Evolution of Blood Pressure Regulation in Humans

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The human propensity for hypertension is a product, in part, of our evolutionary history. Adaptation to climate, first in Africa and then throughout the world, has driven our evolution and may have shaped current patterns of hypertension susceptibility. This article reviews human evolution and the impact of climatic adaptation on blood pressure physiology. Evidence suggests that genetic susceptibility to hypertension is ancestral and was magnified during early human evolution. Furthermore, differential susceptibility among human populations is due to differential selection during the out-of-Africa expansion 30,000 to 100,000 years ago. The most important selection pressure was climate, which produced a latitudinal cline in hypertension susceptibility. Therefore, the current epidemic of hypertension is likely due to new exposures of the modern period (eg, higher salt intake) interacting with ancestral susceptibility. Worldwide populations may differ in susceptibility to the new exposures, however, such that those from hot, arid environments are more susceptible to hypertension than populations from cold environments.

Introduction

A majority of people in industrialized countries will develop hypertension. By one estimate, 90% of middle-aged men and women living in the United States can expect to become hypertensive [1]. Other countries have similar burdens and in many the prevalence is even higher [2,3]. What is the source of the human propensity to develop hypertension? As discussed in this review, accumulating evidence suggests that susceptibility to hypertension was present at the origin of our species and was further magnified during early human evolution in Africa. The first anatomically modern humans expanded out of Africa approximately 30,000 to 100,000 years ago. During this expansion, they were exposed to widely divergent ecological conditions, which contributed to human diversification. Do populations differ in their susceptibility to hypertension as a result? In the United States, for example, hypertension occurs earlier, more often, and with greater severity among people of African descent compared to those of European descent. Although variation in the prevalence of risk factors accounts for most of the variance in hypertension, genetic susceptibility to hypertension may differ as well. This article discusses the evidence suggesting that differential susceptibility among human populations arose during the out-of-Africa expansion due to differential exposure to selection pressures.

Hypertension Susceptibility Is Ancestral

The evolution of hypertension susceptibility begins in Africa. The weight of evidence suggests that our lineage evolved in Africa until approximately 100,000 years ago. For most of this time, Africa was wetter than now, and, until approximately 15 million years ago, all African primates were adapted to this hot, wet climate. Salt sensitivity, the propensity to retain salt and water, may have been adaptive in this ancestral environment [4,5].

Effective heat dissipation is essential in hot environments and is achieved most efficiently through evaporative heat loss [6]. Sweating, however, can lead to loss of large amounts of salt and water [6], eventually leading to hypovolemia and decreased capacity to dissipate heat [7]. In addition, humans and nonhuman primates living in tropical climates have very low salt intakes [8]. Low salt intake and large salt losses due to sweating made a robust salt appetite and renal sodium conservation essential to survival. Studies of nonhuman primates support the argument that susceptibility is ancestral. Chimpanzees are morphologically similar to our common ancestor and live in a similar hot, humid environment [9]. They are also salt-sensitive [10]. When fed a high-salt diet, most chimpanzees will experience an increase in blood pressure. Weight also increases, consistent with salt and water retention. If the common ancestor of humans and chimpanzees were physiologically similar to modern chimpanzees, as suggested by similar skeletal morphology and habitat [9], the majority were likely salt avid as well.

Chimpanzees and humans also share hypertension susceptibility alleles in at least two genes, *angiotensinogen* (*AGT,* National Center for Biotechnology Information [NCBI] GeneID 183) and the *epithelial sodium channel γ subunit* (*ENaCγ,* NCBI GeneID 6340). Alleles in these two genes, *AGT A–6G* and *ENaCγ A-173G,* are functional, affecting gene expression or function in experimental studies, and are associated with high blood pressure. These alleles are also the ancestral alleles, fixed in chimpanzees and other nonhuman primates, suggesting that a portion of our shared genetic susceptibility to hypertension is ancestral. As Di Rienzo and Hudson [11•] have discussed, many alleles that increase susceptibility to hypertension, coronary artery disease, and type 2 diabetes are ancestral. This evidence suggests that the genetic origins of susceptibility to common chronic disease are due to adaptations to ancestral environments. As originally discussed by Neel [12] and expanded by others [13], these alleles improved survival in ancestral environments characterized by salt scarcity, low-calorie diets, and regular physical activity. In the current environment of salt and calorie excesses and infrequent physical activity, these alleles can be detrimental, leading to obesity, type 2 diabetes, and hypertension.

Hypertension Susceptibility Was Magnified During Early Human Evolution

Hypertension susceptibility may have been further magnified during early human differentiation. In contrast to the wet conditions of the early Miocene, the environmental context of hominin evolution since the mid-Miocene was characterized by increasing aridity [14–16]. Many human characteristics represent adaptations to these new conditions. For example, many of the features that distinguish humans from nonhuman primates facilitate heat dissipation, including hairlessness and a markedly enhanced capacity to sweat [17]. Because heat dissipation through sweating results in large volume losses, further enhancement of salt and water avidity and cardiovascular reactivity were likely part of our adaptation to hot, dry African environments since the Miocene.

As previously discussed, Africa was covered with a dense rainforest and mid-Miocene primates were adapted to life in its canopy [16,18]. From 15 million years ago (Ma) to 6 Ma, Africa experienced a gradual cooling and drying, resulting in fragmentation of the rainforest and expansion of woodland [16]. Smaller primates remained in the canopy while larger primates adapted to the forest floor [18]. Between 6 Ma and 3.2 Ma, Africa experienced a subtle warming [16]. In the resulting mosaic of rainforest, woodland, and savannah, bipedal primates with tree-climbing ability spread across Africa [19]. From 3.2 Ma to 2.5 Ma, and again, around 1.7 Ma, Africa experienced a sharp increase in aridity with expansion of the savannah [14,16,20]. During this time, there was widespread extinction of forest-adapted browsing mammals and expansion of savannah-adapted grazers [20–22]. The dominant bipedal primates before this period were the *Australopithecines*. With the sharp shift to dryer conditions, the *Australopithecines* were replaced by *Paranthropus,* a genus also adapted to the mosaic of forest, woodland, and savannah [22]. A second emergent genus, *Homo,* was the first hominin to fully commit to the expanding savannah, a commitment made possible through enhanced heat dissipation.

The savannah offered new challenges for early *Homo*. Unlike forest and woodland, savannah productivity is concentrated in migrating herbivores rather than in variety of plants. Therefore, our diet shifted from plants to animals, requiring the evolution of wide-ranging mobility [23]. One of the most striking morphologic differences between *Australopithecines* and *Homo*—the much greater size of the latter—allowed our genus to significantly expand its range [24,25]. This greater mass had both a thermodynamic advantage (increased heat storage) and a thermodynamic disadvantage (increased heat production). Increased heat storage served as a heat reservoir, offsetting the much cooler nighttime temperatures on the savannah. The disadvantage of increased heat production during the day was mitigated by distributing the greater body mass over a taller, but relatively thinner, frame, creating the high surface area–to–volume ratio required for heat dissipation [17,26].

Bipedality, which had developed earlier, was thermodynamically advantageous as well [6,23,27–30]. Compared to forest and woodland, the savannah is dry, windy, and sun-exposed. Bipedality decreases exposure to direct sun [31] and raises most of the body off the ground where the air is cooler and faster moving [29,31]. Hairlessness also facilitated heat dissipation [32,33]. Hair blocks radiant heat absorption during the day and promotes heat retention at night, an important consideration for smaller mammals [34]. However, daytime sun exposure is less important in the shade of the forest canopy. Therefore, among forest-adapted primates, hair density decreases as body size increases [35], suggesting that *Australopithecus* was relatively hairless. On the more sun-exposed savannah, the disadvantage of hairlessness is minimized by adaptations that reduce radiant heat absorption, such as bipedal posture, shade-seeking at midday, and hair on the scalp (the most sun-exposed portion of a bipedal animal) [36]. More importantly, hairlessness facilitates heat loss via sweating [25,32,33], perhaps our most important thermodynamic adaptation. Evaporative heat loss is especially effective in hot, dry, windy environments [6]. Accordingly, humans have an unmatched capacity to sweat, and are able to sustain a sweating rate of 2 L/h [37,38]. A robust salt appetite and enhanced renal salt avidity would offset daytime volume losses from sweating with nighttime volume expansion. Furthermore, increased arterial tone and force of cardiac contraction would support blood pressure

and organ perfusion during periods of low blood volume that might occur during the day or during a prolonged drought. Therefore, genetic variation that enhances arterial and cardiac contractility may be protective in hot, arid environments.

Consistent with the notion that hypertension susceptibility was magnified in *Homo,* many alleles that increase susceptibility to hypertension are common but are not ancestral, suggesting that hypertension susceptibility was magnified after the divergence of the line leading to *Homo* approximately 6 million years ago. Although the hypertension susceptibility alleles *AGT G-6A* and *ENaCγ-173G* are ancestral, other functional variants that increase hypertension susceptibility are not. For example, *AGT G-217A,* G protein β3 subunit (*GNB3,* NCBI GeneID 2784) *C825T,* β2 adrenergic receptor (*ADRB2,* NCBI GeneID 154) *G47A* and *G79C,* epithelial sodium channel α (*ENaCα,* NCBI GeneID 6337) *A-946G* are only present in humans, rising to high frequency during the period of our adaptation to increasing aridity. To illustrate, *GNB3* is one of five distinct beta subunits that in combination with alpha and gamma subunits form signal transducing G proteins. G proteins couple cell surface receptors to effectors that generate intracellular signals, thereby regulating many biological functions, including blood pressure. Vasoactive agents such as endothelin-1, angiotensin II, and noradrenaline produce greater vasoconstriction when their receptors interact with G proteins containing a *GNB3* subunit with thymine (825T) rather than cytosine (825C) at cDNA position 825 [39–41]. *GNB3 825T* is the derived allele, rising to high frequency in many heat-adapted populations. Therefore, although a portion of hypertension susceptibility is ancestral, salt avidity and cardiovascular reactivity were likely magnified during early human evolution prior to the out-of-Africa expansion of anatomically modern humans.

Differential Susceptibility to Hypertension Is Due to Differential Exposure to Selection Pressures During the Out-of-Africa Expansion

Our genus originated in Africa, then expanded out-of-Africa to inhabit the rest of the world. By 1.75 to 1.0 Ma, *Homo* had reached as far north as Dmanisi, Georgia, and as far east as east Asia [42]. In Africa, our genus continued to adapt to aridity, eventually evolving into our species by 160,000 years ago. By 35,000 years ago, the last Paleolithic wave of anatomically modern populations had swept out of Africa [43]. These people were uniquely adapted to hot, dry conditions as illustrated by long, thin extremities, narrow hips, and short trunks [44–46]. By the end of the last glacial period, our species ranged from the tip of Africa to the Arctic Circle. Exposure to widely divergent ecological conditions contributed to human diversification, and the development of differential susceptibility to hypertension.

Human variation is characterized in part by a latitudinal cline in body size and shape. This clinal variation is common for species with a wide latitudinal range [47]. In fact, the association is stronger for humans than for many other species [47,48]. Similarly, limb length varies by latitude such that as latitude increases, limb length decreases. This association is also found in humans [26,48,49]. Both ecological rules serve to facilitate heat dissipation at the equator by maximizing the ratio of surface area to volume, and to conserve heat toward the poles by minimizing this ratio. Changes in body shape that occurred in Europe over the past 30,000 years illustrate the rapidity of physical adaptation to climate. Prior to the Last Glacial Maximum, people with body proportions approximating those of savannah-adapted equatorial groups expanded into Europe. Within 20,000 years, these populations had developed high-latitude body proportions characterized, in part, by a smaller limb length–to–trunk ratio [26,44]. Indeed, the evolution of clinal variation in body size and shape has occurred throughout Eurasia and, to a limited degree, among native populations in the Americas [17,26,48,50]. The morphologic cline among New World populations has evolved over 10,000 to 30,000 years. The rapidity of evolution across a latitudinal cline is well described in other species [51,52], and is one of the strongest selection forces known [51].

A cline in body size and shape is the phenotypic signature of selection by latitude, but what are the genetic signatures? Latitudinal selection results in the evolution of clinal variation in allele frequencies [53]. For example, latitudinal variation is common for glycolytic enzymes among organisms that do not control their internal temperature. This variation serves to optimize reaction kinetics and enzyme viability for an organism's normal environmental temperature. Mechanisms that control internal temperature vary by latitude as well. For example, human mitochondrial genes demonstrate evidence of selection by latitude [54]. This variation may influence the efficiency of oxidative phosphorylation and, therefore, cellular heat production, an important adaptation to external temperature. Similarly, the biological systems that regulate blood volume and cardiovascular reactivity facilitate the maintenance of body temperature through evaporative heat loss. As the primary thermodynamic requirement shifted from heat dissipation to heat conservation, selection for salt and water avidity and cardiovascular reactivity lessened. As a result, people from colder regions have diminished vascular reactivity [55–59] and salt avidity [60,61], actually producing more sweat during heat stress than equatorial populations [62]. This difference in volume avidity and vascular reactivity, a portion of the physiologic source of hypertension susceptibility, may be a consequence of differential exposure to selection pressures since the out-of-Africa expansion.

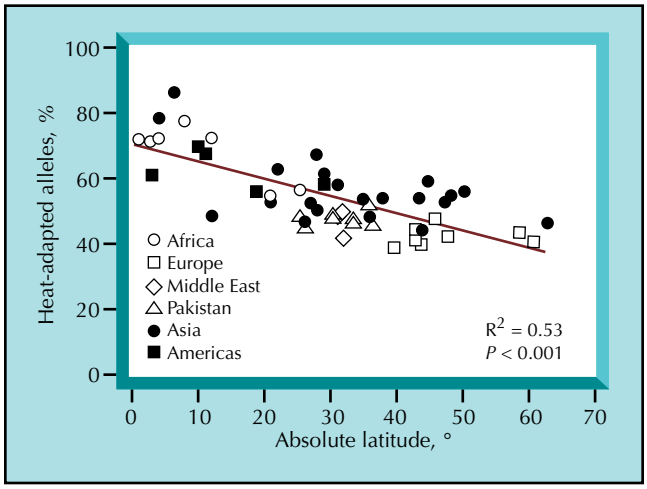

Figure 1. Heat adaptation is strongly associated with absolute latitude among the 53 populations of the Foundation Jean Dausset–Centre d'Etude du Polymorphisme Humain (CEPH) Human Genome Diversity Cell Line Panel.

Hypertension Susceptibility Alleles Are Strongly Associated With Latitude

Differential susceptibility to hypertension may be a consequence of ecological selection during the out-of-Africa expansion. Consistent with this notion, Nakajima et al. [63•] found evidence of positive selection among populations outside of Africa near one of the single nucleotide polymorphisms (SNPs) examined in this work, *angiotensinogen G-6A*. Similarly, Thompson et al. [64•] found evidence of positive selection near another SNP associated with increased salt avidity and hypertension, *cytochrome P450 3A5*1/*3*. For both genes, the allele that increases salt avidity is the major allele among populations near the equator. By contrast, the allele that decreases salt avidity has risen to high frequency outside of Africa, probably due to selection [63•,64•].

My collaborators and I recently described the worldwide distribution of hypertension susceptibility as defined by the prevalence of seven functional alleles in five genes that influence volume avidity or cardiovascular reactivity [65•]. Among the 53 worldwide populations represented in the Foundation Jean Dausset–Centre d'Etude du Polymorphisme Humain (CEPH) Human Genome Diversity Project, populations at low latitudes, or in hot, wet climates, had a high prevalence of hypertension susceptibility alleles, whereas populations at high latitudes, or in cold, dry climates, had a low prevalence of these alleles (Fig. 1). For example, among populations within 10° of the equator, on average 74% of the genetic variants increased hypertension susceptibility. However, only 43% of the variants increased susceptibility among populations within 10° of the Arctic Circle. Across all populations, the association of hypertension susceptibility with temperature and humidity was strong, graded, and continuous.

To assess the significance of the association between hypertension susceptibility and latitude, we compared the worldwide distribution of the functional susceptibility alleles with the distribution of 404 nonfunctional markers. No marker had as strong an association with latitude as the functional alleles *AGT-6A* or *GNB3 825T*. Only one marker was more strongly associated with latitude than *ENaCα-946G* and only seven markers were more strongly associated with latitude than *ENaCγ-173G* or *ADRB2 47A/79c*.

GNB3 C825T and Latitude Are Strongly Associated With Worldwide Variation in Blood Pressure

If selection shaped our susceptibility to hypertension through ecological variables that correlate with latitude, then latitude and the associated functional alleles should have a measurable effect on worldwide variation in blood pressure. To test this hypothesis, my collaborators and I investigated the extent to which latitude and hypertension susceptibility contribute to worldwide blood pressure variation using data from INTERSALT, an epidemiologic study of blood pressure in 52 populations around the world. We estimated the population frequency of *GNB3 825T* for 35 INTERSALT populations using data from the Human Genome Diversity Project and the literature [65•].

Among the 35 INTERSALT populations with allele frequency data, latitude explained 47% of the worldwide variation in blood pressure. With an increase of 1° of latitude north or south, population-average systolic blood pressure increased by 0.3 mm Hg. When *GNB3 825T* was included in the analysis, we were able to explain 64% of worldwide variation in blood pressure. With each 1% increase in *GNB3 825T* allele frequency, blood pressure increased 0.19 mm Hg. When body mass index (BMI) was added to the model, 74% of the variation in mean systolic blood pressure was explained. The addition of sodium excretion, BMI, or alcohol intake did not diminish the effect of latitude and *GNB3 825T* on blood pressure variation.

The strong association of latitude and *GNB3 825T* frequency with worldwide blood pressure variation is partly due to the use of population-level data in this analysis. Latitude represents several ecological factors (eg, temperature and humidity) that affect blood pressure. Similarly, *GNB3 825T* represents a number of functional alleles that influence hypertension susceptibility. For example, those populations that have a high prevalence of the *GNB3 825T* allele also have a high prevalence of heat-adapted alleles at other locations. It is highly likely that these and other unmeasured hypertension susceptibility alleles that correlate with latitude contribute to the predictive strength of *GNB3 825T* in this model.

Conclusions

The evidence discussed here suggests that at least a portion of susceptibility to hypertension is ancestral, and that this

susceptibility was further magnified during early human evolution. Furthermore, populations differ in susceptibility to hypertension, and this differential susceptibility is due to differential exposure to selection pressure since the out-of-Africa expansion. The most important selection pressure was climate, which produced a latitudinal cline in susceptibility. Consistent with this hypothesis, latitude and the *GNB3 825T* allele explain a large portion of worldwide variation in blood pressure.

What is the source of the current epidemic of hypertension among industrialized populations? As shown in migration studies, the shift in the population average blood pressure occurs as people migrate into developed countries. Therefore, the upward shift in blood pressure distribution among industrialized populations is more likely due to a greater burden of exposures, such as increased salt intake and obesity, rather than increasing hypertension susceptibility. However, evidence suggests that populations may differ in susceptibility to these exposures. Therefore, the current epidemic of hypertension is likely due to the new exposures of the modern period, such as higher salt intake, interacting with ancestral susceptibility. However, populations differ in susceptibility to these new exposures such that those from hot environments are more susceptible to hypertension than populations from cold environments. This differential susceptibility is due to our history of adaptation to climate.

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The original article reporting worldwide variation in hypertension susceptibility defined by seven functional alleles in five genes. Contains further results and figures not discussed in this article.