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

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Keywords: population genetics, natural selection, human evolution, human pigmentation, complex traits

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-Eurasians (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.

Author Summary

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

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

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

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

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

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

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).

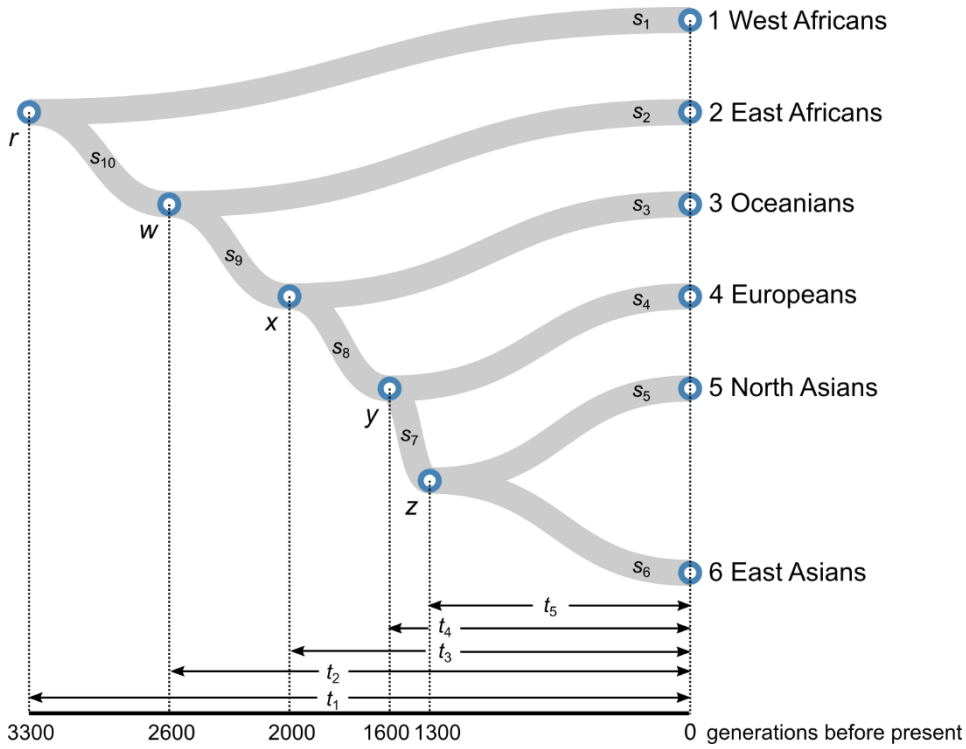

Fig. 1. Time-varied selective pressures on an evolutionary tree. We model the evolutionary history of six representative human populations as a binary tree. Here, s_i (i = 0, 1, ..., 10) denotes the selection coefficient of the i-th epoch and can be obtained by estimating selection differences between 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

$$\mathbf{d} = \mathbf{Ts}, \tag{3}$$

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 $\Pr(|\mathbf{s}|^2 > |\mathbf{s}_a|^2 \mid \mathrm{NE}) \geq \Pr(|\mathbf{s}|^2 > |\mathbf{s}_b|^2 \mid \mathrm{NE})$, 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 **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

$$\mathbf{s}^* = \mathbf{T}^+\mathbf{d}, \tag{4}$$

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

Table 1. Selection differences with 95% CI associated with human pigmentation between populations (× 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

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

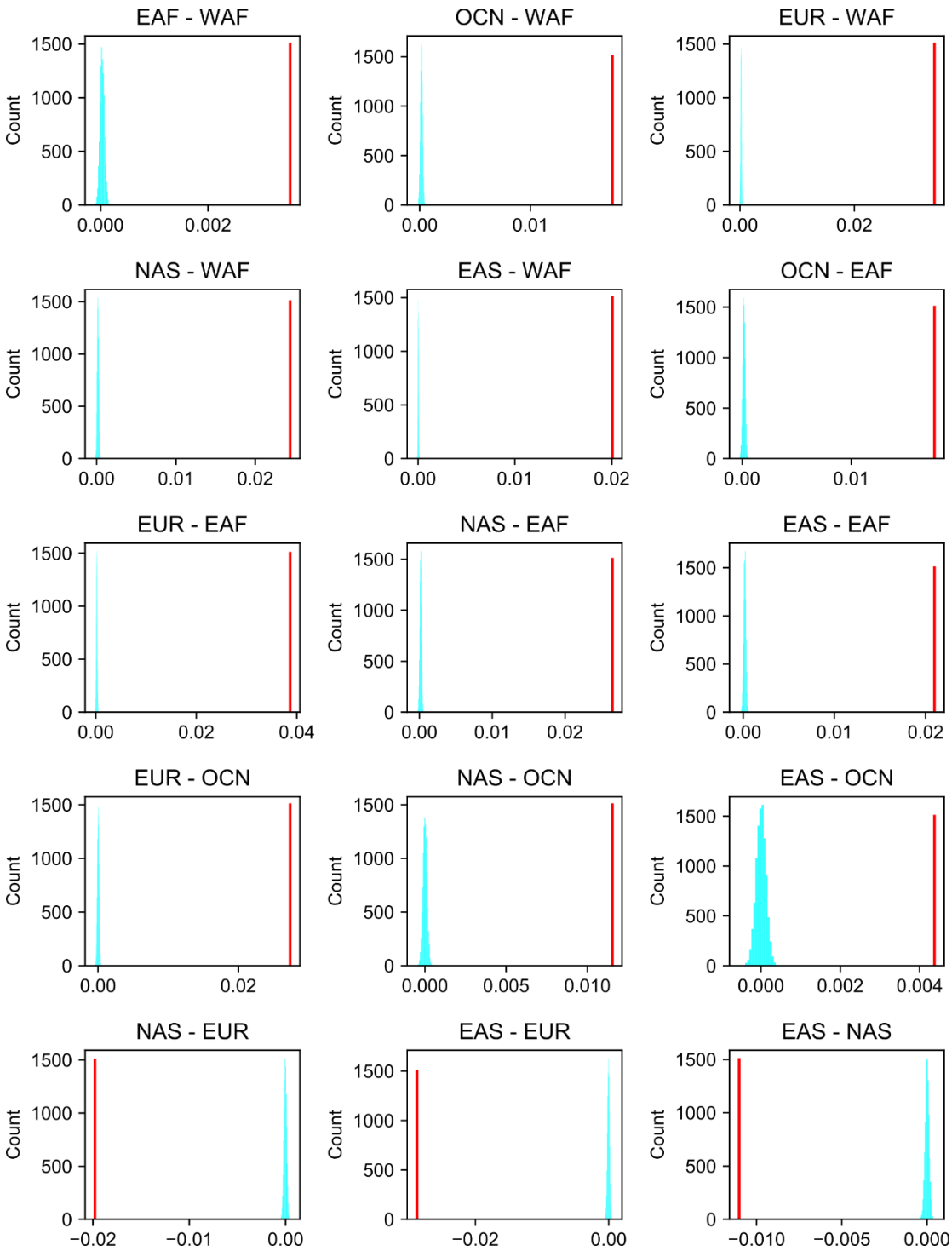

Fig. 2. Significance levels of the selection differences associated with human pigmentation between populations. The blue bars are the empirical distributions of population differences using 10,000 random sets of 31 SNPs in the genomes. The red lines are the selection differences between populations 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).

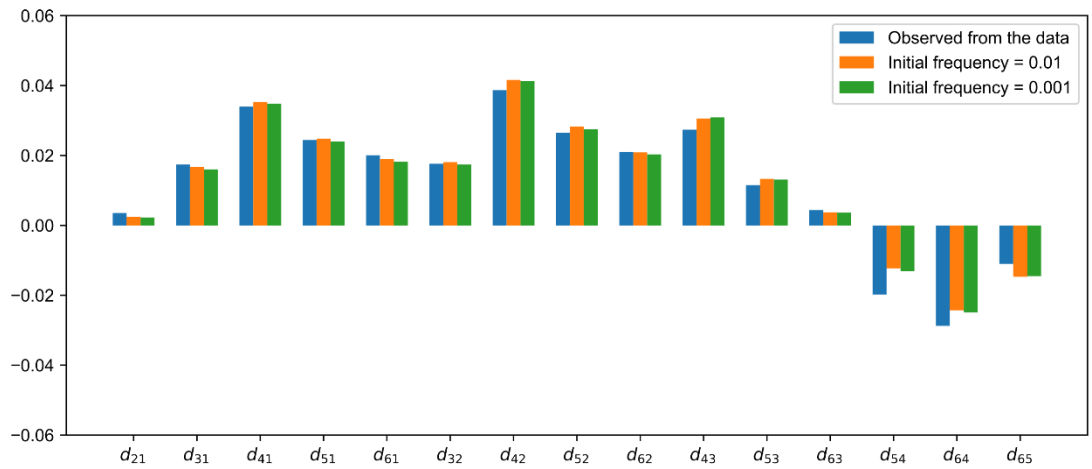

Fig. 3. Comparisons between selection differences from simulation and the data. The selection differences are: d_{21}, differences between East Africans and West Africans; d_{31}, differences between Oceanians and West Africans; d_{41}, differences between Europeans and West Africans; d_{51}, differences 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).

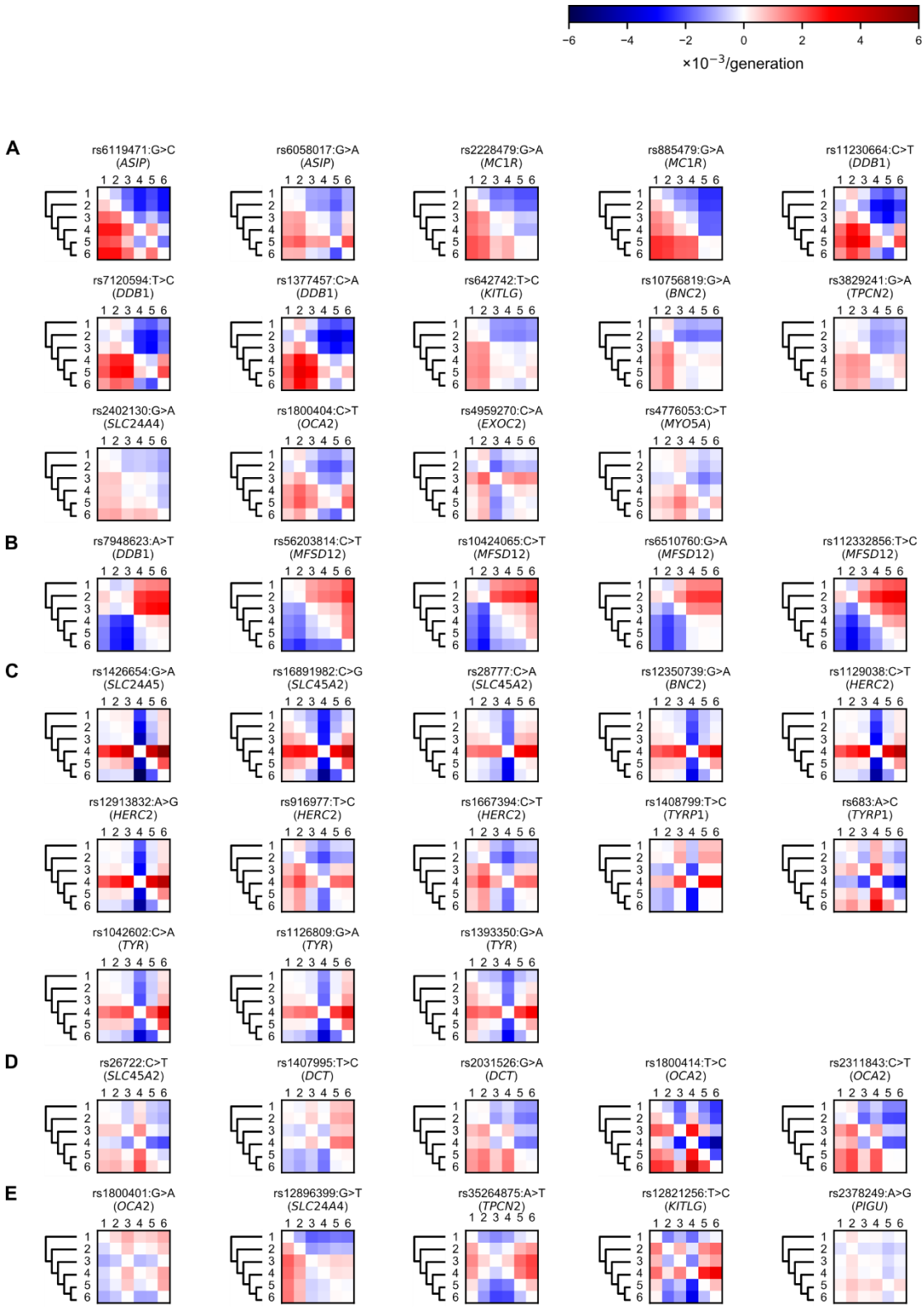

Fig. 4. Selection differences in individual loci between populations. We used Eq. 1 to quantify the selection differences of 42 SNPs associated with human pigmentation, and categorized them into five kinds of patterns: (A) Derived alleles affected by Eurasian-shared selection; (B) Derived alleles affected 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 liftovered 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.

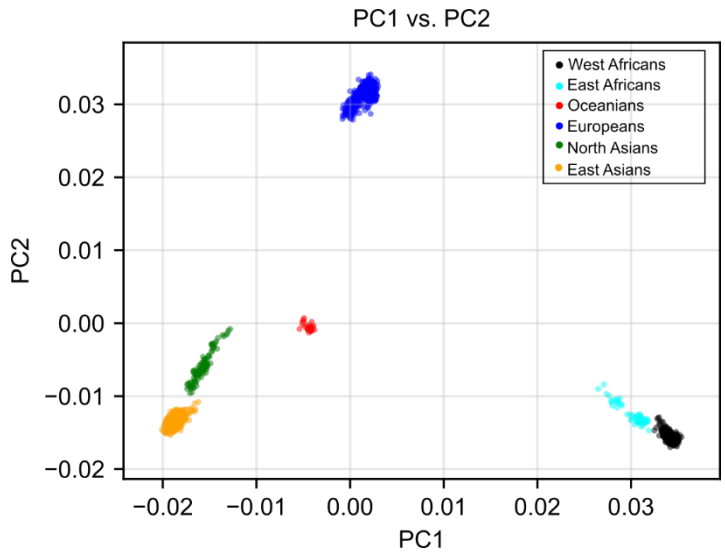

Fig. S1. PCA plots of 2346 samples.

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.

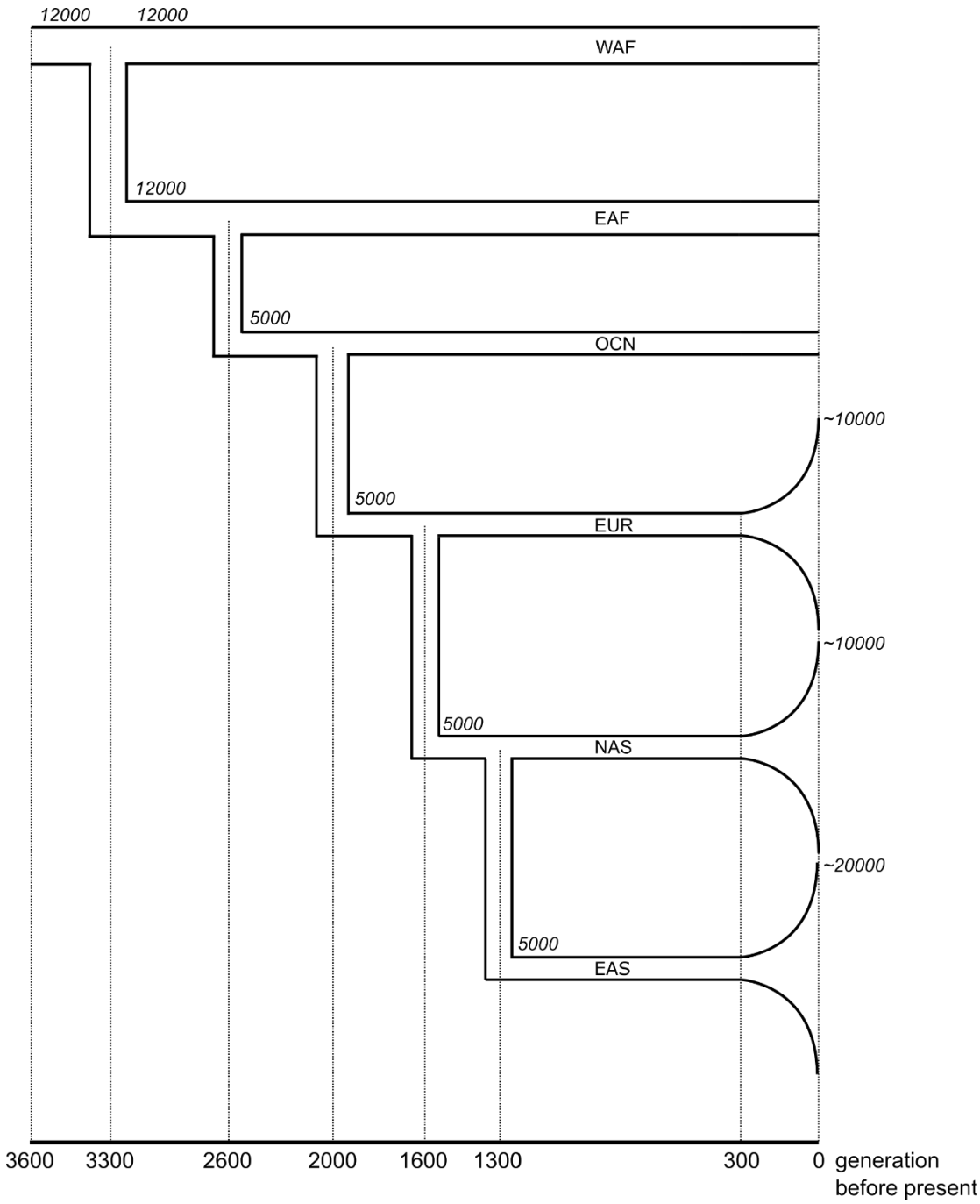

Fig. S3. The demography model for simulation. The italic numbers indicate population sizes at different time periods. Population abbreviations: WAF, West Africans; EAF, East Africans; OCN, Oceanians; EUR, Europeans; NAS, North Asians; EAS, East Asians.

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.

Acknowledgements

This work was supported by grants from National Natural Science Foundation of China (91331109 to Y.H.; 31271338 and 31330038 to L.J.; 31322030 and 91331108 to S.W.). Y.H. is also grateful for support from the SA-SIBS scholarship program and the Youth Innovation Promotion Association of Chinese Academy of Science (2012216). L.J. was also supported by the Shanghai Leading Academic Discipline Project (B111) and the Center for Evolutionary Biology at Fudan University. S.W. was also awarded by the National Thousand Young Talents Award, the Max Planck-CAS Paul Gerson Unna Independent Research Group Leadership Award, and open projects from the State Key Laboratory of Genetic Engineering at Fudan University. X.H. is grateful to Dr. Minxian Wang, Dr. Yuchen Wang, Dr. Haiyi Lou and Dr. Lin Tang for comments on the manuscript.

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.

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Supporting information

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

Table S3 Candidate SNP information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Text S1. The effects of migration and substructure.

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

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

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

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

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

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

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

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

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

because $a_{\min} \le a_i$.

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

The effect of migration

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

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

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

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

Further, we have

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

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, $p_i q_j - q_i p_j > 0$.

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

$p_i \frac{\alpha}{1-\alpha} q_j > q_i \frac{\alpha}{1-\alpha} p_j$. From Inequality 1, we know $\frac{\hat{p}_i}{\hat{q}_i} < \frac{p_i}{q_i}$. Similarly, we also have $\frac{\hat{q}_j}{\hat{p}_j} = \frac{q_j + \frac{\beta}{1-\beta} q_i}{p_j + \frac{\beta}{1-\beta} p_i} < \frac{q_j}{p_j}$, 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 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 migration exists between populations *i* and *j*, the estimated selection difference is lower than the true value.

The effect of substructure

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

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 allele frequency in the subpopulation *k* of the population *j*. And N_j is the population size of the population *j*, $N_j = \sum_k N_{jk}$. We denote the minimum of p_{jk} as $\min\left(p_{jk}\right)$. Because $q_{jk} = 1 - p_{jk}$, then $\max\left(q_{jk}\right) = 1 - \min\left(p_{jk}\right)$. Based on Inequality 2, $\hat{p}_j > \min\left(p_{jk}\right)$, $\hat{q}_j < \max\left(q_{jk}\right)$. Therefore, $\ln \frac{\hat{p}_j}{\hat{q}_j} > \ln \frac{\min\left(p_{jk}\right)}{\max\left(q_{jk}\right)}$. We have

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

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

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 p_{il} as $\max\left(p_{il}\right)$. Then $\hat{p}_i < \max\left(p_{il}\right)$, $\hat{q}_i > \min\left(q_{il}\right)$. Therefore, $\ln \frac{\max\left(p_{il}\right)}{\min\left(q_{il}\right)} > \ln \frac{\hat{p}_i}{\hat{q}_i}$, and we have $\ln \frac{\max\left(p_{il}\right)}{\min\left(q_{il}\right)} - \ln \frac{\hat{p}_j}{\hat{q}_j} > \ln \frac{\hat{p}_i}{\hat{q}_i} - \ln \frac{\hat{p}_j}{\hat{q}_j} > 0$.

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

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

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

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

```
initialize() {
	initializeMutationRate(1e-8);
	initializeMutationType("m1", 0.5, "f", 0.0);
	initializeMutationType("m2", 0.5, "f", 0.0);
	m1.mutationStackPolicy = "f";
	m2.mutationStackPolicy = "f";
	initializeGenomicElementType("g1", m1, 1.0);
	initializeGenomicElement(g1, 0, 999999);
	initializeRecombinationRate(1e-8); }

1 {	sim.addSubpop("p1", 12000); }
1 late() {
	// Set the initial frequency of the beneficial allele to 0.001
	targets = sample(p1.genomes, 24);
	targets.addNewDrawnMutation(m2, 499999); }
300 {
	// Add West Africans
	sim.addSubpopSplit("p2", 12000, p1); }
1000 {
	// Add East Africans
	sim.addSubpopSplit("p3", 12000, p1);
	p1.setSubpopulationSize(5000); }
1600 {
	// Add Oceanians
	sim.addSubpopSplit("p6", 5000, p1); }
2000 {
	// Add Europeans
	sim.addSubpopSplit("p4", 5000, p1); }
2300 {
	// Add North Asians and p1 becomes East Asians
	sim.addSubpopSplit("p5", 5000, p1); }
3300:3600 {
	t = sim.generation - 3300;
	// Expansion in Europeans and North Asians
	// Final effective population size becomes ~10,000
	p4_size = round(5000 * exp(0.0023 * t));
	// Expansion in Asians
	// Final effective population size becomes ~20,000
	p1_size = round(5000 * exp(0.0046 * t));
	p4.setSubpopulationSize(asInteger(p4_size));
	p5.setSubpopulationSize(asInteger(p4_size));
	p1.setSubpopulationSize(asInteger(p1_size)); }
// s1 = -0.0188/31*2 = -0.001213
```

```
301:3600 fitness(m2, p2) { return 0.998787; }
// s10 = 0.00398/31*2 = 0.0002568
301:1000 fitness(m2, p1) { return 1.000257; }
// s2 = -0.0204/31*2 = -0.001316
1001:3600 fitness(m2, p3) { return 0.998684; }
// s9 = 0.00813/31*2 = 0.0005245
1001:1600 fitness(m2, p1) { return 1.000525; }
// s3 = -0.00614/31*2 = -0.0003961
1601:3600 fitness(m2, p6) { return 0.999603; }
// s8 = 0.00665/31*2 = 0.0004290
1601:2100 fitness(m2, p1) { return 1.000429; }
// s4 = 0.0249/31*2 = 0.001606
2001:3600 fitness(m2, p4) { return 1.001613; }
// s7 = 0.000218/31*2 = 0.0000141
2001:2300 fitness(m2, p1) { return 1.000014; }
// s5 = 0.00622/31*2 = 0.0004013
2301:3600 fitness(m2, p5) { return 1.000401; }
// s6 = -0.00480/31*2 = -0.0003097
2301:3600 fitness(m2, p1) { return 0.999690; }
3600 late() {
	mut1 = sim.mutationsOfType(m2);
	cat("Count:"
		+ "\t" + "WAF\t" + sim.mutationCounts(p2, mut1) + "\t"
		+ "\t" + "EAF\t" + sim.mutationCounts(p3, mut1) + "\t"
		+ "\t" + "OCN\t" + sim.mutationCounts(p6, mut1) + "\t"
		+ "\t" + "EUR\t" + sim.mutationCounts(p4, mut1) + "\t"
		+ "\t" + "NAS\t" + sim.mutationCounts(p5, mut1) + "\t"
		+ "\t" + "EAS\t" + sim.mutationCounts(p1, mut1)
		+ "\n");
	sim.simulationFinished(); }
```