j} \right) / t$
 702 is affected by population migration and substructure in theory. Here, $\hat{p}_i$ and $\hat{q}_i$ are the
 703 observed derived and ancestral allele frequencies in the population i , respectively; $\hat{p}_j$ and
 704 $\hat{q}_j$ are the observed derived and ancestral allele frequencies in the population j , respectively;
 705 and t is the divergence time from populations i and j to their most recent common ancestor.
 706 We demonstrated that $\hat{d}_{ij}$ provides a lower bound of selection difference between
 707 populations i and j when migration or substructure exists. We first provide two inequalities
 708 that will be used later.

709 **Inequality 1:** If $a > b > 0$, $c > d > 0$, then $ac > bd$ and $\frac{a+d}{b+c} < \frac{a}{b}$.

710 Proof: $a > b > 0$, $c > d > 0$, then $ac > bc$, $bc > bd$. Therefore, $ac > bd$. Furthermore,
 711 $ac + ab > bd + ab$, which is the same as $a(b+c) > b(a+d)$. Therefore, $\frac{a+d}{b+c} < \frac{a}{b}$.

712 **Inequality 2:** If $a_1 > 0, a_2 > 0, \dots, a_n > 0$, $\bar{a} = \sum_{i=1}^n a_i / n$, then $\max\{a_1, a_2, \dots, a_n\} \geq \bar{a}$,
 713 $\min\{a_1, a_2, \dots, a_n\} \leq \bar{a}$.

714 Proof: Let $a_{\max} = \max\{a_1, a_2, \dots, a_n\}$, then

$$\begin{aligned} a_{\max} - \bar{a} &= \left(\sum_{i=1}^n a_{\max} - \sum_{i=1}^n a_i \right) / n \\ &= \sum_{i=1}^n (a_{\max} - a_i) / n \geq 0 \end{aligned}$$

716 because $a_{\max} \geq a_i$.

717 Let $a_{\min} = \min\{a_1, a_2, \dots, a_n\}$, then

$$\begin{aligned} \bar{a} - a_{\min} &= \left(\sum_{i=1}^n a_i - \sum_{i=1}^n a_{\min} \right) / n \\ &= \sum_{i=1}^n (a_i - a_{\min}) / n \geq 0 \end{aligned}$$

719 because $a_{\min} \leq a_i$.

720 For the proofs in below, we assume $\hat{d}_{ij} > 0$ without loss of generality. If $\hat{d}_{ij} < 0$, then
721 we can exchange i and j , and still obtain $\hat{d}_{ji} > 0$.

722 The effect of migration

723 Suppose there is α proportion of individuals in the population i , which actually come from the
724 population j ; also, there is β proportion of individuals in the population j , which actually come
725 from the population i . Here, $\alpha, \beta \in \left[0, \frac{1}{2}\right)$, because we assume migrants should not become
726 the majority of another population. Then we have

$$\begin{aligned} \hat{p}_i &= (1-\alpha)p_i + \alpha p_j \\ \hat{q}_i &= (1-\alpha)q_i + \alpha q_j \\ \hat{p}_j &= (1-\beta)p_j + \beta p_i \\ \hat{q}_j &= (1-\beta)q_j + \beta q_i \end{aligned}$$

728 Here, p_i and q_i are the true derived and ancestral allele frequencies in the population i ,
729 respectively; p_j and q_j are the true derived and ancestral allele frequencies in the
730 population j , respectively. Therefore,

$$\begin{aligned} \hat{p}_i \hat{q}_j &= [(1-\alpha)p_i + \alpha p_j][(1-\beta)q_j + \beta q_i] \\ &= (1-\alpha)(1-\beta)p_i q_j + \alpha(1-\beta)p_j q_j + \beta(1-\alpha)p_i q_i + \alpha\beta q_i p_j \\ \hat{q}_i \hat{p}_j &= [(1-\alpha)q_i + \alpha q_j][(1-\beta)p_j + \beta p_i] \\ &= (1-\alpha)(1-\beta)q_i p_j + \alpha(1-\beta)p_j q_j + \beta(1-\alpha)p_i q_i + \alpha\beta p_i q_j \end{aligned}$$

732 Further, we have

$$\begin{aligned} \hat{p}_i \hat{q}_j - \hat{q}_i \hat{p}_j &= (1-\alpha)(1-\beta)(p_i q_j - q_i p_j) + \alpha\beta(q_i p_j - p_i q_j) \\ &= [(1-\alpha)(1-\beta) - \alpha\beta](p_i q_j - q_i p_j) \\ &= (1-\alpha-\beta)(p_i q_j - q_i p_j) \end{aligned}$$

734 Because $\alpha, \beta \in \left[0, \frac{1}{2}\right)$, then $1-\alpha-\beta > 0$; and $\hat{p}_i \hat{q}_j > \hat{q}_i \hat{p}_j$, therefore, $p_i q_j - q_i p_j > 0$.

735 We also have $\frac{\hat{p}_i}{\hat{q}_i} = \frac{(1-\alpha)p_i + \alpha p_j}{(1-\alpha)q_i + \alpha q_j} = \frac{p_i + \frac{\alpha}{1-\alpha}p_j}{q_i + \frac{\alpha}{1-\alpha}q_j}$. Because $p_i q_j - q_i p_j > 0$, we have

736 $p_i \frac{\alpha}{1-\alpha} q_j > q_i \frac{\alpha}{1-\alpha} p_j$. From Inequality 1, we know $\frac{\hat{p}_i}{\hat{q}_i} < \frac{p_i}{q_i}$. Similarly, we also have

737 $\frac{\hat{q}_j}{\hat{p}_j} = \frac{q_j + \frac{\beta}{1-\beta} q_i}{p_j + \frac{\beta}{1-\beta} p_i} < \frac{q_j}{p_j}$, therefore, $\frac{\hat{p}_i \hat{q}_j}{\hat{q}_i \hat{p}_j} < \frac{p_i q_j}{q_i p_j}$. According to the monotony of the

738 logarithmic function, we have $0 < \ln \frac{\hat{p}_i \hat{q}_j}{\hat{q}_i \hat{p}_j} < \ln \frac{p_i q_j}{q_i p_j}$; thus, $0 < \hat{d}_{ij} < d_{ij}$. In other words, if

739 migration exists between populations i and j , the estimated selection difference is lower than
740 the true value.

741 **The effect of substructure**

742 **Scenario 1:** The population j has k subpopulations.

743 If the population j has k subpopulations, then $\hat{p}_j = \frac{\sum_k N_{jk} p_{jk}}{N_j}$. Here, p_{jk} is the derived

744 allele frequency in the subpopulation k of the population j . And N_j is the population size of

745 the population j , $N_j = \sum_k N_{jk}$. We denote the minimum of p_{jk} as $\min(p_{jk})$. Because

746 $q_{jk} = 1 - p_{jk}$, then $\max(q_{jk}) = 1 - \min(p_{jk})$. Based on Inequality 2, $\hat{p}_j > \min(p_{jk})$,

747 $\hat{q}_j < \max(q_{jk})$. Therefore, $\ln \frac{\hat{p}_j}{\hat{q}_j} > \ln \frac{\min(p_{jk})}{\max(q_{jk})}$. We have

748 $\ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\min(p_{jk})}{\max(q_{jk})} > \ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\hat{p}_j}{\hat{q}_j} > 0$.

749 **Scenario 2:** The population i has l subpopulations.

750 If the population i has l subpopulations, then $\hat{p}_i = \frac{\sum_l N_{il} p_{il}}{N_i}$. We denote the maximum of

751 p_{il} as $\max(p_{il})$. Then $\hat{p}_i < \max(p_{il})$, $\hat{q}_i > \min(q_{il})$. Therefore, $\ln \frac{\max(p_{il})}{\min(q_{il})} > \ln \frac{\hat{p}_i}{\hat{q}_i}$, and

752 we have $\ln \frac{\max(p_{il})}{\min(q_{il})} - \ln \frac{\hat{p}_j}{\hat{q}_j} > \ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\hat{p}_j}{\hat{q}_j} > 0$.

753 **Scenario 3:** The population i has l subpopulations, and the population j has k subpopulations.

754 Based on Scenario 1 and 2, we have $\ln \frac{\max(p_{il})}{\min(q_{il})} - \ln \frac{\min(p_{jk})}{\max(q_{jk})} > \ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\hat{p}_j}{\hat{q}_j} > 0$.

755 In summary, if populations i and j have subpopulations, and their estimated selection
 756 difference is larger than zero, then at least one pair of their subpopulations has selection
 757 difference larger than zero. Moreover, the estimated difference is smaller than the largest
 758 difference between subpopulations.

759

```

760 Text S2. A sample script for simulation with SLiM 2.
761 initialize() {
762     initializeMutationRate(1e-8);
763     initializeMutationType("m1", 0.5, "f", 0.0);
764     initializeMutationType("m2", 0.5, "f", 0.0);
765     m1.mutationStackPolicy = "f";
766     m2.mutationStackPolicy = "f";
767     initializeGenomicElementType("g1", m1, 1.0);
768     initializeGenomicElement(g1, 0, 999999);
769     initializeRecombinationRate(1e-8); }
770
771 1 { sim.addSubpop("p1", 12000); }
772 1 late() {
773     // Set the initial frequency of the beneficial allele to 0.001
774     targets = sample(p1.genomes, 24);
775     targets.addNewDrawnMutation(m2, 499999); }
776 300 {
777     // Add West Africans
778     sim.addSubpopSplit("p2", 12000, p1); }
779 1000 {
780     // Add East Africans
781     sim.addSubpopSplit("p3", 12000, p1);
782     p1.setSubpopulationSize(5000); }
783 1600 {
784     // Add Oceanians
785     sim.addSubpopSplit("p6", 5000, p1); }
786 2000 {
787     // Add Europeans
788     sim.addSubpopSplit("p4", 5000, p1); }
789 2300 {
790     // Add North Asians and p1 becomes East Asians
791     sim.addSubpopSplit("p5", 5000, p1); }
792 3300:3600 {
793     t = sim.generation - 3300;
794     // Expansion in Europeans and North Asians
795     // Final effective population size becomes ~10,000
796     p4_size = round(5000 * exp(0.0023 * t));
797     // Expansion in Asians
798     // Final effective population size becomes ~20,000
799     p1_size = round(5000 * exp(0.0046 * t));
800     p4.setSubpopulationSize(asInteger(p4_size));
801     p5.setSubpopulationSize(asInteger(p4_size));
802     p1.setSubpopulationSize(asInteger(p1_size)); }
803 // s1 = -0.0188/31*2 = -0.001213

```

```

804 301:3600 fitness(m2, p2) { return 0.998787; }
805 // s10 = 0.00398/31*2 = 0.0002568
806 301:1000 fitness(m2, p1) { return 1.000257; }
807 // s2 = -0.0204/31*2 = -0.001316
808 1001:3600 fitness(m2, p3) { return 0.998684; }
809 // s9 = 0.00813/31*2 = 0.0005245
810 1001:1600 fitness(m2, p1) { return 1.000525; }
811 // s3 = -0.00614/31*2 = -0.0003961
812 1601:3600 fitness(m2, p6) { return 0.999603; }
813 // s8 = 0.00665/31*2 = 0.0004290
814 1601:2100 fitness(m2, p1) { return 1.000429; }
815 // s4 = 0.0249/31*2 = 0.001606
816 2001:3600 fitness(m2, p4) { return 1.001613; }
817 // s7 = 0.000218/31*2 = 0.0000141
818 2001:2300 fitness(m2, p1) { return 1.000014; }
819 // s5 = 0.00622/31*2 = 0.0004013
820 2301:3600 fitness(m2, p5) { return 1.000401; }
821 // s6 = -0.00480/31*2 = -0.0003097
822 2301:3600 fitness(m2, p1) { return 0.999690; }
823 3600 late() {
824     mut1 = sim.mutationsOfType(m2);
825     cat("Count:"
826         + "\t" + "WAF\t" + sim.mutationCounts(p2, mut1) + "\t"
827         + "\t" + "EAF\t" + sim.mutationCounts(p3, mut1) + "\t"
828         + "\t" + "OCN\t" + sim.mutationCounts(p6, mut1) + "\t"
829         + "\t" + "EUR\t" + sim.mutationCounts(p4, mut1) + "\t"
830         + "\t" + "NAS\t" + sim.mutationCounts(p5, mut1) + "\t"
831         + "\t" + "EAS\t" + sim.mutationCounts(p1, mut1)
832         + "\n");
833     sim.simulationFinished(); }
834

```