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Interaction Between Environmental Temperature and Craniofacial Morphology in Human Evolution: A Focus on Upper Airway

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1. INTRODUCTION

The variation and evolution of craniofacial skeletal morphology in hominids is the result of a complex interplay between genetic factors (e.g., Adhikari et al. 2016; Pickrell et al. 2016; Shaffer et al. 2016; Zaidi et al. 2017; Claes et al. 2018) and biomechanical pressures related to brain growth, mastication, and respiration (e.g., Moss and Young 1960; Enlow 1990; Richtsmeier et al. 2006; Lieberman 2011; Bastir and Rosas 2013), as well as multiple environmental factors including diet, activity level, and ecogeographic variables such as temperature (e.g., Steegmann and Platner 1968; Roseman 2004; Rae et al. 2006; Evteev et al. 2014; Menendez et al. 2014; Sardi 2018; Wroe et al. 2018; Martin et al. 2021). Although developmental shifts in brain ontogeny and selective pressures in response to the biomechanical forces related to mastication and respiration appear to be predominant in human skull evolution (for a recent comprehensive review, see Lesciotto and Richtsmeier 2019), environmental factors might still have a significant influence, though possibly more challenging to disentangle from other processes.

The influence of these environmental factors, particularly temperature, has been addressed in prior research, mainly focusing on their impact on infra- or post-crania morphology and body proportions (e.g., Holliday 1997; Ruff 2002; Holliday and Hilton 2010). The pioneering work of Bergmann (1847, translated in James 1970) states that homoeothermic organisms maintain stable internal body temperature by balancing the production of warmth within the volume of their body and the loss of warmth from its surface. In this thermoregulation process, the surface area-to-volume ratio of the body is therefore a predominant factor. According to Bergmann's rule, within a broadly distributed genus, species of larger size are found in colder environments, while species of smaller size are found in warmer environments. This rule, though still debated (e.g., Scholander 1955; Mayr 1963; McNab 1971, 2010, 2012; Crognier 1981a; Ruff 1994; Katzmarzyk and Leonard 1998; Ashton et al. 2000; Meiri and Dayan 2003; Ochocinska and Taylor 2003; Blackburn and Hawkins 2004; Meiri et al. 2004; Rodriguez et al. 2006; Clauss et

al. 2013; Foster and Collard 2013; Alhajeri and Steppan 2015; Gohli and Voje 2016; Brown et al. 2017; Nunes et al. 2017; Sargis et al. 2018), also applies to the genus *Homo*. Allen's rule, based on another foundational work concerning the influence of environmental temperature on the morphology of homeothermic organisms (Allen 1877), states that in colder climates individuals tend to possess shorter limbs and extremities, thus reducing the surface area-to-volume ratio and the associated heat dissipation. In warm climates, the opposite phenomenon is observed. However, Bergmann's and Allen's rules were based on observed variation of the postcranial skeleton and may not apply to the craniofacial skeleton. The impact of environmental temperature on the variation and evolution of skull phenotypes remains less clear, for example, in Neanderthals (e.g., Steegmann et al. 2002, but see Weaver 2009). Moreover, attempts to provide mechanistic hypotheses to explain craniofacial morphological variation attributed to environmental temperature remain scarce. Hence, in the present chapter, we will review research relevant to two critical questions, which, from our perspective, are related and need to be addressed together to increase our comprehension of the role of climate in the evolution of craniofacial morphology:

- What anatomical and functional units of the skull exhibit temperature associated patterns of morphological variation?
- What developmental processes (genetic, molecular, and cellular) involved in craniofacial growth and development are sensitive to temperature and could contribute to the explanation of such variation?

Among the different anatomical and functional units of the skull, the facial skeleton shows clear signs of morphological variation related to environmental temperature. In particular, temperature-related variation of the shape and size of the nasal cavity has been a focus of research in paleoanthropology and physical anthropology for many years. The nasal cavity forms the gateway to the respiratory system (Enlow 1990). As such, the morphology of this interface region has long been considered a reliable proxy for studying the link between hominins and their environment (e.g., Davies 1932; Weiner 1954; Carey and Steegmann 1981; Yokley 2009; Noback et al. 2011). Two main hypotheses have been put forward to interpret how adaptive pressures impact nasal cavity morphology. These hypotheses are not mutually exclusive and relate to two factors that might simultaneously influence nasal morphology. The first hypothesis considers the morphology of the nasal cavity in relation to its air conditioning function and climatic adaptation (Charles 1930; Shea 1977; Cole 1982b; Churchill et al. 2004; Yokley 2009; Butaric et al. 2010; de Azevedo et al. 2017; Butaric and Klocke 2018; Evteev and Grosheva 2019; Heuzé 2019). The air conditioning function of the nasal cavity is the process by which the inspired air reaches body core temperature and a full saturation with water vapor to protect the alveolar lining in the lower airway (Elad et al. 2008; Wolf et al. 2004). The second

hypothesis emphasizes the role of the nasal cavity as the upper part of the respiratory system regulating the amount of air inhaled and is thus closely related to the energetic demands of the body (Hall 2005; Froehle et al. 2013; Holton et al. 2014, 2016; Wroe et al. 2018).

Neanderthals, who lived in Eurasia until about 28 kya ago (Finlayson et al. 2006), have received much attention on these matters. The morphology of the Neanderthal appendicular and facial skeletons has often been interpreted as cold adapted (e.g., Steegmann et al. 2002) and/or as the result of genetic drift (Weaver 2009). In the facial region, this variation includes a larger nasal cavity in Neanderthal relative to anatomically modern *Homo*. This larger nasal cavity would allow an increased incoming airflow, associated with a larger volume of the ribcage to meet the high energetic demands of large-brained and heavy-bodied Neanderthals (Coon 1962; Franciscus and Churchill 2002; Garcia-Martinez et al. 2018; Wroe et al. 2018) while providing an efficient way to condition air in cold climates (de Azevedo et al. 2017, but see Bastir 2019). Using computational fluid dynamics methods, one can quantify several airflow features characterizing respiration, as well as air conditioning efficiency in extant normal and pathological samples (Burgos et al. 2017; Kim et al. 2017). These methods have recently been used to study Neanderthals (de Azevedo et al. 2017; Wroe et al. 2018), though the virtual reconstruction of nasal mucosa of fossil specimens, achieved by morphing the modern human airway to fossil nasal cavities (see also Bourke et al. 2014), might be problematic (Evtsev and Heuzé 2018). Indeed, based on a relatively small sample ($N = 30$), Heuzé (2019) reported a rather low correlation between the volume of the bony nasal cavity and the negative volume defined by the nasal mucosa, that is, the functioning nasal airway, thus preventing robust direct interpolation of nasal airway volume on the basis of nasal cavity volume.

In this chapter, we take a step back and address the question of the interaction between environmental temperature and facial skeletal morphology from a new perspective. Our purpose is to provide an overview of the current knowledge of the temperature-related morphological variation of nasal and paranasal structures and to explore the temperature-sensitive pathways that might have a role in this variation. Genes sensitive to temperature are obviously of importance in temperature-related morphological variation, and examples are provided in this chapter. However, genes do not directly produce phenotypes (Cohen and McLean 2000; Richtsmeier and Lesciotto 2020). Rather, phenotypes are the products of complex interactions between the genome and the internal and external environment. A concept central to these interactions is developmental plasticity, which is the response of cells, tissues, organs, and/or an individual organism to environmental variation that occurs within the lifespan of an individual with a single genotype and results in the formation of more than one phenotype (Hall and Witten 2018). Acknowledging the key role of cellular processes in the making of phenotypes, this review focuses on the cellular response to temperature changes. In doing so, our purpose is to pave the way to a better understanding of the mechanisms that

explain the relationship between climate variation and the morphology of the structures involved in respiration. We believe that such an approach will shed a new light on the role of temperature in human evolution.

2. UPPER AIRWAY MORPHOLOGY

As stated, the nasal cavity forms the gateway to the respiratory system (Enlow 1990). The covariation of environmental air temperature and humidity with morphology of the nasal structure has consequently been extensively addressed and these ecogeographic factors are considered a driving force in the expression of phenotypic variation and adaptation (Thomson 1913; Thomson and Buxton 1923; Davies 1932; Woo and Morant 1934; Negus 1952; Weiner 1954; Cottle 1955; Negus 1960; Wolpoff 1968; Hiernaux and Froment 1976; Carey and Steegmann 1981; Crognier 1981a, 1981b; Franciscus and Trinkaus 1988; Franciscus and Long 1991; Franciscus 1995; Roseman 2004; Roseman and Weaver 2004; Harvati and Weaver 2006a, 2006b; Marquez and Laitman 2008; Hubbe et al. 2009; Yokley 2009; Butaric et al. 2010; Bastir et al. 2011; Noback et al. 2011; Evteev et al. 2014; Jaskulska 2014; Butaric 2015; Maddux et al. 2016a; Zaidi et al. 2017; Marks et al. 2019). In the following, we discuss nasal anatomy and physiology and summarize what is currently known about climate-related phenotypic variation. Finally, we focus on the paranasal sinuses, their role in respiratory energetics, and current hypotheses about their covariation with nasal morphology and environmental factors.

2.1. Nasal anatomy and physiology

The nasal cavity is the area of the craniofacial skeleton that contains the nasal airway, the first anatomical region of the respiratory system involved in respiratory energetics and air conditioning. Conditioning of the inspired air in the nasal airway is achieved through contact with the respiratory mucosa producing heat exchange via convection and moisture exchange via evaporation (Cole 1982a; Naclerio et al. 2007; Yokley 2009). Skeletally, the nasal cavity is bounded and defined by maxillary, nasal, palatal, vomer, sphenoid, frontal, ethmoid, and lacrimal bones. The shape, size, and relative position of these bones affect the morphology of the nasal cavity that, at least indirectly, conditions the quantity of air that can be inhaled and the air conditioning performances. The dimensions of the entry (piriform aperture) and exit (choanae) points significantly influence respiratory energetics (Swift and Proctor 1977; Bastir and Rosas 2013). Maddux et al. (2016b) argued that nasal cavity height was more likely to be associated with energetics, while nasal cavity width and length play an important role in air conditioning (Noback et al. 2011).

The mucous membrane lining the nasal cavity delimits the nasal airway that can be divided into three different units (Figure 1) (Mlynski et al. 2001; Bastir et al. 2020). The first part, the

inflow tract, directs and diffuses the airflow, and contains the vestibulum, isthmus, and anterior cavum. The second part, the functional tract, includes the nasal turbinates. The third part, the outflow tract, directs warmed and humidified air toward the lower respiratory tract and is composed of the posterior cavum, choanae, and nasopharynx.

The thickness of the highly vascularized mucous membrane of the nasal airway fluctuates by contraction and expansion, depending on physiological factors such as blood pressure, nasal cycle, and nasal function (Cauna 1982; Elad et al. 2008; Yokley 2009; White et al. 2015). The variation in mucosa thickness causes congestion and decongestion of the nasal airway and affects its size and shape. Consequently, the speed, volume, and direction of airflow are also affected (Cauna 1982), as well as the efficiency of air conditioning processes (Churchill et al. 2004; Naftali et al. 2005; Zhao and Jiang 2014; Ma et al. 2018). Indeed, the nasal airway is the place where air conditioning takes place, which is necessary to optimize gas exchanges in the pulmonary alveoli and thus participate in global homeostatic thermoregulation (Havenith 2005; White 2006) while protecting the lungs from thermal damage, desiccation, and infection (Proetz 1951, 1953; Walker and Wells 1961; Cole 1982b; Proctor 1982; Keyhani et al. 1995; Williams 1998; Keck et al. 2000; Eccles 2002; Wolf et al. 2004; Yokley 2006; Doorly et al. 2008; Elad et al. 2008; Yokley 2009; Hildebrandt et al. 2013). A large mucosal surface and a narrow channel generally facilitate heat and moisture exchange (Schmidt-Nielsen et al. 1970; Collins et al. 1971; Hanna and Scherer 1986; Schroter and Watkins 1989; Lindemann et al. 2009).

The nasal turbinates (or conchae) are complex, curled structures that extend from the side and upper walls of each nostril and play a major role in respiratory processes. These structures are divided into lower, intermediate, and upper turbinates (Moore 1981; Smith et al. 2006; Maier and Ruf 2014). They are covered with an epithelium that is olfactory for the upper turbinate (Zhao 2004; Sahin-Yilmaz and Naclerio 2011) and respiratory for the intermediate and lower turbinates (Doorly et al. 2008; Wen et al. 2008; Xiong et al. 2008; Sommer et al. 2012; Kim et al. 2017; Marks et al. 2019). Beneath the turbinates lie the superior, middle, and inferior meatuses that communicate posteriorly with the outflow tract; the middle meatus also holds the opening of the maxillary sinus (ostium maxillare). Ontogenetically, the turbinates and the associated meatuses develop from the six furrows, resembling ethmoturbinals, appearing on each lateral branch of the cartilaginous nasal capsule during weeks 9 to 10 of human fetal development (Jankowski 2013). Postnatally, lower turbinates include numerous seromucous cells, providing a significant input of water vapor required in the air humidification process (Cole 1982b; Tos 1982; Keyhani et al. 1995; Naftali et al. 2005; Na et al. 2012). Studies using computational fluid dynamics methods have demonstrated the role of the two lower turbinates in mediating the velocity and direction of airflow (Keyhani et al. 1995; Wang et al. 2005; Inthavong et al. 2007; Doorly et al. 2008; Zhu et al. 2011; Na et al. 2012; Li et al. 2017; Inthavong et al. 2018).

2.2. Climate-related variation of nasal structures

Numerous studies focusing on the nasal area have shown an association between its morphology and environmental factors (e.g., air temperature, humidity, altitude). Two main proxies for nasal morphology have been used to study this relationship: the negative volume defined by bone (i.e., nasal cavity) and the negative volume defined by soft tissue (i.e., nasal airway).

The first studies that accurately demonstrated a relationship between nasal morphology and eco-geographical factors were conducted using dry skulls and based on measurements of the facial skeleton and nasal aperture (Thomson 1913; Thomson and Buxton 1923; Davies 1932; Weiner 1954; Hoyme 1965; Wolpoff 1968; Hiernaux and Froment 1976; Carey and Steegmann 1981; Crognier 1981a, 1981b; St. Hoyme and Işcan 1989; Franciscus and Long 1991; Roseman 2004; Hubbe et al. 2009; Leong and Eccles 2009). Later studies addressed the morphology of the entire nasal cavity and confirmed this relationship (Yokley 2009; Noback et al. 2011; Evteev et al. 2014; Fukase et al. 2016). Comparative inter-population studies have demonstrated that the only area of the nasal complex affected by variation related to eco-geographic factors is the internal nasal cavity (Maddux et al. 2016b). This area is also the main site of heat and moisture exchange within the nasal complex (Ingelstedt 1956; Cole 1982b; Keck et al. 2000; Naftali et al. 2005; Elad et al. 2008).

The results of these studies show that, when humans live in cold environments, they appear to possess a nasal cavity that is reduced mediolaterally and increased anteroposteriorly and superoinferiorly (Churchill et al. 2004; Doorly et al. 2008; Yokley 2009; Holton et al. 2011, 2013; Maddux et al. 2016b). Narrow nasal passages facilitate heat and moisture exchange by increasing the mucosal surface area relative to air volume (SA/V) ratio. This configuration increases nasal resistance for conditioning incoming airflow but also increases the amount of heat and water recovered during exhalation, thereby improving the conditioning capacity of the inner nasal cavity (Schmidt-Nielsen et al. 1970; Collins et al. 1971; Hanna and Scherer 1986; Schroter and Watkins 1989; Lindemann et al. 2009). In addition, when the anteroposterior dimension of the nasal cavity increases, so does the time that airflow occurs in the nasal cavity, which also contains a larger volume of mucous membrane along this dimension, increasing efficiency of air conditioning (Inthavong et al. 2007; Noback et al. 2011). Last, the variation in nasal cavity height might be related to another aspect of climatic adaptation: energy demands. Several studies have shown that individuals with higher metabolic demands for oxygen consumption, which is generally the case in colder and/or drier environments, tend to have taller nasal cavities (Froehle 2008; Bastir and Rosas 2013, 2016; Holton et al. 2016). Furthermore, the increase in nasal height of individuals living in cold climates might also compensate for the reduction of nasal breadth that

is also observed in these environmental conditions, thus maintaining a sufficient volumetric intake capacity (Maddux et al. 2016b).

While the nasal cavity has often been studied, the nasal airway has only become the focus of studies in the last few years. An *in vivo* study (Yokley 2009) measured the SA/V ratio of individuals from European and African ancestry and observed that this SA/V ratio was only higher in European individuals when the nasal airway was fully decongested (i.e., nasal mucosa fully contracted). When the nasal mucosa was not fully contracted, the SA/V ratio showed no significant differences between the individuals from European and African ancestry. This study underlines the importance of focusing not only on the nasal cavity but also on the volume delimited by the mucosa (i.e., nasal airway) and its morphology. An important issue when addressing nasal airway morphology is to take into consideration the nasal cycle, which consists of the alternative partial congestion and decongestion of the right and left sides of the nasal airway during breathing, thus optimizing respiratory air conditioning (Hasegawa and Kern 1977; Cauna 1982; Eccles 1982, 1996; Watelet and Cauwenberge 1999; White et al. 2015; Pendolino et al. 2018). The influence of the periodicity of these nasal cycles on airway morphology needs to be addressed by studying larger samples and measuring the right and left sides separately (Heuzé 2019).

2.3. Function of the paranasal sinuses

The paranasal sinuses are mucous membrane-lined cavities within bones that surround the nasal area (Figure 2). These include: the frontal sinuses, communicating with the nasal region through the meatus; the maxillary sinuses, communicating with the nasal region through the semilunar hiatus; and the sphenoid sinus. Ethmoidal air cells, which are thin-walled cavities located in and defined by the ethmoidal labyrinth, are also often considered paranasal sinuses. However, ethmoid bone development in humans starts during the first trimester of gestation, while the other paranasal sinuses develop entirely after birth in aerial conditions, which could ontogenetically grant them another status (Jankowski 2013). Furthermore, the mechanisms of paranasal sinus formation differ from those of the ethmoidal complex. One theory explaining paranasal sinus development -the epithelial theory- states that the maxillary, frontal, and sphenoid sinuses are produced via epithelial diverticula overflowing from the ethmoid labyrinth and causing a pneumatization of the surrounding bones (Zuckermandl 1893; Zollikofer and Weissmann 2008).

Several functions have been assigned to paranasal sinuses without real consensus. One theory is that these structures were involved in reducing the weight and increasing pneumatization of the skull (O'Malley 1923; Tillier 1977). Another theory raised the hypothesis of a potential role in thermal insulation of the brain and the eyes or in voice resonance (Masuda 1992). A third hypothesis, the mechanistic theory, sees the paranasal sinuses as simple

residual cavities that result from morphological changes in the surrounding structures that are constrained by biomechanical forces during craniofacial development (Rae et al. 2003; Holton et al. 2013; Jankowski 2013; Butaric 2015; Butaric and Maddux 2016; Noback et al. 2016; Maddux and Butaric 2017; Buck et al. 2019; Evteev and Grosheva 2019). An additional hypothesis focuses on the role of the paranasal sinuses in the warming and humidification of inspired air (Gannon et al. 1997).

Another function attributed to the paranasal sinuses is the production of nitric oxide by the inner membranes of the sinuses, under the action of the enzyme I-NOS (NOS-2) (Lundberg et al. 1995, 1996). Nitric oxide is a powerful vasodilator, particularly involved in the cellular functions of the respiratory, nervous, and immune systems (Lundberg 2008; Keir 2009; Marquez et al. 2014). It is produced by the endothelial cells of sinus blood vessels and relaxes the muscle fibers of the vascular nasal wall when pumped into incoming airflow, thus regulating the intranasal temperature (Lundberg et al. 1995; Holden et al. 1999). In addition, nitric oxide may help maintain a sterile environment in the respiratory tract through two mechanisms: (1) nitric oxide is toxic to many viruses and bacteria and may therefore play a role in protection against infections (Mancinelli and McKay 1983; Croen 1993), and (2) the level of nitric oxide affects the beat frequency of the cilia of airway epithelial cells that propel mucus-trapped debris and particles out of the lungs (Jain et al. 1993).

The proximity of the paranasal sinuses to the nasal structures and their role in respiratory processes has led researchers to study the relationship between the paranasal sinuses and climatic factors (e.g., Rae et al. 2011; Butaric 2015; Evteev and Grosheva 2019). While the sinuses show a high level of within- and between-group variation (Evteev and Grosheva 2019) and are strongly correlated with craniofacial size (Rae et al. 2011; Butaric 2015), a covariation has been measured between the maxillary sinus and nasal structures (Butaric 2015). Indeed, individuals from cold-dry climates tend to have a larger maxillary sinus volume associated with a medial displacement of the lateral nasal walls, thus causing a reduction of the internal nasal breadth (Holton et al. 2013; Butaric 2015; Butaric and Maddux 2016; Evteev and Grosheva 2019). Nevertheless, some confusion remains about the exact function of each of these sinuses, their relationship with neighboring structures, and how variation in paranasal sinuses relates to skeletal morphology of the entire face, not just the nasal aperture, and environmental factors.

3. EFFECTS OF ENVIRONMENTAL TEMPERATURE ON BONE FORMATION

The studies summarized previously focus on the correlation or covariation between ecogeographic factors (mainly temperature) and morphology of the nasal region and the hypothesized advantages of these phenotypes in cold or warm environments. Though it is widely acknowledged that the morphology of the nasal region depends in large part on the

articulation of bones that surround it, the processes that contribute to bone formation that underlie this variation and generate its expression are rarely addressed. For instance, we do not yet understand the relative roles of heredity and developmental plasticity in the production of craniofacial phenotypes (Lovejoy et al. 2003). Here we present an overview of the manifestation of thermoregulation in extreme climatic environments and propose hypotheses on how stress caused by extreme temperature could modify bone formation processes and the resulting morphology of the nasal region. We then address the interaction between genes and the environment in the production of a phenotype through the identification of pathways or temperature-sensitive genes that could have an effect on the nasal and paranasal structures via cellular processes involved in bone and cartilage development.

We emphasize that trying to explain a phenotype as the direct result of temperature influence is unrealistic, as many other factors must be considered to explain craniofacial skeletal morphology. Diet, nutrition, and activity levels are examples of environmental inputs that can influence bone metabolism (e.g., Kiliaridis et al. 1985; Paschetta et al. 2010; Menendez et al. 2014). Furthermore, temperature is not the only parameter defining ambient air, which also depends on the less acknowledged factor of humidity. Another major consideration is the integration among structures constituting the craniofacial skeleton that can induce a secondary variation in some specific area that is a response to the variation of its surrounding bony environment (Sardi et al. 2018; Scott et al. 2018). Age can also affect craniofacial morphology. Tooth loss and subsequent bone resorption in the maxillary area would induce a modification of palate morphology that could also affect the nasal and paranasal structures (Albert et al. 2007; Joganic and Heuzé 2019). Though not meant to be exhaustive, we present some temperature-sensitive genes, pathways, and cellular processes involved in bone and cartilage formation and that could influence aspects of craniofacial morphology.

3.1. Thermoregulation in extreme climatic environments

Thermoregulation includes all the mechanisms used by an organism to control its body temperature and ensure optimal regulation of all metabolic processes (Iwen et al. 2018; Romanovsky 2018). In homeothermic species, the production of internal body heat must always be balanced with body surface heat loss in order to maintain homeostasis. To this end, various mechanisms have evolved, including skin vasodilatation, sweating, behavioral adaptations, insulation of the body by fur, clothing, and/ or intradermal fat accumulation (Cannon and Nedergaard 2004; Kasza et al. 2014; Alexander et al. 2015; Fischer et al. 2016; Kasza et al. 2016). Biological responses such as vasoconstriction and vasodilatation also allow heat to be retained or lost by the extremities. For instance, cold temperature leads to vasoconstriction that directs the blood flow towards the trunk and vital organs to reduce the

dispersion of blood heat in the extremities (Tansey and Johnson 2015). Indeed, the extremities of homeothermic species are characterized by their regional heterothermy, that is, the ability to drop temperature of the limbs while maintaining that of the trunk (Harrison and Clegg 1969; Ponganis et al. 2003; Serrat et al. 2008).

Experimental studies have measured an interaction between temperature, cell proliferation, and bone matrix production, which may affect cartilage growth and thus modify the morphology of endochondral bone (Serrat et al. 2008, 2010, 2015; Serrat 2014). Hence, temperature can affect vertebral number in ectothermic and homoeothermic vertebrates (Hall 2015), as well as limb and extremity length, which tend to shorten in response to a decrease in temperature (Allen 1877; Feldhamer 2007). One of the explanations of limb shortening proposed by Serrat (2014) is that the vasoconstriction induced by cold stress leads to a decreased blood flow in the extremities, altering the transport of important nutrients, oxygen, and hormones, and ultimately affecting endochondral ossification. Indeed, growth plates, though avascular, benefit from the nutritional support of the surrounding vasculature that transports solutes diffusing through the extracellular matrix to reach the cartilaginous cells (Brookes and Revell 1998). An alteration in blood flow might therefore affect this nutrient supply, thus affecting normal growth. Interestingly, the effects of temperature on limb length can be observed within a single generation of outbred mice reared at warm and cold temperatures during the postnatal growth period (Serrat et al. 2008). These observations underscore the potential role of phenotypic plasticity. When driven by environmental factors, phenotypic plasticity is considered a greater evolutionary force than random mutation (West-Eberhard 2005), but few studies have addressed the potential effect of phenotypic plasticity on morphological variation of the upper airway. Rae et al. (2006) contributed to this question in their study of the dry crania of cold- and warm-reared rats. Their results show that cold stress causes subtle but significant changes in facial shape as well as maxillary sinus and nasal cavity volumes, suggesting developmental plasticity of the craniofacial skeleton in response to climatic variation.

3.2. Mechanisms of temperature influence on upper airway bone and cartilage

Potential responses of the craniofacial skeleton to cold stress are not well understood, but some authors have proposed hypotheses that might explain how temperature influences craniofacial variation. For example, a recent study on nasal turbinate morphology (Marks et al. 2019) hypothesized that the modification of cartilage development in cold environments could also apply to nasal turbinate cartilage and all cartilages of the nasal capsule of the forming chondrocranium. If this change occurred, the morphology of the surrounding non-cartilaginous skeletal structures developed through intramembranous ossification (e.g., the maxillary, premaxillary and nasal bones) would also likely be affected (Chae et al. 2003; Egeli et al. 2004; Opperman et al. 2005; Wealthall and Herring 2006; Al Dayeh et al. 2013; Hall and Precious

2013; Hartman et al. 2016; Holton et al. 2018). By altering the expression of genes and pathways that affect cellular processes involved in cartilage metabolism, temperature could then have an indirect effect on growth of the facial bones.

Selective brain cooling (SBC) is the mechanism that keeps the brain at a cooler temperature than the rest of the body through the precooling of the blood supplying the brain and provides an example of complex interaction between blood flow intensity and morphological variation. This mechanism is achieved by dilation or constriction of the veins. For example, constriction of the veins returning blood from the nose and face pre-cools that blood that will then be supplied anteriorly to the brain (Caputa 2004). Regulation of the evaporation of water at the mucosal surfaces of nasal turbinates also contributes to SBC (Irmak et al. 2004). Furthermore, ethmoidal air cells and the sphenoid sinus could potentially help cool the adjacent brain lobes and vessels by thermal conduction. Part of the morphological variation of craniofacial structures might reflect adaptive changes in growth patterns that produce morphology ensuring a more effective SBC specific to the environment. Finally, we know that cold stress implies greater oxygen consumption, due to the sympathetic activity associated with brown adipose tissue production and muscle activation during nonshivering thermogenesis (Lowell and Spiegelman 2000). The increase of incoming airflow, which is closely related to the energetic demands of the body, could also play a role in the morphological variation of nasal structures (see also Maddux et al. 2016b).

3.3. Temperature-sensitive developmental pathways

Temperature not only affects the skeleton but almost every system in the body, causing many interactions among tissues that may experience different consequences of thermal stress (Tattersall et al. 2012). Although the number of genome-wide studies on the molecular basis of craniofacial morphology have been expanding in the last few years (e.g., Adhikari et al. 2016; Weinberg et al. 2018; Xiong et al. 2019), our understanding of the genetic basis for craniofacial variation is incomplete. It is therefore not an easy task to identify the temperature-sensitive genes that might directly and/or indirectly affect craniofacial morphology. Here, we highlight a few of these genes and associated pathways that were identified through *in vivo* and *in vitro* studies and which may explain some of the temperature-related variation of nasal and paranasal morphology (Figure 3). We begin by noting that the production of a “cold phenotype” or a “warm phenotype” does not necessarily imply mechanisms that would be opposites. Note that variation is expected in the phenotypic response to the temperature-sensitive genes and associated pathways. Some of these phenotypic responses might be continuous and proportional to the temperature variation, while others might be expressed only when a threshold is reached. Additionally, temperature variation at certain developmental

stages can have different phenotypic outcomes varying both in pattern and intensity (e.g., Hall 2015).

Some researchers have demonstrated that temperature can have a direct effect on bone formation and growth by altering the activity of bone-forming osteoblasts and bone-resorbing osteoclasts. An *in vitro* study using cells derived from rat trabecular bone (Patel et al. 2012) has shown that, after 14–16 days of culture, the activity of calvarial osteoblasts was reduced by 75% in mild hypothermia and by 95% in severe hypothermia. A reciprocal effect of hypothermia was also observed on osteoclastogenesis, that showed a 1.5- to 2-fold stimulation, thus increasing bone resorption.

Temperature was also shown to affect preosteoblast activity *in vitro*, including mesenchymal stem cell differentiation (Shui and Scutt 2001; Chung and Rylander 2012). When subject to heat stress, preosteoblast cells can promote expression of osteocalcin and osteopontin, two proteins involved in bone mineral density and metabolic regulation. However, the combination of heating and osteoinductive growth factors leads to the expression of heat shock proteins (HSPs), osteoprotegerin, and vascular endothelial growth factor (VEGF). Osteoprotegerin is involved in bone resorption through its role as a decoy receptor in the RANKL/RANK pathway (Aubin and Bonnellye 2000), and VEGF stimulates angiogenesis and controls bone formation (Dai and Rabie 2007). HSPs are multifunctional proteins that can be induced by heat stress or cold stress (Rylander 2005; Barna et al. 2012; Patil and Paul 2014; Hang et al. 2018). HSP70, for example, increases the proliferation and differentiation of osteoprogenitor cells, which are bone marrow-derived stromal cells (Shui and Scutt 2001), and regulates both the resorption activity of osteoclasts via the RANKL/RANK pathway and the bone production activity within osteoblasts by activating the ERK and Wnt/ β -catenin pathway (Hang et al. 2018). The temperature of the cell culture also influences HSP27, which is particularly involved in the regulation of bone cell physiology through upregulation of TGF- β (Hatakeyama et al. 2002), estrogen (Cooper and Uoshima 1994), endothelin-1 (Tokuda et al. 2003), and prostaglandins (Kozawa and Tokuda 2002). These results point to HSP27 as a potentially important factor in the modulation of cellular events in bone and cartilage.

Clock genes are also involved in cell proliferation in cartilage. Clock genes are transcriptional activators that play a central role in the regulation of circadian rhythms, the 24-hour cycles in physiology that precisely regulate organ function (Reppert and Weaver 2001). The expression of clock genes is directly dependent on temperature, and their mutation can lead to an altered regulation of bone volume or deficiencies in long bone growth because of their control of chondrocyte differentiation (Gossan et al. 2013; Marks 2018; Steindal and Whitmore 2019). Circadian clocks might also have a potentially important role in bone growth and maintenance and the production of morphology (Takarada et al. 2012).

Temperature can also affect global human DNA methylation and RNA editing (Garrett and Rosenthal 2012; Shi et al. 2020), as well as telomere length (e.g., Romano et al. 2013). Genes with methylation status have been shown to be affected by temperature changes. For example, low temperature induces the hypermethylation of ZKSCAN4, expressed by an increase of blood pressure (Xu et al. 2020), an indirect pathway that could affect bone growth. Another study addressed the contribution of cold-inducible RNA-binding protein (CIRP) to tissue remodeling in chronic rhinosinusitis (Shi et al. 2020). This cold shock protein is a chaperone that is upregulated under mild hypothermia and facilitates mRNA translation. CIRP seems to be involved in cold-induced suppression of cell proliferation, but its precise role is still poorly understood.

Finally, temperature can alter the endocrine system, which has a fundamental role in homeostasis. By affecting extracellular matrix proteins, cold stress can modify the diffusion rates of endocrine and paracrine growth regulators affecting the diffusion and transport of hormones and ultimately skeletal morphology. Among the endocrine hormones that could affect the skeleton (Massaro and Rogers 2004), thyroid hormones and leptin are probably the best studied.

It has been shown that thyroid hormones play a very important role in the regulation of homeostasis (Iwen et al. 2018). These hormones modify the transcription rate of uncoupling protein 1, localized in brown adipose tissue and involved in nonshivering thermogenesis (see Chapter 6 by Devlin; Enerback et al. 1997; Golozoubova et al. 2001), increase metabolic rate, and can directly influence the sodium/potassium and calcium pumps in skeletal muscle (Silva 2006), as well as the vasoconstriction and vasodilatation of blood vessels (Warner et al. 2013). Thyroid hormone levels also influence intramembranous and endochondral ossification and, consequently, craniofacial development (Bassett and Williams 2016). Indeed, skeletal hypothyroidism is expressed in a delayed ossification of the skull, which can cause defects such as wider and/or persistent cranial sutures and fontanelles. Conversely, skeletal hyperthyroidism causes advanced ossification that can manifest as malformations including craniosynostosis. Interestingly, the phenotypes produced by an altered thyroid status display similarities with loss-of-function or gain-of-function mutations affecting FGF (fibroblast growth factor), IGF (insulin-like growth factor) and WNT (Wingless-related integration site) signaling pathways, which are key pathways in craniofacial development. Since thyroid hormone T3 induces FGF, FGFR, IGF1, and IGF1R expression and enhances MAPK signaling in chondrocytes and osteoblasts but also enhances WNT signaling and RUNX2 (runt related transcription factor 2) expression in chondrocytes and inhibits WNT signaling in osteoblasts, it is possible that these signaling pathways interact in the regulation of craniofacial development together with thyroid hormones (see for review Leitch et al. 2020).

Leptin, a pleiotropic adipocyte derived hormone, is also known to increase with cold exposure and plays an important role in cold acclimatization and thermogenesis (Korhonen et al. 2008; Zhao 2011; Robbins et al. 2018). For example, studies have identified leptin target neurons that are involved in the sympathetic control of brown adipose tissue (e.g., Cannon and Nedergaard 2004). Brown adipose tissue is prevalent in newborns and hibernating mammals but is also metabolically active in human adults for nonshivering thermogenesis (Shum et al. 1991; Nedergaard et al. 2007; Saito et al. 2009; Devlin 2015; Oreskovich et al. 2019). Leptin is also involved in the regulation of bone growth (Kishida et al. 2005) and can regulate angiogenesis (new vessel formation) (Rezai-Zadeh and Munzberg 2013), which would permanently modify the blood flow and directly affect intramembranous ossification (Percival and Richtsmeier 2013).

4. IMPLICATIONS FOR HUMAN CRANIOFACIAL EVOLUTION

To improve our understanding of climate-related patterns of craniofacial morphological variation in human evolution and the developmental processes underlying this variation, several paths could be explored.

First, to refine our understanding of the phenotypic expression of climate-related craniofacial variation, additional quantitative studies are needed to evaluate morphological differences between populations living in regions with recorded differences in temperature and/or humidity. Medical images of modern individuals living in different climates would enable measures of bone and nasal mucosa morphology that are crucial to obtain valid estimates used in the evaluation of the covariation between these two anatomical structures (Heuzé 2019). Studying the covariation between nasal cavity and nasal airway will help with the interpretation of the results obtained on dry skulls in terms of respiratory energetics and air conditioning.

Second, studies of the influence of ambient temperature on growth and development of rodents (e.g., Rae et al. 2006; Serrat 2014) have shown that experimental studies of animals could be used to better understand the effects of temperature on the morphology of nasal structures. The use of laboratory animals can help sort genetic causes from other variables, like temperature, that potentially affect morphology. Experiments on inbred mice could enable quantitative comparison of the volume and morphology of upper airway structures between groups of animals exposed to either cold or warm environments. These studies could help determine the extent to which morphological variation can be explained by a genetically driven adaptation and/or by a physiological response to environmental factors, that is, by phenotypic plasticity. Animal models would also allow exploration of the cellular processes involved in the morphological response to temperature. An *in vitro* study on hyperthermia effects on the proliferation of bone and cartilage cells (Flour et al. 1992) showed that chondrocytes might be

thermoreistant and osteogenic cells thermosensitive. To our knowledge, such results still need to be tested *in vivo*. Future studies based on animal models could investigate the effects of temperature (both hypo- and hyperthermia) on the differentiation of osteochondroprogenic cells into osteoblasts and chondrocytes (Hall 2015) and on the proliferation of bone and cartilage cells. Laboratory mice could serve as a useful model system for this purpose, which would then help us discuss the effects of temperature on nasal morphology for other mammals such as primates.

Finally, the use of computational fluid dynamics offers great opportunities to achieve a better understanding of respiratory energetics. The complex structures of the nasal airway tend to restrict *in vivo* studies of nasal airflow, but computational fluid dynamics enables a valid and accurate numerical simulation of airflow patterns within the nasal cavity (e.g., Inthavong et al. 2007; Chen et al. 2010; Keck and Lindemann 2010; de Gabory et al. 2020). Thoughtful use of this technique applied on modern samples of healthy or pathological individuals could contribute greatly to the discussion about how thermoregulation, respiratory energetics, and climate interact to produce differential phenotypes in humans. Integrating these three approaches would allow a more precise definition of the anatomical and functional units of the craniofacial skeleton showing climate-related patterns of morphological variation, which would in turn expand our knowledge of developmental processes that are sensitive to temperature, providing potential explanations at the cellular, organ, and organismal levels of this observed morphological variation.

5. CONCLUSION

Previous research has shown that human morphological variation can correspond with differences in climate. We provided a review of the temperature-related morphological variation of nasal and paranasal structures and a discussion of genetic, cellular, and systemic temperature-sensitive pathways that might have a role in the production of morphological variation of the nasal cavity. We observe that temperature both directly and indirectly affect bone formation, either by altering the activity of preosteoblast cells, bone-forming osteoblasts, and bone-resorbing osteoclasts or by affecting proteins or hormones (e.g., heat shock proteins, clock genes, thyroid hormones, leptin) involved in the activity of bone cells. Beyond providing a review on ecogeographic patterns of morphological variation in upper airway and cellular processes that potentially influence this morphology, our purpose in this chapter is to highlight the need for studies integrating these two areas of research. Such research could ultimately improve our understanding of the role of climate in the evolution of craniofacial morphology.

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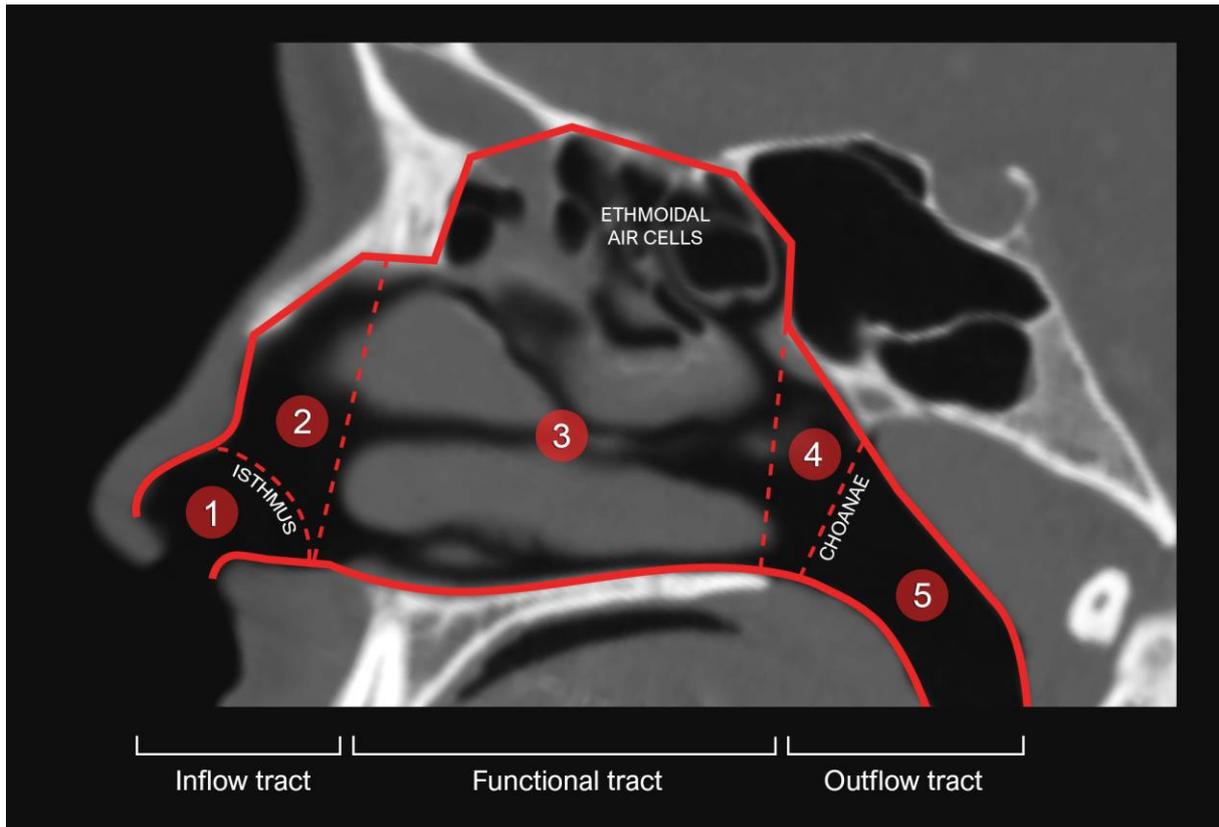


FIGURE 7.1 Sagittal cross-section from a CT scan showing the structural elements of the incoming nasal airflow pathway in lateral view. The inflow tract consists of the vestibulum (1) and the anterior cavum (2), which are separated by the isthmus. The functional tract is the area of the turbinates (3). The outflow tract is composed of the posterior cavum (4), choanae, and nasopharynx (5).

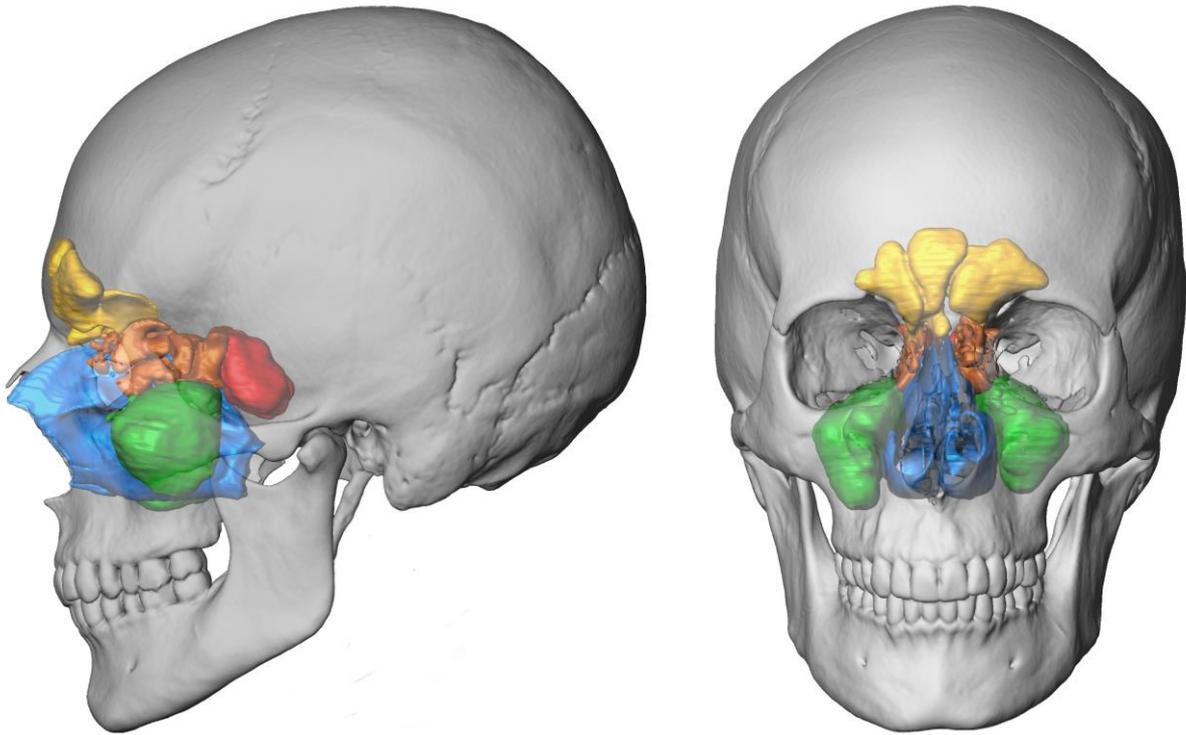


FIGURE 7.2 3D reconstruction of a human adult skull allowing the visualization (transparency) and localization of nasal and paranasal structures: nasal airway (blue), ethmoidal air cells (orange), frontal sinuses (yellow), sphenoid sinus (red), and maxillary sinuses (green).

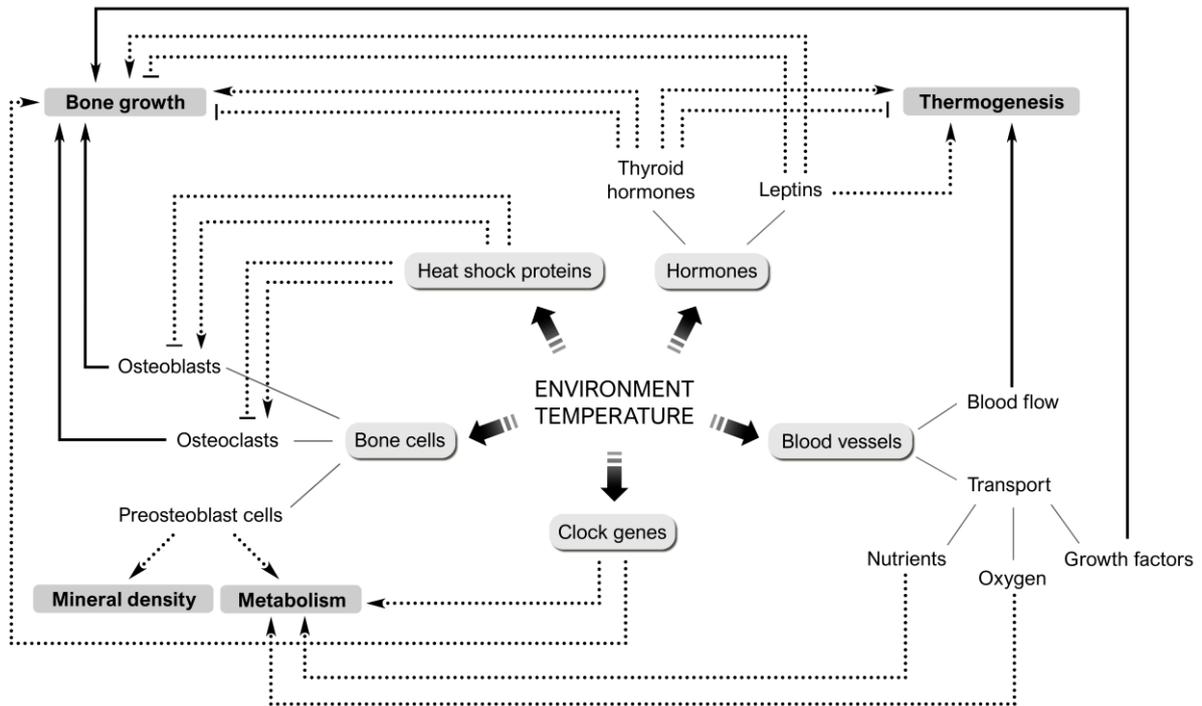


FIGURE 7.3 Diagram summarizing the major physiological pathways through which environmental temperature could influence nasal and paranasal morphology. Solid lines show direct temperature influences on bone growth and metabolism. Dashed lines indicate indirect ways through which temperature can alter bone cells. Indirect pathways include the endocrine system (e.g., thyroid hormones and leptin play a role in thermogenesis and bone growth), the circulatory system (temperature variation can induce a vasoconstriction or a vasodilatation, thus affecting blood flow and the transport of nutrients, oxygen, and hormones involved in bone metabolism), and other temperature-sensitive proteins and genes (e.g., HSP and clock genes both influence bone growth and metabolism).