
Genodynamics: A New Biophysical Approach to Modeling Adaptation in Human Populations

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Abstract: Using *genodynamics*, the Howard University biophysics research and interdisciplinary development group transforms genomic sequence data into genomic energy measures to explore the science of genome variation in population diversity and human biology. Genodynamics utilizes the statistical distribution of single nucleotide polymorphism (SNP) data from the Haplotype Map project to mathematically model whole genome-environment interactions in human adaptation to environmental stressors/stimuli by functionally parameterizing the interplay between the biophysical and environmental factors in a quantifiable manner. Our double-blind computer program flagged smooth mathematical function relationships between allelic energies of two SNPs in intron one of the egl-9 family hypoxia inducible factor 1 (EGLN1) and the environmental parameter averaged ancestral annual ultraviolet radiation exposure. EGLN1 is a gene on chromosome 1 known to play an essential role in the regulation of the hypoxia inducible factor pathway. We have demonstrated that our genodynamics approach can quantify, through adaptive forces, the effects that environmental stressors/stimuli have had on patterns of common variation in the human genome and by doing so offer an alternative means of investigating the implications of SNP information dynamics on natural selection in human populations.

Keywords: Population Diversity, Modeling Whole Genome Adaptation, SNP Information Dynamics, Genodynamics, Natural Selection in Human Populations

1. Introduction

Modeling population diversity is fundamental to gaining a better understanding of the biology of whole genome variation. Modern humans have settled in disparate regions of the globe with environments ranging from high altitude plateaus to the frigid temperatures of the Arctic. Within these diverse environments, human populations have not only survived but thrived; this has been achieved through adaptation at the genome level. Genomic adaptation can occur through selective pressures (e.g., high altitude, ultraviolet radiation (UVR) exposure, etc....) in the environment acting on ancestral genome sequence variation present in the population. For example, high altitude populations such as the Tibetans, Andeans, and Ethiopians have signatures of positive selection on genes in the hypoxia pathway [1].

Likewise, in populations living at lower latitudes, there are signatures of positive selection in the pigmentation pathway due to high UVR exposure than those living in higher latitudes [2]. Additionally, pathogens have imposed selective pressures on human populations as indicated by more than 300 immune and immune-related genes reported to have signatures of recent positive selection correlated with specific groups of microbes such as viruses, protozoa, and parasitic worms [3-5].

Genome-wide association studies (GWAS), whole genome sequencing, and genome-wide SNP data have generated a plethora of resources, such as the database of short genetic variations (dbSNP), the Haplotype Map (HapMap), and the GWAS Catalog, all of which have contributed to a new era in population genetics. The 21st century era of '*genomic mining*' offers unprecedented opportunities to investigate evolutionary forces that have shaped genome variation in

natural populations. Genome-wide systems of common variation allow population geneticists to investigate how selection has influenced the architecture of the human genome in modern humans. As useful as these datasets are for research on natural selection, a major challenge in this research is the difficulty of correlating indigenous population allelic frequencies in the context of local environmental stressors [6]. To address this challenge, we have used our genodynamics method to derive biophysical metrics that allow us to mathematically model whole genome-environment interactions [7]. This method explores the biophysical underpinnings of common variants (e.g., SNPs) to better understand the functional aspects of natural variation in the genome. Using principles of thermodynamics and statistical physics to derive such biophysical metrics, we have discovered environmentally induced adaptive forces that reflect the functionality of SNP data in indigenous populations. In this paper, adaptive forces are used to gain a better understanding of the complex interplay between SNP data and molecular mechanisms underlying whole genome adaptation to environmental stressors.

2. Materials and Methods

2.1. SNP Data Set

We confined our analysis to phase III data from the International Haplotype Map Project [8] since this dataset represents the broadest set of populations with fairly uniform genotyping. The populations included in this dataset are: African Americans in the Southwest USA (ASW), Utah residents with ancestry from Northern and Western Europe (CEU), Han Chinese in Beijing China (CHB), Chinese in Metropolitan Denver Colorado USA (CHD), Gujarati Indians in Houston Texas USA (GIH), Japanese in Tokyo Japan (JPT), Luhya in Webuye Kenya (LWK), Mexican Americans in Los Angeles California USA (MXL), Massai in Kinyawa Kenya (MKK), Toscani in Italia (TSI), and Yoruba in Ibadan Nigeria (YRI). Only those SNPs that met the following criteria were included: (i) associated with one of the environmental parameters of interest in the GWAS Catalog [9] or in the published literature, and (ii) with selection signatures listed in the database of recent positive selection across human populations [10]. The ASW, CEU, CHD and MXL populations were excluded from our analysis because these populations do not reside in their indigenous environments.

2.2. Environmental Parameter – UV Exposure

For our analysis, the averaged ancestral annual UVB radiation exposure will be expressed in units of Joule per square meter (UV radiance) as estimated from [11]. In these units, estimates of annual UV radiance for the CHB population averaged 2180 (ranging from 1500 to 2600); for the JPT population averaged 2400 (ranging from 2300 to 2500); for the LWK population averaged 5764 (ranging from 5450 to 6500); for the MKK population averaged 5624

(ranging from 5000 to 6125); for the TSI population averaged 1507 (ranging from 950 to 2500), and for the YRI population averaged 5129 (ranging from 3500 to 6300).

2.3. Environmental Parameter - Altitude

The altitude values utilized in this study are averaged estimates of elevations of populated regions for ancestral homelands in units of meters (m) using data from [12]. The CHB population's averaged altitude was 22m (ranging from 3m to 48m). The JPT population's averaged altitude was 107m (ranging from 5m to 287m). The LWK population's averaged altitude was 1711m (ranging from 1203m to 2486m). The MKK population's averaged altitude was 1507m (ranging from 712m to 2383m). The TSI population's averaged altitude was 74m (ranging from 1.3m to 143m). The YRI population's averaged altitude was 211m (ranging from 12m to 337m).

2.4. Environmental Parameter - Malarial Susceptibility

We have chosen to present data based upon the Plasmodium falciparum parasite rate (PfPR) which is commonly used as an index of malaria transmission intensity by the World Health Organization [13]. We presume that all the examined populations had higher malarial exposure in the past than at present. Specifically, the TSI population likely had significantly higher malarial exposure in the past than to date, since relatively recent developments have significantly reduced the prevalence of the insects (e.g., concentrated insecticide programs) and treatment of the disease. In units of parasite reproductive rate, estimated of PfPR for the CHB population averaged 0.01 (ranging from 0 to 0.05); for the JPT populations averaged 0.0002 (ranging from 0 to 0.001); for the LWK population averaged 12 (ranging from 2 to 35); for the MKK population averaged 8 (ranging from 1 to 25); for the TSI population averaged 0.8 (ranging from 0 to 5), and for the YRI population averaged 70 (ranging from 20 to 95).

2.5. Information Dynamics of the Human Genome

Quantifiable biophysical dynamics requires the introduction of universal dimensional units that give a measure to the relative pliability and elasticity of information differences between various populations or regions of the genome of the same population, analogous to the additive energy units in the physical sciences. However, in contrast to the fundamental particles of micro-physics, fundamental life units (e.g., individual genomes) cannot maintain in the absence of the environments that support them, which motivates the development of genomic *free energy* variables as the least complicated description of genomic dynamics, rather than environmentally independent energetic measures. The genomic free energy F_{genome} has been developed as a state variable in a manner that optimizes the population's survivability under the complete set of environmental stimuli and stressors, establishing the homeostatic balance between conservation and variation of alleles and traits in the dynamic

of the population distribution.

Motivated by the thermodynamics of physical systems in equilibrium, a dimensional environmental potential, T_E is an intensive state variable that is independent of the size of the population will parametrize the intrinsic, pervasive agitation of the population due to stochastic environmental stimuli (analogous to how temperature parameterize agitation of fundamental physical units in a thermal bath) for populations in homeostasis. Similarly, dimensional allelic and haplotype potentials, $\mu_a^{(S)}$ and $\mu_h^{(H)}$, will quantify the genomic free energy change in a population from the addition of a single individual of all a or haplotype h . For a given haploblock (H), the differential genomic free energy is mathematically

modeled in our 2014 BRIDG publication on the “Development of genodynamic metrics for exploring the biophysics of DNA polymorphisms” [14].

2.6. Distributed Genodynamics

Formulation of the information dynamics of the human genome in terms of genomic free energies directly resulted in well-defined forms for the SNP potentials for SNPs that are not in linkage disequilibrium, and for block potentials for correlated SNPs that are in linkage disequilibrium. In many cases (including GWAS data), associations with biological expression have been made with *individual* SNPs that happen to be in linkage disequilibrium within a block. Thus, there is utility in developing a meaningful mechanism for distributing the uniquely defined block potentials amongst their constituent correlated SNPs. Since the SNP haploblock structure has an emergent form that differs between populations, meaningfully defined distributed potentials will reflect the biology underlying the participation of individual SNPs in the informatic architecture of its correlation with other SNPs in the haploblock. We will require that distributed SNP potentials $\mu_S^{(H)}$ within a haploblock (H) must satisfy the following conditions:

- (1) If the SNP is occupied by an allele that is fixed in the given population, then its distributed SNP potential is the fixing potential μ_{fixed} ;
- (2) The sum of the distributed SNP potentials should be the same as the block potential $\mu^{(H)}$, i.e. $\mu^{(H)}$, i.e. $\langle \mu^{(H)} \rangle = \sum_{S=1}^n \mu_S^{(H)}$; (1)
- (3) The block potential should be linearly distributed amongst the constituent SNPs in accordance with occurrences of the SNP alleles.

The first bullet ensures that if the SNP is not variant within the population, its genomic energy is equivalent to that of a SNP that is not in linkage disequilibrium, and the second bullet requires that the distributed potentials should reconstruct the block potential in an additive way. The third bullet represents a simple mechanism for relating the distributed potentials to the degree of variation in the SNP. For details of the mathematical formulations see Lindesay *et al.*, “Use of Genome Information-Based Potentials to Characterize Human Adaptation” [7].

It should be noted that all distributed potentials are only

defined at the population level and cannot be ascribed to *individuals*. Only the emergent haplotype potentials can be ascribed to individuals within the population. However, since distributed potentials are defined for the population as a whole, they can be quite useful for parameterizing the environmental influences upon that population. *Distributed potentials are particularly useful for describing the adaptation of the population to stressors with known biological correspondence to particular alleles or SNPs.* The description of genomic variants using distributed potentials inherently includes any presently unknown *whole genome* response to specific stressors.

2.7. Measurement of Adaptive Forces on the Human Genome

The development of genomic free energy measures, that are quantified by Genomic Energy Units (GEUs), for individual alleles and genomic regions

allows environmentally induced adaptive forces to be characterized using gradients of those additive measures down the slope of environmental parameters. A single human Genomic Energy Unit ($\mu \equiv 1 \text{ GEU}$) is defined to be the universal allelic genomic free energy necessary to induce maximal variation (2)

within a single non-linked bi-allelic SNP location ($p_{a1} = \frac{1}{2} = p_{a2}$), quantifying a dimensional free energy unit shared amongst all humans. (3)

For a given allele a that can be biophysically associated with a definable environmental parameter λ (such as UV light, etc.), we defined the environmentally induced *adaptive force* on that allele by $f_a \equiv \frac{\partial \mu^a}{\partial \lambda}$, with analogously defined adaptive forces on potentials characterizing SNPs, haploblocks, haplotypes, (4)

genes, and even perhaps whole chromosomes. Such an expression is only meaningful if there is a functional relationship between expression of the biology of the genomic unit and a particular environmental parameter λ . In such cases, as defined positive adaptive forces drive the conservation of the given genomic unit down the slope of the genomic potential. The distribution of the genomic variants for a population in homeostasis with an environment optimizes the *survivability* and sustenance of that population. Under variation of a specific environmental parameter, increased survivability might drive the genomic unit towards more diversity, or more conservation, depending on the nature of the environmental influence upon the homeostatic population. We define homeostasis as any changes occurring in the population distribution requiring many generations to become significant. Quantifying such forces inherently involves comparisons between differing environments.

In many (if not most) cases, the biology of a given genomic variant associated with a redundant multiplicity of pathways and biological functions that are sensitive to several environmental stressors or stimuli. In such cases, the allelic potentials would lie on a multi-dimensional contour parameterizing a landscape of environmental parameters, and

the adaptive force would be a ‘vector’ valued function whose components reflect changes along any environmental parameter. Searches on a single environmental parameter will likely flag only those correlations with genomic variants that have a *dominant* association with that parameter. Our method examines whether the genomic potentials for the SNPs and alleles can be fitted to simple, functional forms (curves) singly dependent on a given environmental parameter. If the root-mean-square (RMS) deviation of the data points for the curves, as compared to the maximum variation of the data, falls within 5%, the SNP and/or alleles are flagged by our computer program and adaptive forces are calculated for the curves. Red points represent SNPs in linkage disequilibrium, while blue points represent those not in linkage disequilibrium. The thickness of the curves in the plots represents the degree of correlation of the data with the fitting curve, with bolder curves indicating stronger correlations.

3. Results and Discussion

A total of one hundred thirty-six SNPs met the criteria for inclusion in our study. Most of the SNPs (116) were associated with altitude, while five SNPs were associated with UV, and fifteen SNPs were associated with malarial

susceptibility. Of the one hundred thirty-six SNPs interrogated, two rs7542797 and rs2486729 on chromosome 1, were flagged for UVR exposure dependencies. Both SNPs are in the egl-9 family hypoxia inducible factor 1 (EGLN1) gene on chromosome 1.

3.1. rs7542797, rs2486729, and UVR

The potentials displayed in Figure 1 represent the block potentials and distributed allelic potentials of A and C for the SNP rs7542797 as a function of UVR exposure. The adaptive force on the SNP is about -0.0001 GEUs per unit of UVR exposure, while allele A, the ancestral allele, is about -0.0004 GEUs per unit of annual UVR exposure towards higher exposure, and the C allele did not meet our criterion for flagging on this environmental dependency. Additionally, for the populations with the lowest UVR exposures, rs7542797 is in linkage disequilibrium (LD) with rs2486729 whereas the populations with the highest UVR exposures rs7542797 is not in LD; suggesting that populations with higher UVR exposure benefit more by not being linked to rs2486729 contrary to the populations with the lowest UVR exposures, where having rs7542797 and rs2486729 in LD is advantageous.

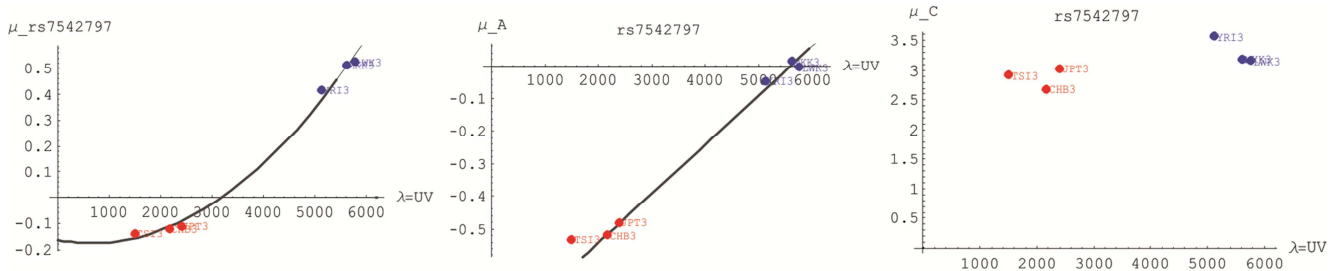


Figure 1. Genomic potentials of polymorphisms rs7542797 on chromosome 1. The horizontal axis labeled by the environmental parameter λ is UV in units of UV radiance. The vertical axis gives the SNP (μ_{rs7542797}) and allelic (μ_A, μ_C) potentials in genomic energy units (GEUs).

The SNP rs2486729 whose genomic potentials are displayed in Figure 2 was flagged for UVR exposure dependency. The adaptive force on the SNP potential is about -0.00005 GEUs per unit of annual UVR exposure, with increased genomic conservation for populations with lower UVR exposure whereas for the YRI and MKK populations, increased variation is favored while the LWK population exhibits the highest degree of genomic conservation

indicative of the importance of this SNP with regard to this environmental dependency for the LWK population. The adaptive force on allele T is about -0.003 GEUs per unit of annual UVR exposure with significant GEU cost for the maintenance of the T allele in environments with elevated UVR exposure attesting to the significance of this allele. As with rs7542797, the C allele did not meet our criterion for flagging with this environmental dependency.

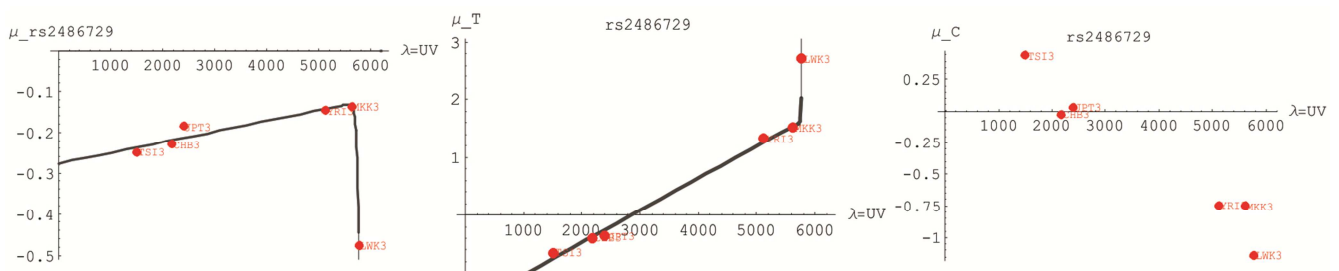


Figure 2. Genomic potentials of polymorphisms rs2486729 on chromosome 1. The horizontal axis labeled by the environmental parameter λ is UV in units of UV radiance. The vertical axis gives the SNP (μ_{rs2486729}) and allelic (μ_T, μ_C) potentials in genomic energy units (GEUs).

3.2. The HIF Pathway, EGLN1, and UVR

Our program found a functional correlation between two SNPs in intron 1 of the *egl-9* family hypoxia inducible factor 1 (EGLN1) gene and the environmental parameter UV exposure. Though EGLN1's involvement in high altitude adaptation is more well, several studies have shown that the variation present in this gene has strong signatures of positive selection with regard to altitude in both Tibetan and Andean populations [15-19]. However, our study did not corroborate this finding which could be due to the lack of Tibetan and Andean genotype data for which we have plans to rectify in future studies. Furthermore, with regard to the other two environmental parameters, altitude and malarial susceptibility, there was no significant flagging for either. The lack of functional correlations between the chosen variants and the environmental parameters of interest could be due to how the environmental parameter is quantified. Particularly, regarding malarial susceptibility, it is possible that PfPR is not a suitable measurement for correlating this environmental parameter with the variants of interest and perhaps some other means of measuring malarial susceptibility (i.e., the incidence of malaria in a population) might result in better correlations with the chosen variants. Whereas, with altitude, the lack of functional correlations with the variants of interest may be due to a "threshold" effect whereby a certain level, in this case elevation, must be surpassed for there to be significant flagging. This effect could be remedied by the inclusion of populations residing at ultra-high elevations (greater than 3500m).

The protein encoded by EGLN1, *egl* nine homolog 1 (*egl*n1), is a prolyl hydroxylase (PHD) that hydroxylates one of the subunits in the hypoxia inducible factor (HIF) complex, specifically HIF-1 α . When oxygen levels are low, HIF-1 α hydroxylation by *egl*n1 does not occur, resulting in the stabilization of the HIF complex and allowing for the activation of a wide variety of hypoxia responsive genes [20]. Studies conducted by Ivan *et al.* [21] and Jaakkola *et al.* [22], demonstrated that the enzymatic activity of *egl*n1 necessitates the interaction of HIF-1 α with the von-Hippel-Landau protein, a critical member of the E3 ubiquitin ligase complex that polyubiquitylates the HIF complex leading to catabolism by the proteasomes [20]. In addition, their 2001 publications, Ivan *et al.* [21] and Jaakkola *et al.* [22] found that the hydroxylase activity of *egl*n1 was dramatically suppressed in response to hypoxia, suggesting a direct mechanism for cellular oxygen sensing. Moreover, it is worth noting that HIF-1 α contains several evolutionary conserved proline residues, one of which is the target of *egl*n1 [23, 21] further validating its importance.

The epidermis has a mildly hypoxic microenvironment where high levels of HIF-1a have been detected in the basal keratinocytes of both the mouse and humans [24]. In knockdown experiments of HIF-1 α conducted by Rezvani *et al.* [25] in human keratinocytes, there was an inhibition of growth and the formation of a reconstructed epidermis was

impaired. Also, data from studies led by Rosenberger [26] and Bedgoni [27] and Giatromanolaki [28] indicate that HIF activity is essential for normal skin function and its dysregulation has been related to such skin disorders as psoriasis, melanoma, and other cancers of the skin; illustrating the necessity of a fully functioning HIF pathway.

Additionally, it has been shown that HIF-1a proteins are responsive to a number of non-hypoxic stimuli in a reaction oxygen species (ROS)-dependent manner [29]. Particularly, Rezvani *et al.* [30] demonstrated that ultraviolet B (UVB) irradiation has a biphasic effect on HIF-1 α that is directly related to the ROS generation in the cytoplasm and mitochondria of keratinocytes. The early phase of this effect involves the downregulation of HIF-1 α by ROS derived from the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in the cytoplasm while the late phase of this effect results in the accumulation of HIF-1 α due to the production of ROS in the mitochondria [30]. Notably, ROS has been shown to play a significant role in the induction of HIF-1 α through mitogen-activated protein kinase (MAPK) signaling in non-hypoxic conditions [31-33]. The activation of MAPK results from a signal from the mitochondria in response to the ROS generated from exposure to UVB irradiation [30]. When keratinocytes are exposed to UVR, UVB has been shown to stimulate Jun nuclear kinase and p38 thereby leading to the phosphorylation and accumulation of HIF-1 α by the inhibition of PHDs, specifically *egl*n1 [34-35]. Given the essential role *egl*n1 plays in the regulation of HIF-1a, one's ability to modulate, at the genomic level, the HIF pathway effectively could provide an adaptive advantage in an environment where UVB radiation is high.

4. Conclusion

We have established dimensional metrics that describe the statistical information dynamics of SNP variants in the human genome. Specifically, we have been able to quantify and display the adaptive force exerted on the genome in response to an environmental stressor/stimulus to optimize the survival of a population. Thus, the utility of this method is that it offers a novel way of addressing whole genome regulation of adaptation through the discovery of relationships between the environment and common variants in molecular systems.

In summary, we have developed genomic energy measures for the human genome that relate the distribution of alleles in SNPs and SNP haplotypes within a stable population to state variables associated with the environment within which that population resides. The state variables defined by common variations utilize the entropy of the statistical distribution of alleles to establish normalized information measures for persistent dynamic units within regions of the genome, as well as for the genome as a whole. Moreover, the human genome is self-organized network working towards one common agenda, population survival.

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