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Diversity and evolution of human eccrine sweat gland density

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A B S T R A C T

The human eccrine sweat gland is central to the evolution of the human genus, permitting an enormous thermoregulatory sweating capacity that was essential to the human niche of high physical activity in open, hot, semi-arid environments. Despite a century of research inventorying the structure and function of eccrine glands and the physiological responses of human heat acclimation, we do not have a clear understanding of how intraspecific differences in eccrine density affect thermoregulation. Similarly, existing data does not comprehensively catalogue modern human diversity in this trait, nor do we understand the relative influences of evolutionary forces and phenotypic plasticity in shaping this diversity.

1. Introduction

Human heat dissipation capacity is highly derived, far surpassing that of many other mammals (Carrier et al., 1984; Jablonski and Chaplin, 2000; Jablonski, 2004; Lieberman, 2015). The evolutionary roots of this exceptional thermoregulation reach back to basal catarrhine primates, which saw the expansion of eccrine sweat glands from the hands and feet to the body surface. The anthropoid (ape) lineage is characterized by reduced hair follicle density, and in hominins (human ancestors) body hair evolved into microscopic vellus hairs, further increasing the effectiveness of sweating (Kamberov et al., 2018).

Considerable attention has been paid to understanding the physiology of human thermoregulation, particularly the compensatory responses that accompany heat exposure and the acclimation that follows. Research on the human sweat apparatus, including the eccrine sweat glands, has primarily focused on the histology and biochemistry of individual glands. Comparatively little attention has been directed towards understanding interindividual variation in human eccrine sweat gland density. This measure should have significant physiological relevance due to its obvious potential relationship with heat dissipation. It also has evolutionary importance because increased eccrine gland density, and perhaps the ability to adjust active gland density to climate, were likely essential adaptations for human ancestors. At some point in human evolution, hominins started to walk and run long distances in open, semi-arid habitats (Blumenthal et al., 2017) with the genus *Homo* being especially characterized by increased locomotor activity (Bramble and Lieberman, 2004). These thermoregulatory challenges were further compounded by bigger brains which demanded further adaptations to keep cool during physical activity (Lieberman, 2011).

Kuno (1956) was among the first to recognize the importance of variations in eccrine gland density among humans. Based on studies of living humans he hypothesized that eccrine sweat glands become fully functional by age 2.5 via cholinergic innervation, while some proportion of glands remain inactive for life (Kuno, 1956; Thomson, 1954). Further, he proposed that active gland density was phenotypically plastic, with hotter early childhood climates eliciting greater gland activation, resulting in higher gland density in adulthood. In addition to phenotypic plasticity, evolutionary forces may have shaped diversity in eccrine density as humans migrated out of Africa into novel environments. Sixty-three years later Kuno's hypotheses remain largely untested. Similarly, existing data on inter-population diversity in eccrine density are insufficient owing to small sample sizes, inconsistency in methodology across studies, and methodological limitations (Taylor, 2006).

Characterizing diversity in human eccrine gland density and assessing the contributions of phenotypic plasticity and evolutionary history to this diversity are essential to understanding the evolution of human thermoregulation. Thus, in this review we aim to: 1) provide context for understanding the role of eccrine glands in modern human thermoregulation, and in the span of human evolution; 2) summarize current methods for measuring variation in human eccrine gland density and what these variations imply; 3) present potential mechanisms through which eccrine density may be shaped by both evolutionary forces and climate-driven plasticity; and 4) discuss future avenues of research to better understand human eccrine gland diversity.

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2. Eccrine glands and human heat acclimation

2.1. Biology of eccrine glands

The base of the eccrine gland is a coiled structure, lying in the dermis and surrounded by a capillary cage that provides water and electrolytes for sweat production (Yamamoto, 1990). The secretory coil leads to a duct that extends through the epidermis and opens onto the skin surface as a pore. Each gland is innervated by multiple sudomotor nerve fibers of the sympathetic nervous system (Kennedy et al., 1994) using the neurotransmitter acetylcholine. When stimulated by these nerve fibers, sweat produced in the secretory coil is forced out onto the skin surface; evaporation of sweat cools the skin hence underlying venous blood, thus lowering core temperature. Sweat production in the secretory coil relies upon active transport which is fueled by intracellular and plasma glucose via both aerobic and anaerobic metabolism (Sato and Dobson, 1973; Sato, 1977; Smith and Dobson, 1966). During both passive heating and physical activity, greater numbers of sweat glands are gradually recruited (Kondo et al., 1998) and sweat output per gland increases (Amano et al., 2011). Some glands appear to be recruited earlier and more often than others, suggesting variation between glands in stimulation threshold for sweat production (Nishiyama et al., 2001). Recent evidence shows that eccrine glands are sometimes associated with a hair follicle (Poblet et al., 2018) and, like other skin appendages, aid in epidermis wound healing (Rittié et al., 2013).

2.2. Human heat acclimation

The body of research on human heat acclimation is vast and beyond the scope of this review, but a brief summary may provide context for understanding the role of eccrine gland density in the processes of thermoregulation (See Taylor, 2014 for a thorough treatment of the literature on this topic.). Acclimation (phenotypic response) to heat involves multiple physiological and anatomical systems. Short-term acclimation includes increased sweat rate, lowered threshold for onset of sweating, and eccrine gland hypertrophy, as gland size can vary fivefold between individuals and correlates positively with maximum sweat rate (Sato et al., 1989). In contrast, long term acclimation is characterized by decreased sweat output, increased sweating efficiency (calories of heat lost per ml of sweat) via higher skin temperatures, and reduced metabolic heat production (Bae et al., 2006; Gale, 1973; Katsuura et al., 1993), responses seen in individuals with tropical ancestry and temperate peoples with long-term tropical residence. Several studies have claimed reduced sweat output in natives of tropical habitats, with lower reported maximum sweat rates compared to Europeans among Ugandans (McCance and Purohit, 1969), Nigerians (Thomson, 1954), Indians (Edholm et al., 1965; McCance and Purohit, 1969; Samueloff, 1987), New Guineans (Fox et al., 1974), Bedouin (McCance et al., 1974), and Malaysians (Duncan and Horvath, 1988). However, these studies did not control for phylogenetic and geographic ancestry, so they do not inform questions related to phenotypic plasticity vs. evolutionary/genetic adaptation. Finally, attenuated sweat responses may characterize hot-humid as opposed to hot-dry long-term acclimation (Taylor, 2014). Humid air reduces evaporation rate and leads to "wasteful" sweat production in which increased sweating rates fail to produce proportional cooling effects (Garden et al., 1966). Nonetheless, increased sweat rate occurs with short-term humid heat exposure in tropical people just as in temperate people (Mitchell et al., 1976).

3. Diversity in human eccrine gland density

Human eccrine gland density varies across body regions, with the highest densities in the fingers and toes. In these areas, glands function in psychologically induced sweating as well as thermoregulation. Eccrine gland densities on the body surface vary greatly between individuals. A comprehensive review suggests averages of ~200/cm^2 on the forehead and 70–140/cm^2 on the back, torso and limbs, with a total average gland number of 2.03 million glands for a "typical" individual with a 1.8 m^2 body surface area (Taylor and Machado-Moreira, 2013). Differences among body regions may owe partly to, or partly result in, differing heat dissipation properties; however, gland density across individuals is correlated with body surface area (Kuno, 1956; Szabo, 1967; Thomson, 1954) suggesting that intersegmental differences in gland density are mostly resultant from differential body segment growth during development.

Studies quantifying gland density take one of two approaches: counting anatomical glands through direct histological observation of excised or cadaver skin; or counting only "active" glands by inferring the presence of pores via sweat droplets, either through direct observation or indirectly via plastic or vinyl polysiloxane impressions, starch-iodine droplet visualization, or droplets recorded on iodine-impregnated paper. Vinyl polysiloxane impressions are the most sensitive and tend to produce the highest gland counts (Gibbons et al., 2008; Harris et al., 1972); other methods also have high repeatability but direct comparisons cannot be made between methods. Because sweat glands are recruited incrementally during physical activity or heat exposure, an insufficient heat stimulus may produce misleadingly low active gland counts. Therefore pharmacological stimulation, usually with pilocarpine nitrate delivered via iontophoresis or injection, is preferred because it stimulates sweat production in all physiologically active glands (Webster and Rundell, 1982). However, several authors report comparable gland counts from pilocarpine compared to a sufficiently robust thermal exposure (Kuno, 1956; Sato et al., 1970). Additionally, glands that respond to pilocarpine but not thermal stimulation are effectively "inactive" because they don't contribute to thermoregulation in real-world conditions, so this distinction may be unimportant.

3.1. Are there "inactive" eccrine glands?

Since Kuno (1956), several researchers (Thomson, 1953; Folk and Semken, 1991; Taylor and Machado-Moreira, 2013; Machado-Moreira and Taylor, 2017) have proposed that some proportion of human eccrine glands are wholly inactive—that is, they appear normal in structure but fail to produce sweat in response to thermal exposure, physical activity, or pharmacological stimulation. If true, the existence of morphologically developed, non-functional glands presents the possibility of phenotypic plasticity in active eccrine gland density. It is therefore important to assess the evidence supporting this claim.

Kuno (1956) was among the first to report the existence of inactive sweat glands. He observed sweating with a microscope on the fingertip, where sweat pores are readily visible on the dermal ridges. Some pores never discharged sweat after repeated applications of varying heat stimulus-for example, six out of 29 pores in a 5 mm^2 area on the index finger. However, these glands are not primarily used in thermoregulation, and pharmacological stimulation may have recruited more of them. Ogata (1936, as reported by Kuno, 1956) found comparable counts of active sweat glands by applying "extreme" heat to acclimated subjects and from stimulation with acetylcholine delivered via iontophoresis, concluding that repeated high thermal stress produced gland activation equal to that of pharmacological stimulation. Ogata then used passive heating at 45 °C, coated the skin of his own forearm, thigh, and leg, and the forearm of another volunteer in oil and directly observed sweat droplet formation via microscope. Following this, he excised 0.3 cm^2 of skin from these areas to count glands histologically. He found that these anatomical counts always exceeded gland counts obtained from counting sweat droplets, and concluded that some glands fail to respond to any stimulation. These data, though limited, revealed active to inactive gland ratios ranging from nearly 1:1 to 16:1. Glands which failed to produce sweat were identical in structure to functional glands. Finally, to rule out the possibility that glands with very low

sweat production were mistaken as inactive, Ogata observed sweat droplet formation during passive heating in 10 consecutive sessions during winter. Sweat output per gland increased, as expected with heat acclimation, but the location of active sweat pores was consistent across the 10 trials.

Since Ogata's work we are aware of only one other study showing evidence for completely inactive glands. Thomson (1953) chemically burned skin, removed the blistered layers, counted the eccrine glands present, and compared these figures with sweat droplet counts made from plastic impressions during heat-induced sweating on the same areas of skin. In three individuals all droplet impressions corresponded to an eccrine gland. In two individuals, two out of 48 glands and three out of 60 glands respectively did not have a corresponding hole in the impression. This was taken as evidence that these glands were inactive, though conceivably these observations may have resulted from an insufficient heat stimulus or lack of fidelity in the impressions.

One potential method for identifying inactive glands would entail locating eccrine pores in vivo and noting those which do not produce sweat. Thomson (1953) attempted this by pressing plastic impression material into non-sweating skin, but despite the high resolution of the material (which recorded hair follicles), pore openings were not visible except on the fingers and toes. We recently confirmed these results by pressing a vinyl polysiloxane material into non-sweating skin and cadaver skin and searching the resulting impressions with laser confocal microscopy (Best and Kamilar, unpublished data). Even at skin locations where an active gland was confirmed through sweat stimulation pores were not recorded in the impressions. We concluded that existing noninvasive measures are insufficient to identify pores when not producing sweat, perhaps because pores are forced open during sweat expulsion and are effectively closed otherwise (Sato et al., 1979). Thus, we argue that sweat droplet quantification followed by skin excision and histological gland counting is the best way to confirm the presence of physiologically inactive sweat glands. To our knowledge Ogata (1936, as reported by Kuno, 1956) and Thomson (1953) are the only researchers to have used this approach, perhaps due to its invasiveness, but references to inactive glands are nonetheless found in published literature. Folk and Semken (1991) claimed that some human eccrine glands appear normal but “are actually functionless”, but this statement is made without reference to data or published literature. Several other papers (Randall, 1946; Willis et al., 1973) have been erroneously cited as providing evidence for inactive glands. Randall (1946) reported that “extreme” thermal stimulation was required to attain gland recruitment numbers equal to that of pharmacological stimulation, and suggested that Ogata incorrectly inferred the presence of inactive glands because his thermal regime was not sufficiently strenuous; this objection appears unlikely, though Ogata's quantification methods (observing sweat droplets under a layer of oil and wax) may be insensitive. Willis, Harris and Moretz (1973) provided validation of a silicone impression technique, finding that at least 95% of the same sweat ducts were identified in impressions spanning a 4–8 week period.

Several researchers doubt the existence of inactive eccrine glands. Harris, Polk and Willis (1972) suggest that Kuno's technique was insensitive and he simply missed some active glands. Gordon and Maibach (1968) claimed that the outer layer of keratinized skin cells may block sweat ducts, but Johnson and Shuster (1970) refuted this and provided evidence that sweat duct occlusion is not a common occurrence in healthy skin. In short: the existence of inactive, fully-formed sweat glands is unresolved.

Finally, it is worth considering whether a gland must be wholly incapable of producing sweat to merit interest when considering diversity in gland density. Glands which consistently produce only small amounts of sweat will contribute little to thermoregulation, making them just as relevant to this discussion as “inactive” glands, and several studies demonstrate their existence. Saito (1934, as reported by Kuno, 1956) characterized some glands in the palm as poorly active. Using pilocarpine iontophoresis and a silicone impression technique, Willis et al. (1973) made successive gland counts over 4–8 weeks on the same body sites, and described < 10% of active glands as “poorly functional”: glands which were found to produce only tiny holes in the impression material in week 1 continued to produce low or variable output over the succeeding weeks. This implies that low-functioning glands may not be observed in single-session gland counts and may therefore be mistakenly labeled as “inactive”. From a physiological perspective this distinction may be overstated because 1) phenotypic plasticity may result in poorly-active glands via the same mechanisms as wholly inactive glands; and 2) poorly active glands will contribute little to thermoregulation. Thus, for the purposes of assessing differences in active gland density and the physiological relevance of these differences, we will maintain the use of “inactive” to mean both wholly-inactive and poorly active.

4. Evolutionary origins of human eccrine gland density

4.1. Comparative eccrine biology

Eccrine glands do not fossilize, but evolutionary questions are informed by the comparative biology of eccrine glands in extant species. Mammals have eccrine glands on the volar surfaces of the paws which are thought to aid in frictional gripping (Adelman et al., 1975). In humans and some other primate species, eccrine sweat glands are also found over most of the body surface and are principally used in thermoregulation. Eccrine glands should not be confused with the apocrine sweat glands, also found in the skin of some body areas (axillae and pubic regions in humans). Apocrine glands are associated with a hair follicle; a few ungulates such as horses and camels employ these glands in thermoregulation (Bullard et al., 1970; Whittow, 1971), and some evidence suggests that apocrine glands also perform this role in non-human primates (Whitford, 1976).

Eccrine gland profusion on the body surface first evolved near the base of the catarrhine primate clade (Montagna and Yun, 1963; Montagna et al., 1964; Montagna and Machida, 1966; Folk and Semken, 1991; Best and Kamilar, 2018), a group comprised of monkeys and apes from Africa and Asia. Eccrine density continued to increase during the evolution of apes and even more so in fossil hominins (human ancestors). Several primates are known to perform thermoregulatory sweating (Johnson and Elizondo, 1979; Lemaire, 1967; Mahoney, 1980; Sato et al., 1990) though none match the heat dissipation capacity of humans.

Kamberov et al. (2018) provides the most rigorous comparative study to date on eccrine density in extant primates. Chimpanzees and macaques were found to have similar eccrine density while that of humans is 10 times higher. Macaques were found to have higher hair follicle density than either chimpanzees or humans, who intriguingly had similar hair follicle density. The near-naked skin of humans, then, is due not to fewer hair follicles but a shift from terminal pigmented hair to microscopic, unpigmented vellus hair. This observation has important implications for the evolution of eccrine sweating in the human lineage. First, hair follicle density decreased in the ape lineage, which was then followed by a terminal-to-vellus hair transition and increased eccrine density in the hominin lineage (Kamberov et al., 2018). Hair follicles and eccrine glands develop from the same epithelial buds, and a shift in the timing and location of the changeover from hair follicles to eccrine glands endowed humans with greater eccrine density. Together, these adaptations are likely the product of selection for increased heat dissipation capacity.

Until Kamberov et al.‘s work, most information on primate eccrine gland counts came from a series of papers in the 1960's and 1970's, e.g., (Ellis and Montagna, 1962; Ford and Perkins, 1970), and others, which recorded qualitative and semi-quantitative histological characteristics of primate skin, including the distribution, structure, and histochemical composition of eccrine glands. We compiled these data (Best and Kamilar, 2018) for a phylogenetic analysis finding that glycogen

concentration (a fuel substrate powering eccrine gland metabolism) and degree of capillarization (enabling greater water, glucose and electrolyte delivery) were significantly correlated with climate across species. Specifically, primate taxa living in warm and dry climates tended to have greater eccrine glycogen stores and greater capillarization surrounding the eccrine glands. These results provide evidence for the evolution of increased sweating capacity in hot-dry climates but not hot-humid. Importantly, thermoregulatory sweating in extant primates occurs despite pronounced terminal (vs. vellus) body hair, suggesting that some increases in sweating capacity are not necessarily dependent upon increased physical activity or reduced terminal hair.

4.2. Human evolution and sweating capacity

Since early hominins such as *Sahelanthropus* and *Ardipithecus* (~7-3 mya) diverged from a last common ancestor with chimpanzees, it is likely they had apelike eccrine gland densities. Given their many other apelike characteristics (Pilbeam and Lieberman, 2017), it is not unreasonable to infer that thermoregulatory sweating in early hominins was comparable to chimpanzees. Humanlike thermoregulation evolved later, but it is unclear whether this shift began with *Australopithecus* or *Homo*.

Although *Ardipithecus* and other early hominins were probably facultative bipeds that climbed frequently and did not walk like humans, there are multiple lines of evidence that species in the genus *Australopithecus* (~4-1 mya) were effective, efficient striding bipeds while retaining some adaptations for climbing trees, perhaps for a measure of safety while sleeping (Barak et al., 2013; Raichlen et al., 2008; Sellers et al., 2005; Ward, 2013). We can infer only a little about thermoregulation in these hominins. Bipedalism might have conferred at least some thermoregulatory benefit if they were walking in hot, open habitats because upright posture reduces the body surface area exposed to solar radiation (Wheeler, 1991). However, it is unknown how long *Australopithecus* day ranges were and other skeletal traits associated with long-distance locomotion, including running, had not yet evolved (Bramble and Lieberman, 2004). These observations, together with evidence for a diet based largely on plants (Peterson et al., 2018; Quinn, 2019) have led to a consensus opinion that *Australopithecus* ranging was limited. However, Lieberman (2015) has suggested there might have been selection for enhanced thermoregulatory capacities in *Australopithecus*. Like all bipeds, australopiths were necessarily slow because they can generate speed with only two legs, and thus must have been vulnerable to predation. It would therefore have been advantageous for them to travel to foraging locations in the middle of the day when it was hot and predators are less active, thus favoring individuals with increased eccrine gland density and body hair reduction. (Lieberman, 2015).

For the time being we can only hypothesize about australopith thermoregulatory capacities, but there are many indications that by the time of the genus *Homo* more modern human sweating capacities had evolved. First, skeletal adaptations associated with long distance walking and running ability evolved in *Homo erectus* in Africa by 1.8 mya. This behavior was likely necessary to enable hominins to hunt and scavenge in an increasingly open savannah environment where food is widely dispersed, a hypothesis supported by butchery evidence and studies of contemporary hunter-gatherers who successfully run prey to heat exhaustion (Bramble and Lieberman, 2004; Liebenberg, 2006). Running in hot ambient temperatures poses an enormous thermoregulatory challenge and selection would have strongly favored enhanced heat dissipation, particularly via hair reduction and increased eccrine density. Second, increased body size in *Homo* produced a less favorable body surface area to volume ratio, compounding the thermoregulatory challenge imposed by increased locomotor behavior. Third, there is no doubt that the environment in Africa where early *Homo* has been found was hot and semi-arid (Blumenthal et al., 2017) and even walking, let alone running, would have produced great thermal strain. Still, questions remain about eccrine evolution in our genus. Sweating depletes body water reserves, leading us to wonder how selection produced a compromise between the need to cool and the need to avoid dehydration, a question we will address later (see “Does gland density matter?“). It seems plausible that plasticity, or perhaps differential selection across populations, similarly matches sweat gland density to demand, but as we will describe in the next section, this idea needs further testing.

Finally, heat dissipation via eccrine sweating declines with age (Inoue and Shibasaki, 1996; Inoue et al., 1998; Smith et al., 2013), perhaps starting as young as age 40 (Larose et al., 2013). Thus, along with other age-related physical decrements such as reduced muscular strength and aerobic capacity, reduced ability to dissipate heat would have further impaired ranging and locomotor activity in older hominins relative to that of younger individuals. Though, the impact that this would have on hominin life history evolution would probably be minimal since most individuals would reproduce well before 40 years old.

5. Current evidence for factors influencing variation in modern human eccrine gland diversity

5.1. Phenotypic plasticity due to climate

Kuno (1956) hypothesized that a hot environment during infancy prompts more glands to become physiologically active (i.e. capable of sweating) while a cooler environment produces lower active gland density, presumably because some glands were seldom recruited for sweating and became “inactive”. Further, he proposed a critical developmental window of approximately 2.5 years, based on his cross-sectional study of 16 individuals aged 35 days to 35 years. Kuno found that total gland number over the body surface increased up through age 2.5 and did not change thereafter. These results should be interpreted with caution because this study was not longitudinal and therefore the observed gland count differences may by the result of inter-individual variation. But his hypothesis is plausible. The specific phenotype for many biological traits is determined within a set developmental period (West-Eberhard, 1989) and there is evidence that active gland number does not increase with heat acclimation (Inoue et al., 1999).

Kuno's hypothesis for phenotypic plasticity is based on two studies. First, Kawahata and Sakamoto (1951) found higher active gland density in tropical southeast Asians than in Russians and Ainu, indigenous peoples of Japan and Russia. Unfortunately, this study design does not allow us to distinguish the effects of ancestry or phenotypic plasticity. Second, Kuno tested 26 people who were ethnically Japanese but raised in tropical Southeast Asian locations. Using a thermal stimulus and direct microscopic observation of the skin to count active sweat glands, Kuno found that these people had greater numbers of active sweat glands than Japanese-born individuals that were raised in Japan but emigrated to tropical climates in adulthood. It appears that he did account for body surface area as gland counts are reported as whole-body estimates but effect sizes and statistical significance are not reported. Only a handful of researchers have tested Kuno's hypothesis since these initial findings. Ojikutu (1965) observed higher active gland counts in 108 Nigerian-born males living in Nigeria compare to 13 Ghanaian and Liberian-born males who moved to Germany as adults and resided there for 1–5 years. Interestingly, while Kuno's data suggest phenotypic plasticity in gland density during childhood, Knip (1975) provides evidence for increases in active gland density during adulthood. Studying people born and living in the Netherlands compared to those born in the Netherlands but living as adults in Suriname for four months to nine years, he found the latter to have more active glands after adjusting for body surface area. Further, he used a sensitive plastic imprint technique and sampled up to 144 cm^2 of skin, an enormous area compared with other studies. Still, it is hard to reconcile these results with existing dogma stating that active gland density cannot be

increased after childhood. Knip suggests that such increases are possible only with long-term acclimation, though to our knowledge these results have not been replicated.

Existing evidence for Kuno's phenotypic plasticity hypothesis appears to be limited to three studies. Yet, Kuno's hypothesis is influential and often repeated. In fact, the 2016 edition of *Gray's Anatomy* states, "People indigenous to warmer climates tend to have more sweat glands than those indigenous to cooler regions". Unfortunately, there is scant evidence to support this statement. While existing direct evidence on eccrine gland data in populations from varying climatic conditions is insufficient, a growing body of data on mechanisms of phenotypic plasticity (how traits with the same genetic basis can be altered due to different environments of development) lends credence to this idea, as we will discuss later (see "proximate mechanisms influencing eccrine gland density".)

5.2. Evolution and variation among modern human populations

The combined results of Best et al. (2018) and Kamberov et al. (2018) reinforce earlier hypotheses that natural selection drove eccrine evolution in hominins and early humans. More research is needed, but selection may have continued to shape eccrine density in *Homo sapiens* as they expanded out of Africa and into novel environments. In cooler environments where heat dissipation was less important, selection may have been relaxed, and neutral evolutionary processes such as genetic drift and gene flow may also have influenced eccrine density in the human lineage. Regardless of the evolutionary force, such gland density diversity across populations should be measurable today. Existing data is sparse and problematic but worth a brief consideration and is summarized below.

Limited research assessing differences in total and active eccrine gland density across human populations generally shows low variation, with a few exceptions. Kawahata and Sakamoto (1951) reported higher active gland counts in people indigenous to tropical regions in Asia compared to indigenous peoples of Japan and Russia, though again he does not provide statistical analyses. Kawahata and Adams (1961) found more active glands in European-Americans than African-Africans, though Taylor (2006) re-analyzed these data and found this difference to be statistically insignificant. Using iontophoresis of carbachol (a chemical which apparently induced unpleasant physical side effects) and a starch-iodine paper method, Toda (1967) reported greater active gland density in Indonesian compared to Japanese populations. However, it is not clear if he accounted for body surface area, and puzzlingly the iontophoresis current applied to Indonesians was greater than that used with Japanese volunteers. At the molecular level, Kamberov et al. (2013) found evidence of positive selection for a gene variant (EDARV370A) of the EDAR gene, which originated in Central Asia approximately 30,000 years ago. This allele has pleiotropic effects, including increased eccrine gland density in the finger tips, reduced hair follicle density, and increased mammary ductal branching. While this work is important for connecting genotype to gland density, selection for this allele appears to have occurred within one population and the specific trait (e.g. hair follicle density, mammal duct branching) selected for remains unknown. This limits our ability to make inferences about gland evolution across populations.

Other studies have sought population level (evolutionary) differences in anatomical and active gland density based on geographic ancestry and have found little or no differences. In a comprehensive review Taylor (2006) concluded that small sample sizes and methodological limitations render the existing body of work on gland differences across populations almost immaterial, and concludes that any observed differences result from phenotypic plasticity. We agree that existing data is problematic and insufficient, but as such, we also cannot confidently attribute variation to plasticity.

6. Proximate mechanisms influencing eccrine gland density

It is reasonable to hypothesize that variations in human eccrine density may be influenced by climate, both through natural selection acting on genes regulating eccrine development and through phenotypic plasticity. But what proximate causes underlie differences in eccrine density? Evidence from developmental biology suggests several potential mechanisms.

Anatomical (total) eccrine gland number is determined early during development and may conceivably provide a mechanism for evolutionary and/or plasticity-driven changes in gland numbers. Studying the medial volar skin of mice—a region where, like much of the human body surface, hair follicles and eccrine glands are interspersed—Kamberov et al. (2015) identified *En1* gene expression as a driver of eccrine and hair follicle density. Hair follicles and eccrine glands develop from the same epidermal buds. Modulation of *En1* activity increases the number of eccrine glands at the expense of hair follicles, representing a potential mechanism through which selection or other evolutionary forces may change appendage ratios by changing the fate of epidermal buds from hair follicles to eccrine glands. Lu et al. (2016) found that hair follicle and eccrine gland specification is temporally regulated: hair follicles develop first from epidermal buds, and an increase in bone morphogenic proteins inhibits sonic hedgehog activity, triggering eccrine gland development. It is easy to imagine how this changeover may be triggered earlier by other genes (an evolutionary change). A potential though less likely scenario is that thermoregulatory stress experienced by the mother from the external climate is signaled to the embryo, a phenomenon shown to impact many developmental processes in humans (Barker, 2003). As predicted by the hypothesis of symmorphosis, phenotypes of costly physiological traits such as muscle hypertrophy and the pathway for oxygen are under selection to match capacity with demand (Weibel et al., 1991). However, for sweat gland development to be suppressed or augmented to accommodate future demands, these signals would need to occur very early in development before placode differentiation, and the cost of making glands is probably trivial compared to the costs of body water loss and the risk of hyperthermia.

A more likely mechanism of phenotypic plasticity that affects eccrine gland density is modulating the innervation of glands during infancy. Eccrine glands are fully formed at birth, but early in the postnatal period the neurons innervating the glands change phenotype from noradrenergic to cholinergic (Taylor and Machado-Moriera, 2013) and thereafter respond to acetylcholine. In paw eccrine glands of the rat, it appears that this change occurs in the population of nerve fibers that originally innervated the gland, rather than replacement of a new cholinergic population of fibers; this nerve change is induced by the gland itself. Further, responsiveness of the gland's secretory coil is dependent upon continued cholinergic innervation (Landis, 1990). Thus, for a gland to be functional, it must induce a phenotypic change in the nerve fibers innervating it early in postnatal life, and this innervation in turn induces changes in the gland enabling it to produce sweat (Landis, 1990). Factors influencing this process could result in modified active gland number. Here is perhaps the most plausible mechanism for Kuno's climate-driven developmental window hypothesis: glands that aren't recruited for sweating early in life may not acquire the mature phenotype, and therefore remain unresponsive to stimuli thereafter. This model of gland maturation may also explain development of poorly-active glands. Glands are innervated by multiple nerve fibers (Kennedy et al., 1994) and sweat production may be dependent upon the summed stimulation from these multiple inputs (Machado-Moreira and Taylor, 2017). Perhaps poorly-active glands are those innervated by a low ratio of mature to immature nerve fibers.

A final possibility is that previously active glands may lose function later in life. This fits with the "use it or lose it" nature of exercise capacity, but there is little evidence to suggest this occurs. The reverse process is unlikely as well, as active gland density has not been seen to

increase following acclimation (Inoue et al., 1999), with the exception of Knip's data described previously (Knip, 1975).

7. Does gland density matter?

Sweating is not the only component determining human thermoregulatory capacity, and improvements in heat dissipation following acclimation which can be attributed to sweat glands appear to be due largely to increased sweat rate per gland, enabled in part by gland hypertrophy (Sato et al., 1989). Still, all else being equal, increased gland density should permit a higher maximal sweating capacity. Several observations support this idea. First, progression of sweating during thermoregulatory challenge involves the gradual recruitment of more glands (Kondo et al., 1998), indicating that active gland number (or density) directly impacts heat dissipation. Second, gland density correlates with thermoregulatory capacity across primate taxa, suggesting that selection favors higher gland density as a solution to thermoregulatory challenges.

As mentioned previously, a potential consequence of higher gland density—or at least higher whole-body sweat production—is greater body water loss. Attenuated sweat responses in living peoples of long-term tropical residence suggest that humans evolved phenotypic plasticity to make sweating more efficient. Still, the adaptive advantage of increased gland density (be it evolutionary or phenotypic plasticity) is surely to permit higher maximal sweating rates. Thus, increased sweat gland density evolved in hominins despite increasing the risk of dehydration. While hyperthermia and dehydration were both physiological challenges faced by human ancestors, the former was clearly more deleterious to evolutionary fitness, perhaps because there are fewer avenues through which it can be ameliorated. Active hominins on the African savannah necessarily faced unavoidable thermal strain. Meanwhile, the human body has multiple responses to prevent and cope with dehydration. Heat acclimation improves ability to buffer against dehydration: body water increases 5–7%, due to increases in fluid-conserving hormones and changes in renal function; and thirst improves, leading to greater fluid intake (Périard et al., 2015). Additionally, behavioral adaptations can help prevent dehydration, while similar options for preventing hyperthermia are few if midday physical activity is required. For example, the digestive system can be used as a sort of canteen, banking water for several hours' worth of physical activity. Before a persistence hunt covering 15–40 km in extreme heat, Kalahari hunter-gatherers consume large quantities of water and complete the hunt with no further drinking and without apparent dehydration (Liebenberg, 2006).

How this informs predictions about variation in modern human eccrine density depends upon which proximate mechanism(s) are responsible for this variation. Because sweating is less efficient in humid environments (increased sweat production is not related in a linear fashion to heat dissipation), we may expect selection and/or plasticity to produce lower gland densities in these climates. However, the most likely proximate mechanism for phenotypic plasticity—gland recruitment in infancy leading to nerve fiber maturation and subsequent gland activation—would be blind to humidity. In this model, glands that are recruited for sweating become active for life; as discussed previously, thermal stress is met with copious sweating even in humid air. While this is conjecture, we predict that phenotypic plasticity leads to higher active gland density in hot climates, both dry and humid.

8. Future directions

Quantifying variation in eccrine gland density of living people, and assessing the relative influence of evolutionary forces and phenotypic plasticity in shaping this variation, will require higher-quality data than currently exists, controlling for environmental factors during development and collected with consistent methods. Two approaches could be taken when recruiting volunteers for such research. First, recruitment could cast a wide net and seek individuals from many geographic ancestries and childhood climates. In addition, to test effects of phenotypic plasticity due to climate while controlling for population history, recruitment could target closely related human populations living in disparate habitats, such as high- and lowland Andean populations. Presently, we are conducting a research study following the first strategy: recruitment of volunteers from varying childhood climates and geographic ancestry and gathering active sweat gland density with pilocarpine iontophoresis and vinyl polysiloxane impressions. Additionally, we plan to assess the relationship of active gland density and heat dissipation with exercise testing in a metabolic chamber. This work will help elucidate the physiological implications of active gland density.

Measuring the ratio of active to inactive glands is a potential way of directly testing effects of phenotypic plasticity. To do this, Ogata's methods would be necessary: skin excision following sweat induction. Recruiting a sufficient sample size for such an invasive procedure would likely prove prohibitive, however. A simpler approach may yield some insight. Eccrine pores are readily visible in the fingers and toes, and while their function differs from those on the body surface their developmental origin is likely identical. This suggests that gland densities here may reflect evolutionary history or phenotypic plasticity just as body surface glands might. (Kamberov, personal communication.)

Finally, to fully understand the evolution of eccrine sweating in hominin evolution, we need to determine the timing of body hair reduction and transition to microscopic vellus hairs. Data from Kamberov et al.'s comparative analysis of humans, chimpanzees and macaques (Kamberov et al., 2018) suggests that humans owe their exceptional sweating capacity not just to increased eccrine density but also to loss of thick hair (rather than wholesale loss of hair follicles). Further, the development of these structures is linked, as both hair follicles and eccrine glands originate from placodes and share a developmental program (Biggs and Mikkola, 2014). The fossil record has revealed perhaps all the clues it can about sweating, and other avenues of inquiry-developmental biology, comparative primatology, and characterizing diversity in current humans-holds the most promise for filling in the remaining gaps in the story of human sweating.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2019.07.024.

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