Quantitative and population genetic approaches for testing modern human out-of-Africa models

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ABSTRACT

Molecular and morphological data are essential for reconstructing phylogeny across taxa and population history within a species. While both lines of evidence can be used in tandem to reconstruct the human past, they sometimes lead to conflicting results. This cumulative dissertation aims to use molecular and morphological data in parallel for testing competing modern human out-of-Africa dispersal hypotheses. Founded on common evolutionary theory, population genetic and quantitative genetic methods are used correspondingly with genomic and cranial shape data of populations sampled from Africa, Asia, and Australia.

The first study explores the association of neutral genomic variation with cranial shape variation, quantified respectively with single nucleotide polymorphisms (SNPs) and three-dimensional anatomical landmarks. This study identifies temporal bone shape variation as most proportional to neutral genomic variation. Thus, the temporal bone retains a population history signal of the neutral differentiation of modern humans. In the second study, SNPs and the temporal bone are used as independent lines of evidence for testing competing out-of-Africa dispersal hypotheses. The dispersal hypothesis supported by both lines of evidence is one in which anatomically modern humans expanded into Asia along a southern route as early as the terminal Middle Pleistocene and later into Eurasia along a northern route during the Late Pleistocene. The third study integrates cranial shape data of fossils from Middle and Late Pleistocene Africa and the Levant. Applying quantitative genetics methods, the competing dispersal hypotheses are again tested, finding renewed support for a multiple dispersals model. These results are critically discussed in the fourth manuscript of this dissertation, which is a review of the fossil and genetic evidence for the out-of-Africa expansion process. In order to reconcile conflicting lines of evidence and on-going debates, a more nuanced out-of-Africa scenario that considers an early dispersal into Southwest Asia and a delayed expansion into Eurasia is proposed. Finally, the fifth study is an exploration on the association between cranial shape variation and language vocabulary variation, discussing the extent to which linguistic data may be utilized for reconstructing the human past.

This dissertation productively uses two lines of evidence in order to address a pivotal research question concerning the evolution and diversity of modern human populations. In doing so, it emphasizes the advantage of employing multidisciplinary approaches under a common evolutionary framework. The prospect of incorporating linguistic data confronts the challenge of developing an evolutionary synthesis for reconstructing the biological and cultural aspects of the human past.

List of publications for cumulative dissertation

a) Accepted papers

Appendix 2:

Reyes-Centeno H, Ghirotto S, Détroit F, Grimaud-Hervé D, Barbujani G, and Harvati K (2014). Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. *Proceedings of the National Academy of Sciences of the United States of America* 111(20):7248-7253.

Appendix 3:

Reyes-Centeno H, Hubbe M, Hanihara T, Stringer C, and Harvati K (*In Press*). Testing modern human out-of-Africa dispersal models and implications for modern human origins. *Journal of Human Evolution*. doi:10.1016/j.jhevol.2015.06.008

b) Submitted manuscripts

Appendix 4:

Reyes-Centeno H (*Under review*). Out of Africa and into Asia: Fossil and genetic evidence on modern human origins and dispersals. *Quaternary International*.

c) Manuscripts ready for submission

Appendix 1:

Reyes-Centeno H, Ghirotto S, Harvati K (*To be submitted*). Genomic validation of the differential preservation of population history in modern human cranial anatomy.

Appendix 5:

Reyes-Centeno H, Harvati K, Jäger G (*To be submitted*). Tracking modern human population history from linguistic and cranial phenotype.

1. Introduction

In the late twentieth century, discussion of modern human origins steered primarily between two opposing hypotheses. In one scenario, hominin admixture is pervasive amongst Pleistocene populations that evolve multiregionally in Africa and Eurasia, following a series of divergence and reticulation events (Weidenreich 1947; Wolpoff 1989; Frayer et al. 1993). In another model, anatomically modern humans originate in Africa and largely replace all other hominin populations as they disperse within and out of the continent (Clark 1975; Cann et al. 1987; Cavalli-Sforza et al. 1988; Stringer and Andrews 1988). Because neither of these models could completely explain the genetic and morphological diversity observed in extant and fossil populations of modern humans, other intermediate and more nuanced scenarios were considered. For example, some accepted the distinctive African origin of anatomically modern humans but emphasized admixture with other hominins rather than their replacement (Howells 1976; Bräuer 1984a, b, c; Smith et al. 1989). Others considered that modern human populations were structured within Africa and that multiple dispersals from the continent could account for the diversity observed in extant humans (Harpending et al. 1993; Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). In all cases, a central concern was the tempo and mode of modern human range expansion.

While debate on modern human origins and dispersal continues in the twenty-first century, evidence has accumulated on the important role that the African continent played both for the emergence of modern human anatomy and as the primary source of genetic and morphological variation of extant human populations. At the turn of the century, analyses of neutral genetic markers found that levels of intra-population diversity decreased as a function of geographic distance from Africa (Eller 1999; Harpending and Rogers 2000). Subsequent studies confirmed this association, additionally finding that levels of inter-population diversity and linkage disequilibrium increased relative to geographic distance from Africa (Prugnolle et al. 2005; Ramachandran et al. 2005; Liu et al. 2006; Jakobsson et al. 2008; Li et al. 2008; Deshpande et al. 2009). The primary interpretation was that such patterns were the demographic signature of the modern human expansion out of Africa and that the majority of genetic variation in extant populations could be attributed to genetic drift. Studies of skeletal and linguistic variation also confirmed some of the associations to geographic distance from Africa (Manica et al. 2007; Hanihara 2008; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009, 2012; Atkinson 2011). Despite the growing consensus on an African origin of

anatomically modern humans, the tempo and mode of dispersal remains controversial, with disagreement centered on the timing of the out-of-Africa expansion, the primary routes of dispersal, and the occupation time of Eurasia and Australia by modern humans. Resolving these matters is important for the modern human origins debate since the expansion process can inform how the genetic and phenotypic structure of extant human populations was generated. The tempo and mode of expansion also has implications for the degree of contact that modern humans had with other hominins.

The central goal of this dissertation is to test competing out-of-Africa models. In order to do so, this dissertation departs from the aforementioned consensus that (*i*) the origin of anatomically modern humans can be attributed to the African continent and that (*ii*) neutral evolutionary processes have generated most of modern human biological diversity following range expansion from Africa. Two independent lines of biological evidence are used in a common quantitative manner, namely genomic markers and cranial shape of extant and fossil human populations. The dissertation ends with a prospectus on integrating linguistic data in a comparable quantitative manner. In all, this dissertation is a contribution toward developing a synthesis of modern human biological and cultural evolution.

1.1 Theoretical background: The genome and phenome

The modern synthesis in evolutionary biology (Huxley 1942; Jepson et al. 1949; Mayr and Provine 1980) reconciled the genetic principles of Mendelian inheritance with Darwinian evolutionary concepts. In a sense, theoretical and experimental laboratory work by geneticists became compatible with observations of adaptation, selection, and admixture by field biologists and ecologists. Initially, paleontology played a relatively minor role in the construction of the modern synthesis, but its champions eventually concerned themselves with questions of human origins and the paleontological record (e.g. Dobzhansky 1944; Mayr 1950; Simpson 1950), bringing to the forefront the study of extant and fossil human variation. In spite of this, paleontology in general, and paleoanthropology in particular, has been slow to adapt the theory and methods developed since the modern synthesis (Tattersall 2000; Foley 2001; White 2009a, b). This is largely due to challenges in applying population models to individual specimens and a fragmentary fossil record. At the turn of the century, Howell (1999) proposed that the increase in hominin fossil discoveries made it possible to face this challenge by characterizing spatio-temporally bounded fossils in the paleontological record as

paleo-demes. This dissertation adopts this concept. Another challenge in paleoanthropology's implementation of contemporary evolutionary theory has been a shift toward emphasizing molecular approaches independent of the fossil record or considered superior to it (Edwards 2009; Horsburgh 2015). However, it has long been recognized that in addition to the importance of identifying the stochastic mechanisms of genetic sequence change, non-stochastic (e.g. environmental) mechanisms affecting such changes are a necessary component of evolutionary theory (Waddington 1968; Lewontin 1974).

Waddington (1968) and Lewontin (1974) conceived of a conceptual mapping scheme to describe genomic and phenotypic change of populations. Such a map consists of genotype and phenotype spaces, each signifying the possible profiles of populations in an evolutionary timescale (Fig. 1a). While the genotype is a primary constraint on the resulting phenotype, variation in the latter is also determined by environmental variation affecting a space that Waddington (1968) considered to be characterized by "epigenetic operators." Since natural selection acts on phenotypes, the genotype is modified by this epigenetic space (Fig. 1b). Therefore, evolution takes place within the possible genotypic and phenotypic spaces, filtered by an epigenetic space responding to environmental variation. In paleoanthropology, a strong emphasis has been in understanding whether certain skeletal phenotypes may better represent the genotype compared to other skeletal parts (e.g. Hlusko 2004; Harvati and Weaver 2006b; Cardini and Elton 2008; von Cramon-Taubadel and Smith 2012). Such an endeavor entails the identification of phenotypic markers that are less prone to modifications in epigenetic space. In figure 1b, such a situation is represented by the first three generations ($G_{1\text{-}3}$ and $P_{1\text{-}3}$). As this dissertation departs from the consensus that neutral evolutionary processes, rather than natural selection, have generated most of modern human biological diversity, it is necessary to consider skeletal elements that have the most direct association to neutral genotype space. The temporal bone has been considered to retain a strong phylogenetic signal in hominoids and to largely reflect neutral phenotypic evolution in modern humans (Lockwood et al. 2002, 2004; Harvati and Weaver 2006a, b; Smith et al. 2007, 2013; Smith 2009), but it is debated whether such signals are stronger than for other parts of the cranium or than the cranium as a whole (von Cramon-Taubadel 2009a, b, 2011; von Cramon-Taubadel and Smith 2012). Therefore, this dissertation must first seek to shed light on this debate.

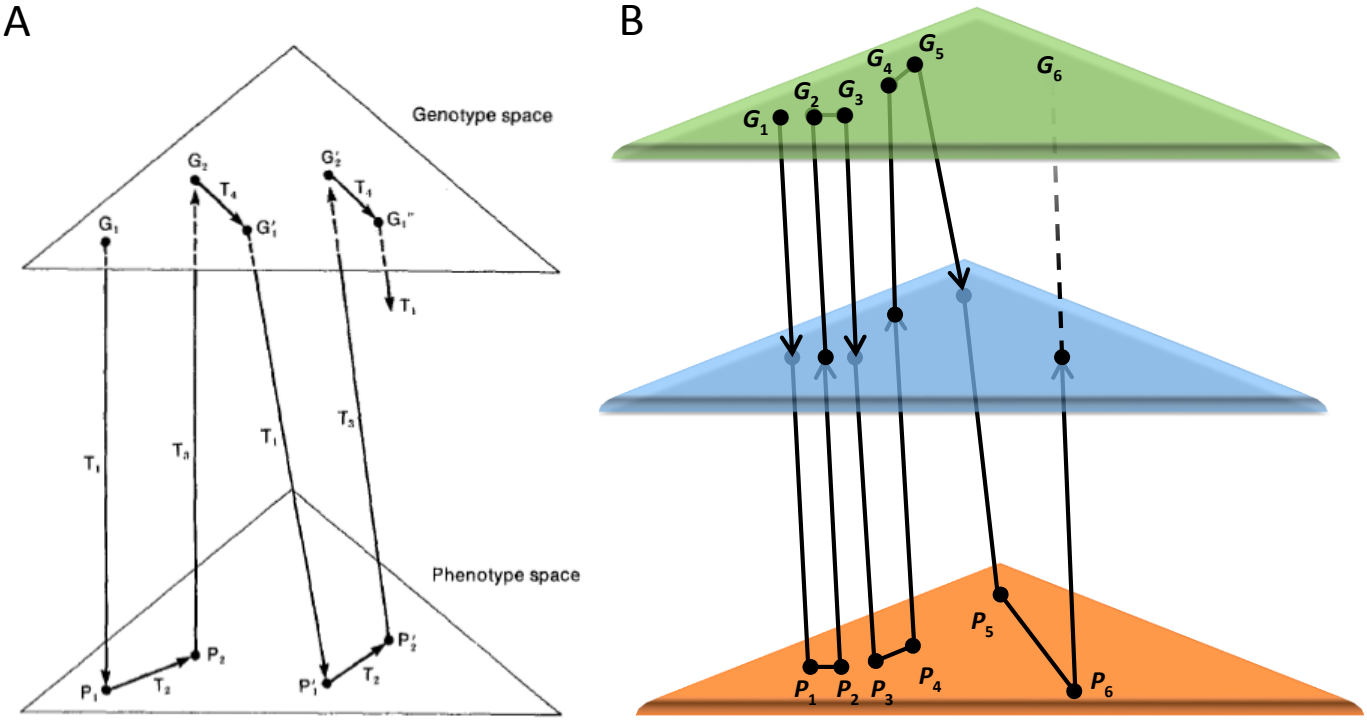

Figure 1. Genotype-phenotype maps. A: Lewontin's (1974) schema representing the transformation paths of genotype and phenotype from one generation to the next, where *G* is genotype, *P* is phenotype, and *T* is time. B: a schema that additionally considers Waddington's (1968) "epigenetic operators" that respond to environmental variation in epigenetic space (middle blue triangle). In B, variation in genotype and phenotype of the first three generations ($G_{1\text{-}3}$ and $P_{1\text{-}3}$) is relatively small compared to the subsequent generations ($G_{4\text{-}6}$ and $P_{4\text{-}6}$). The first three generations can be said to evolve largely under neutrality while the latter are subjected to natural selection.

An appreciation for the genotype-phenotype map concept has brought forth the growing field of epigenetics (Goldberg et al. 2007). Broadly, epigenetics seeks to characterize Waddington's epigenetic operators in order to understand variation in phenotypic traits that is not directly mediated by the underlying genotype. Understanding the association of genotypes and phenotypes in individuals and populations has led to the call for a systematic and comprehensive study of the latter in an emerging field of "phenomics" (Gerlai 2002; Freimer and Sabatti 2003; Houle 2010; Houle et al. 2010; O'Leary and Kaufman 2011; Roseman 2013). While epigenetics is primarily concerned with epigenetic space and its cellular mechanisms, phenomics deals with the phenotype at a broader scale, including morphological, physiological, and behavioral characteristics of organisms and their variation

between and among populations. For the anthropological sciences, this is reminiscent of early anthropometric studies and quantitative biometrical approaches (e.g. Galton 1888; Pearson and Lee 1903; Mahalanobis 1930). Using a contemporary evolutionary framework, this has taken form in the subfield of anthropological quantitative genetics, applying population genetic methods to anthropometric data (Relethford 2007; Roseman and Weaver 2007; von Cramon-Taubadel 2014). These approaches are adopted in this dissertation, using both genomic and phenomic lines of evidence for testing competing out-of-Africa dispersal models.

At the height of the modern synthesis, Sewall Wright (1950) proposed a general theory of evolution that could be extended to the study of language and culture. Broadly, language and culture can be considered to lie in phenotype space. A branch of theoretical population genetics was developed to quantitatively characterize the evolution of language and culture (Cavalli-Sforza 1975; Cavalli-Sforza and Feldman 1981; Feldman and Laland 1996), with substantial work on the association of genetic and linguistic diversity ensuing (Cavalli-Sforza et al. 1988; Derish and Sokal 1988; Sokal 1988; Sokal et al. 1989; Barbujani and Sokal 1990; Excoffier et al. 1991). A "new synthesis" was predicted (Renfrew 1991, 1992), whereby linguistic, archaeological, and biological lines of evidence could be used in tandem for a coherent reconstruction of the human past. The new synthesis has not been fully realized (Renfrew 2010), but it is toward this goal that the last study of this dissertation explores the association of linguistic phenotype variation to cranial phenotype variation, offering a prospectus for future research.

1.2 Methodological background: Population genetics and quantitative genetics

Quantitative genetics can be said to trace its origins to Gregor Mendel's plant experiments (Mendel 1941 (1885)), where the study of inheritance dealt with changes in phenotype rather than direct assessments of the genotype. Today, quantitative genetics is a branch of population genetics, drawing from modern evolutionary theory and concerned with the variation and evolution of phenotypes. In the anthropological sciences, quantitative genetic approaches were employed at a time when molecular genetic data was still limited for extant populations (e.g. Williams-Blangero and Blangero 1989; Relethford and Blangero 1990; Relethford and Harpending 1994; Relethford et al. 1997; Powell and Neves 1999). These methods continue to play an important role in archaeological contexts, where endogenous DNA is either not retrievable, fragmentary, or limited to individual specimens rather than

populations. They are in contrast to biometrical approaches independent of modern evolutionary theory, i.e. "model-free" methods (Relethford and Lees 1982), such as the Mahalanobis measures of variation (Mahalanobis 1930, 1936) that are still widely used today.

The combined use of population genetic and quantitative genetic approaches can be exploited to address a variety of evolutionary questions that concern both the genotype and phenotype of populations. In most cases, the comparison of values measuring the inter-population genotypic and phenotypic variation is used to infer natural selection on phenotype (Spitze 1993; Holsinger and Weir 2009; Leinonen et al. 2013). In figure 1b, this is represented by the changes from the fifth to the sixth generations ($G_{5\text{-}6}$ and $P_{5\text{-}6}$). Selection is inferred when inter-population phenotypic variation is larger than neutral genetic variation. By contrast, genetic and phenotypic variation is expected to be proportional under neutrality (as would be the case in $G_{1\text{-}3}$ and $P_{1\text{-}3}$ in figure 1b). Inter-population genetic distances can be measured under a variety of evolutionary models and are denoted as F_{ST} in population genetics, which is the fixation (F) index comparing the subset ($_S$) genetic diversity within populations to the total ($_T$) genetic diversity of all sampled populations. The analogue in quantitative genetics is referred to as Q_{ST}, following the convention established by Spitze (1993). Leinonen and colleagues (Leinonen et al. 2006, 2013) replace Q_{ST} with P_{ST} in order to make the distinction between measures of phenotype derived from experimental laboratory populations versus populations in the field, where environmental variables that potentially affect the phenotype are not controlled. As this dissertation deals with the latter, P_{ST} is the terminology applied here. Since the primary aim is to test competing out-of-Africa models, F_{ST} and P_{ST} values are used primarily as two independent lines of evidence. Nevertheless, the proportionality of F_{ST} and P_{ST} is discussed in the first study when testing whether some cranial elements follow neutral genetic expectations more than other cranial parts.

In terms of data acquisition, this dissertation draws from two "revolutions" in quantifying phenotypic and genomic variation. The first can be traced to the introduction of geometric morphometrics, which allows for the quantitative comparison of anatomy and form (Rohlf and Marcus 1993; Adams et al. 2004; Bookstein et al. 2004; Adams et al. 2013). It is increasingly used in combination with industrial and medical imaging technology, such as micro computed tomography, in both extant and extinct populations (Weber and Bookstein 2011; Rein and Harvati 2014; Weber 2015). The other methodological breakthrough was the development of high-throughput sequencing and single nucleotide polymorphism (SNP)

genotyping of extant human populations (Cavalli-Sforza and Feldman 2003; Novembre and Ramachandran 2011), increasingly used in combination with genomic material derived from extinct specimens (Der Sarkissian et al. 2014; Burrell et al. 2015; Hofreiter et al. 2015). Following the methodological advances in geometric morphometrics and high-throughput sequencing, original data in this dissertation is in the form of three-dimensional cranial landmarks from recent modern human samples stored in museum collections, as well as from published data of SNPs typed for extant populations. In all, phenotypic and genomic loci are subjected to analysis. The particulars of these datasets are detailed below (section 2) and individually in each study appendix. The general workflow employed for this dissertation, from data acquisition to analysis, is outlined as a flowchart in Fig. 2.

Throughout this dissertation, F_{ST} is calculated following the model and methods of Weir and Cockerham (1984). In this case, populations of the same size are considered to have descended from a common ancestral population, which is assumed to be in Hardy-Weinberg equilibrium and linkage disequilibrium. The calculation of F_{ST} is designed for one allele at one locus; therefore, F_{ST} is averaged across all sampled SNPs. P_{ST} throughout this dissertation is calculated following the model and methods of Relethford and Blangero (1990), which assumes that the phenotype reflects the net effect of polygenic inheritance such that phenotypic variance is proportional to additive genetic variance. Variation in cranial shape is assumed to be continuous and not subject to dominance or epistatic effects. While F_{ST} and P_{ST} values indicate the degree of genetic and phenotypic differentiation between populations, they are not, by themselves, informative of all the mechanisms that generated those differences. In the modern human origins and dispersal debate, the tempo and mode of population movement as well as the size of these populations has been a critical point of discussion. It was proposed, for example, that a multiregional evolution model could be accommodated when considering a larger long-term effective population size in Africa (Relethford 1999). Likewise, a large—and possibly structured—ancestral effective population size in Africa could also be compatible with a recent out-of-Africa hypothesis (Blum and Jakobsson 2011), as predicted in a multiple dispersals scenario. Therefore, quantifying measures of ancestral population size and the time in which populations diverged is desirable for contextualizing F_{ST} and P_{ST} values and for understanding the association that these, in turn, have with geography.

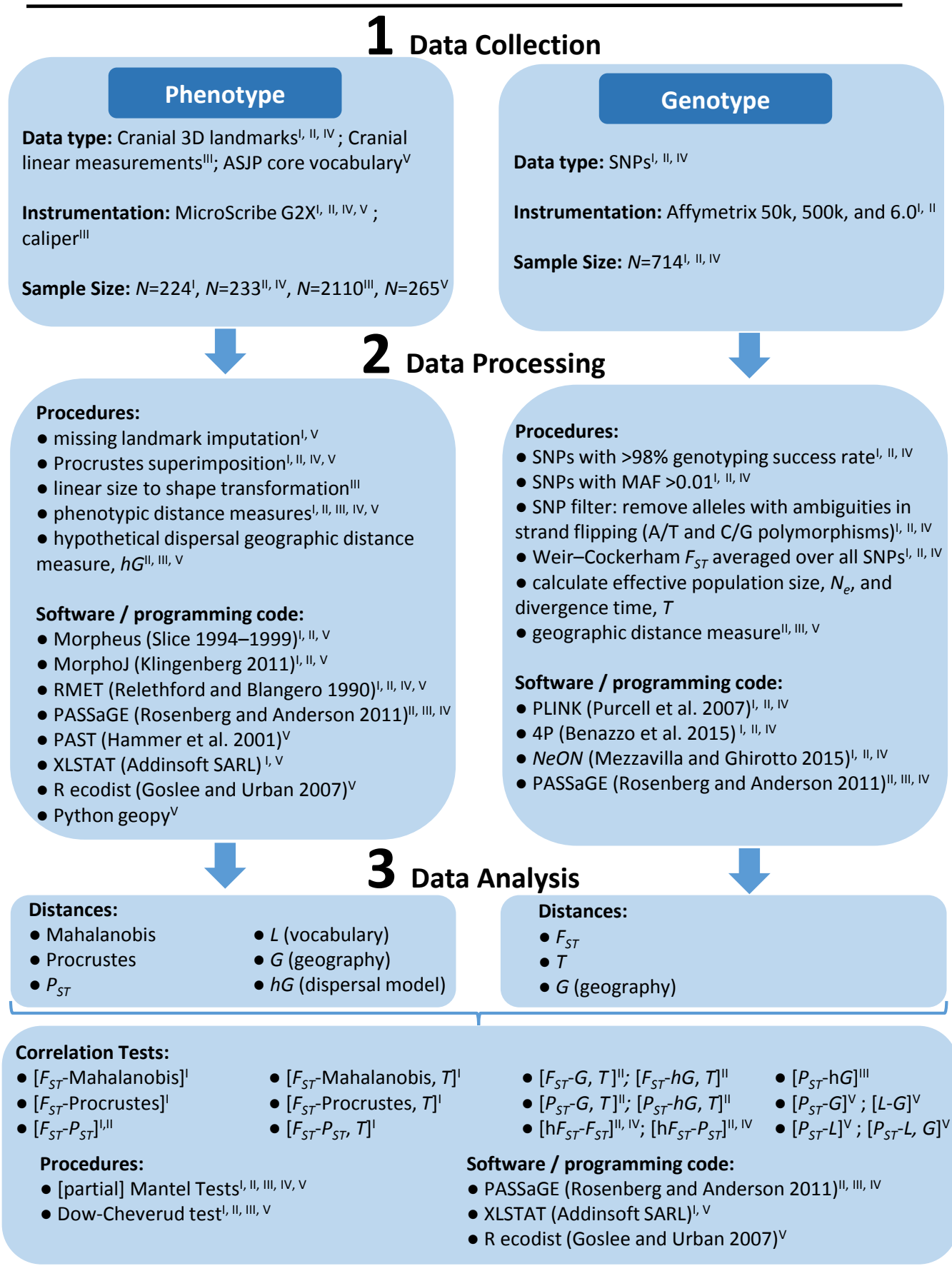

Figure 2. Flow chart of general work flow employed in this dissertation. Superscript numerals correspond to appendix number.

In population genetics, differences between populations, as measured by pairwise F_{ST}, are inversely proportional to their effective population sizes, N_e, and directly proportional to the time elapsed since their separation, *T*. While it is theoretically possible to estimate N_e from F_{ST}, such estimates are unreliable (Holsinger and Weir 2009). Thus, if N_e values are unknown, an infinite number of *T* values can account for the observed F_{ST} values. Therefore, independent estimates of N_e are necessary. Independent estimates of N_e and *T* can also be calculated from genomic patterns of linkage disequilibrium (Sved 1971; Hayes et al. 2003; Tenesa et al. 2007; McEvoy et al. 2011). This approach is particularly appropriate in this dissertation given that patterns of linkage disequilibrium are positively correlated with geographical distance from Africa and pairwise F_{ST} values are also positively correlated with geographic distance between populations (Ramachandran et al. 2005; Jakobsson et al. 2008). *T*, retrieved as generation values, can be converted into calendar dates for comparison with the fossil and archaeological records, under the assumption that inter-generational time in human populations is constant and equal (Tremblay and Vézina 2000; Langergraber et al. 2012). In this dissertation, an inter-generational time of 28 years is assumed, following Fenner's (2005) recommendation, which is informed by a survey of hunter-gatherer and sedentary societies world-wide. Notably, calculating *T* values from patters of linkage disequilibrium circumvents, to some extent, the uncertainties associated when otherwise calculating *T* with estimates of mutation rate (Scally and Durbin 2012).

2. Objectives

The first objective is to validate the theory and methods set out for this dissertation by employing population genetic and quantitative genetic approaches to the original data collected. In particular, it is necessary to address whether cranial phenotype variation follows neutral expectations and whether some cranial parts do so to a greater degree than others (Appendix I). The primary objective of this dissertation—testing out-of-Africa dispersal models—can then be undertaken. Two of the models tested represent a single out-of-Africa scenario while two other models represent multiple dispersals scenarios. In the first study (Appendix II), only data of extant/recent modern human populations is used. In the second study (Appendix III), fossil data is integrated but limited to cranial phenotype data. Appendix IV is a review paper following the two previous studies, updated with two other dispersal tests. It provides a critical discussion of the results of this dissertation alongside the most recent

work from the fields of population genetics, paleo-genetics, and paleoanthropology. Having productively used genomic and phenotypic data in tandem, Appendix V explores the possibility of integrating linguistic data in a quantitative manner in order to address questions of modern human population history. In all, the objectives of this dissertation can be summarized as follows:

1. **Validate theory and methods**
2. **Test competing out-of-Africa dispersal models**
3. **Review associated literature**
4. **Explore the quantitative integration of linguistic data**

Below is a list of research questions addressed toward meeting the objectives delineated above. These are enumerated with respect to the appendices of this dissertation, followed by a description of these studies.

2.1 Appendix I: Do model-bound measures of inter-population distances better approximate genetic distances, as compared to model-free measures?

In order to meet the first objective, this study uses the original cranial landmark dataset to quantify the phenotypic differentiation between populations. Three different distance measures are explored. The first is a classical biometrical measure, the Mahalanobis distance (Mahalanobis 1930, 1936), free of explicit evolutionary models, or "model-free" (Relethford and Lees 1982). The second measure, the Procrustes distance (Gower 1975; Rohlf and Slice 1990; Adams et al. 2004, 2014; Bookstein et al. 2004), is specific to the application of geometric morphometric methods and is also free of evolutionary models. The third, P_{ST}, follows an evolutionary model of equal and additive genetic inheritance for phenotypic traits and is analogous to F_{ST} in population genetics (Relethford and Blangero 1990; Holsinger and Weir 2009; Leinonen et al. 2013). The aim is to understand whether one phenotype distance measure is more correlated to pairwise F_{ST}, calculated from SNP data. This is determined by the correlation values following Mantel tests (Mantel 1967). It is hypothesized that the P_{ST} measure will be most correlated to F_{ST}.

2.2 Appendix I: Differential preservation of population history for the modern human cranium?

Because inter-population differentiation of cranial shape and neutral genetic markers are significantly correlated in modern humans (Harvati and Weaver 2006a, b; Roseman and Weaver 2007; Smith 2009; von Cramon-Taubadel 2009a, b, 2011, 2014), broad consensus has emerged on cranial shape differentiation following a pattern of neutral evolution and thus the preservation of population history. However, there is still debate as to whether certain parts of the cranium follow a neutral pattern to a greater degree than other parts or than the whole cranium itself. This study addresses this debate. Since previous research has been limited to microsatellite genomic data, this study uses the same landmark configuration as in Harvati and Weaver (2006a, b), thereby making a reasonable comparison for the effect that genomic loci may have on the correlation of genotype and cranial phenotype. Following von Cramon-Taubadel (von Cramon-Taubadel 2009a, b, 2011), Dow-Cheverud tests (Dow and Cheverud 1985) are used in this study to address whether P_{ST} of certain cranial parts is statistically more correlated to F_{ST} of SNPs than other cranial parts. Likewise, the regressions of F_{ST} and P_{ST} are visualized for each cranial part in order to better assess their proportionality (Leinonen et al. 2013).

This study additionally seeks to test the hypothesis that the temporal bone reflects deeper population history than other cranial regions (Harvati 2002; Harvati and Weaver 2006b). This hypothesis can be tested by quantifying the correlation of P_{ST} and F_{ST} while controlling for T in a partial Mantel test (Smouse et al. 1986). Computationally, this test computes the correlation of the residuals from the independent correlations of F_{ST}-T and P_{ST}-T. Theoretically, this has the effect of correcting P_{ST} and F_{ST} values from independent estimates of population divergence. Thus, genetic and phenotypic differentiation is contextualized with a more detailed evolutionary context. It is hypothesized that if the temporal bone indeed reflects deep population history, the correlation values of [P_{ST}-F_{ST}, T] will be higher than for [P_{ST}-F_{ST}] alone.

2.3 Appendix II: Single or multiple modern human dispersals out-of-Africa? Evidence from extant human biology

This study forms the core of this dissertation, addressing the second objective using genomic SNP data and cranial shape phenotype data in tandem. Four distinct out-of-Africa

models are tested. Two are proposals for a single dispersal and two are proposals for multiple dispersals out-of-Africa. In a parsimonious scenario, a Late Pleistocene out-of-Africa dispersal commences along a northern Levantine route and continues eastward into Asia, primarily along a latitudinal axis (Liu et al. 2006; Ramachandran and Rosenberg 2011). In another single dispersal scenario, out-of-Africa is in the Late Pleistocene via a southern "beachcomber arc" route that passes through the southern Arabian Peninsula and continues along the Indian Ocean coastal rim (Oppenheimer 2009, 2012a, b). By contrast, one proposal for multiple dispersals from Africa entails both southern and northern route dispersals in the Late Pleistocene (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996; Rasmussen et al. 2011) while another model entails an earlier dispersal as early as the terminal Middle Pleistocene (Stringer 2000; Walter et al. 2000; Petraglia et al. 2010; Armitage et al. 2011). The first multiple dispersals scenario was partly constructed on the observation of phenotypic discontinuity in modern human populations, where certain populations could be considered isolated descendants of the first dispersal (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). For this reason, this study samples cranial landmark and SNP data of hypothetical population isolates and other populations from Africa, Eurasia, and Australasia. Each dispersal scenario is modeled by joining the sampled populations along hypothetical dispersal routes. The geographical space, *G*, that separates populations along these routes can then be related independently to P_{ST} and F_{ST}, with the same modification of *T* as in the previous study. In this way, the genetic and phenotypic differentiation of populations is placed within spatio-temporally explicit models. Correlation and statistical significance values of [F_{ST}-*G*, *T*] and [P_{ST}-*G*, *T*] tests are evaluated using partial Mantel tests. Dow-Cheverud tests are then used to assess whether one hypothetical dispersal model, *hG*, is more significant than a competing model.

In order to validate the above results, an alternative approach is undertaken. *T* is calculated from the archaeological and paleontological records, where populations are assumed to diverge at a time averaged between the chronology of first occupation in the geographical region where the populations were sampled. Pairwise, the average chronology between populations, *C*, can be substituted for *T* in order to arrive at independent estimates of a hypothetical F_{ST}, hF_{ST}, that is also dependent on estimates of N_e (Holsinger and Weir 2009). The empirically derived P_{ST} and F_{ST} values can then be compared independently to hF_{ST} in a Mantel test. This approach ignores dispersal routes since *G* is factored out of the

computations. Nevertheless, it is still informative of the tempo of the out-of-Africa expansion, with a spatial component retained by the fact that *C* is with respect to the populations sampled from a specific geographical region.

2.4 Appendix III: Single or multiple modern human dispersals out-of-Africa? Integrating the fossil record

Another approach for testing competing out-of-Africa dispersal hypotheses is to include fossil evidence. Whereas the previous study uses data of extant human populations and relies on the genomic estimate of *T*, a temporal component can be embedded into the models by using a mix of fossil paleo-demes and extant human populations. The calculation of P_{ST} would therefore account for the variation of hypothetical ancestral populations. Hypothetical paleo-demes from Africa would then be ancestral to extant populations outside of Africa. This theoretical approach is similar to the study by Hubbe and colleagues (2010) for testing dispersal hypotheses into the Americas. In a single dispersal scenario out of Africa, a Late Pleistocene African paleo-deme is ancestral to modern humans. In a multiple dispersals model, a Middle-Late Pleistocene African paleo-deme is ancestral to isolated descendants of the first dispersal, while the Late Pleistocene African paleo-deme is ancestral to all other sampled populations. As the human fossil record between the late Middle Pleistocene and the early Late Pleistocene of Africa remains sparse, it is necessary to include the well-characterized fossil Levantine paleo-deme from Qafzeh and Skhul caves (MacCurdy 1936; Vandermeersch 1981; Schwarcz et al. 1988; Howell 1999; Grün et al. 2005). This also has the advantage of addressing the hypothesis that the Qafzeh-Skhul paleo-deme, or a related population, may be ancestral to modern humans (Stringer 1992; Schillaci 2008).

In this study, the Herto specimen from Ethiopia (White et al. 2003) is included with the Levantine specimens such that a Herto-Qafzeh-Skhul paleo-deme represents the cranial phenotypic variation of Middle-Late Pleistocene anatomically modern humans in Africa and the Levant. The Hofmeyr (Grine et al. 2007; Grine et al. 2010) and Nazlet Khater (Crevecoeur et al. 2009; Crevecoeur 2012) specimens, respectively from South Africa and Egypt, are used to represent a Late Pleistocene African paleo-deme. This study subsets original data collected by external research collaborators, taking advantage of an exceptional dataset that totals over 6,000 modern human crania (Hanihara 2006; Hubbe et al. 2009) and various fossil specimens (Stringer 1992). The raw data here is of linear measurements of cranial dimensions. In order

to make the results methodologically consistent with the previous study, the measurements are size standardized to arrive at variables that reflect cranial shape (Darroch and Mosimann 1985; Jungers et al. 1995). As in the previous study, each dispersal scenario is modeled by joining the sampled populations along geographical dispersal routes. The different dispersal models are then evaluated by Mantel and Dow-Cheverud tests.

2.5 Appendix IV: Can conflicting out-of-Africa scenarios be reconciled with the fossil and genetic lines of evidence?

In the previous studies, the use of fossil data is limited to African and Levantine paleo-demes. A more refined study design would include fossil data from Eurasia and Australia, but such data remains relatively sparse and highly controversial. For example, the presence of anatomically modern humans in Asia is increasingly being pushed back in time with new fossil discoveries. The anatomically modern cranium from Liujiang, China (Woo 1959; Shen et al. 2002) and archaeological assemblages like the one at Jwalapuram (Petraglia et al. 2007) served to push forward the hypothesis that modern humans occupied Eurasia earlier than seventy thousand years before present (70 ka BP). The dating and context of the Liujiang cranium remains controversial, as does the attribution of the Jwalapuram assemblage to modern humans, particularly because they are in conflict with inferences drawn from uni-parental genetic evidence (e.g. Mellars et al. 2013). However, recent discoveries continue to suggest the presence of anatomically modern humans in Asia prior to 70 ka BP. These include the mandible fragment from Zhirendong, China (Jin et al. 2009; Liu et al. 2010); the metatarsal from Callao Cave, Philippines (Mijares et al. 2010); the humerus fragment from Netankheri, India (Sankhyan et al. 2012); and the teeth from Luna Cave, China (Bae et al. 2014). In this manuscript, these and other key fossils are reviewed alongside genomic evidence that may serve to accommodate such an early dispersal scenario. It is a critical review of on-going debates regarding models of modern human origins and the out-of-Africa expansion, placing into context the results of this dissertation, the development of different hypotheses, and a prospectus for future research.

2.6 Appendix V: Exploration of linguistic phenotype and toward a new synthesis

The last manuscript of this dissertation is an exploratory analysis quantifying the association of variation between populations with respect to their vocabulary and cranial shape. In accordance with Sewall Wright's proposal for a general theory of evolution, and Waddington and Lewontin's concept of genotype-phenotype maps, language can be considered to lie within phenotypic space and its variation can be quantified following population genetics theory. As cranial shape has been shown to correlate differentially with neutral genomic variation, comparing its variation to vocabulary variation for the same populations offers a unique opportunity to explore how language may reflect neutral processes and population history. More broadly, such a phenotype-phenotype comparison can offer insights into the challenges involved toward a new synthesis.

This study is an external collaboration applying bioinformatical methods of genomic sequence alignment to vocabulary data (Jäger 2013). The method consists of comparing the variation of forty words that exists across worldwide languages and are resistant to changes in meaning and to word borrowing from one population to another (Holman et al. 2008). For any number of populations, linguistic pairwise distances are calculated based on the alignment of the corresponding words and the subsequent empirical weight of their similarity. As with F_{ST}, values range between 0 and 1 and dissimilarity matrices can be constructed for their comparison with P_{ST}. Cranial shape of eleven populations are sampled for this comparison. As with previous studies, Mantel and Dow-Cheverud tests are used to evaluate the association of cranial shape and linguistic phenotype. It is hypothesized that linguistic variation, L, will be significantly associated with P_{ST} for some cranial segments. In the case that that P_{ST}-L is most correlated for the temporal bone landmark configuration, vocabulary data can be inferred to retain a strong signal of population history, possibly reflecting events of population divergence up to the last common African ancestor, as hypothesized for language phonemes (Atkinson 2011).

3. Results and Discussion

3.1 Appendix I: Mahalanobis distance is an adequate model-free proxy for model-bound P_{ST}

This is the first study to compare systematically the correlation of different phenotypic distances to pairwise F_{ST}. Contrary to the hypothesis set out for this study, both Mahalanobis and P_{ST} distances were found to be comparably correlated to pairwise F_{ST} distances. These results are somewhat surprising since P_{ST} was calculated while also considering effective population sizes, N_e. Nonetheless, the results can be explained by the fact that both Mahalanobis and P_{ST} distances measures are calculated in a similar fashion (i.e. by comparing the subset of diversity within populations relative to the total diversity of all populations sampled). If this pattern is confirmed in subsequent studies, it could imply that N_e has a minimal impact in the differentiation of extant human cranial shape. This study concludes that Mahalanobis distances, as model-free distances, can be considered adequate proxies for model-bound P_{ST} distances. By contrast, this study also determines that Procrustes distances are less reliable proxies. To this end, three interpretations on these results are worth noting. First, the fact that Mahalanobis distances are slightly more correlated to F_{ST} distances suggests that Mahalanobis distance may over-estimate the biological distance of populations in extant human anthropometric studies. Second, the fact that Procrustes distances are less correlated to F_{ST} distances suggests that they may underestimate biological distance of populations in geometric morphometric studies. Third, since Procrustes distances had a generally weaker statistical significance, their use with other measures of dissimilarity (such as F_{ST}) may lead to false negatives or otherwise erroneous results. As both Mahalanobis and Procrustes distances continues to be widely utilized in population studies of phenotype, these results have wide methodological implications. In all, caution is warranted when making evolutionary interpretations with the use of Mahalanobis and, especially, Procrustes distances.

3.2 Appendix I: The temporal bone preserves a signal of deep population history

This study is the first to revisit the differential preservation of population history using SNP data, as all previous studies have utilized microsatellite data or classical genetic polymorphisms. The results indicate that phenotypic distances derived from the temporal bone landmark configuration consistently had higher absolute correlation values with F_{ST}, as

compared to phenotypic distances derived for the whole cranium, the neurocranium, or the face. This is consistent with some previous studies (Harvati and Weaver 2006a; von Cramon-Taubadel 2009a; Reyes-Centeno et al. 2013). Here, the regression plots demonstrate that the high correlation can be attributed to the proportionality that temporal bone distances have with F_{ST} distances. Whereas the regression plot of the temporal bone has a relatively linear pattern, those of the whole cranium, neurocranium, and face deviate from linearity and otherwise do not show another specific relationship (i.e. exponential, polynomial, etc.). In standard quantitative genetic theory, this indicates that temporal bone shape follows a pattern consistent with neutral genetic expectations. Under the assumption that most of recent human evolution can be attributed to neutral genetic processes, the temporal bone thus conserves a relatively stronger population history signal than other cranial parts.

The hypothesis that the correlation values of P_{ST}-F_{ST} would be higher for the temporal bone when controlling for divergence time *T* is supported in this study. Such a pattern was not observed for the other cranial regions or the whole cranium configuration. This implies that the temporal bone preserves a population history signal of deep population divergence, as previously hypothesized (Harvati 2002; Harvati and Weaver 2006b). The [P_{ST}-F_{ST}] correlation was significant for the facial shape configuration but lost when applying the [P_{ST}-F_{ST}, *T*] test. This is interpreted to suggest that while the temporal bone reflects deep population divergence, the face reflects more recent population history. This interpretation must be more rigorously tested, but it is of deep interest when considering that different genomic systems may also evolve at differential rates (Holsinger and Weir 2009; Colonna et al. 2010).

In this analysis, neutral genetic variation, as calculated from SNPs, could be said to explain about 31% of variance in temporal bone shape for the populations sampled. Thus, about 70% of shape variation in the temporal bone remains unexplained. Further work should therefore seek to assess what other factors affect variation in its shape. Likewise, in future studies, the anatomical and genomic loci (i.e. landmarks and SNPs) can be randomized by exclusion in order to assess the effect that specific loci have on the P_{ST}-F_{ST} association.

3.3 Appendix II: Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia

Having established the F_{ST}-P_{ST} proportionality for the temporal bone, only data from this cranial region is used to test competing dispersal models. This methodological decision is particularly appropriate for a study design employing Mantel tests, where the association between variables is interpreted in a statistical framework of Pearson product-moment correlations. Of the four out-of-Africa dispersal models tested, the model that entailed two dispersals from Africa receives support from both temporal bone shape and SNP genomic data. In this model, the first dispersal is along a southern, coastal route into Asia, commencing as early as the terminal Middle Pleistocene, while the second dispersal is along a northern, Levantine route into Eurasia. In the first analysis, the partial correlations are significant for both [F_{ST}-G, T] and [P_{ST}-G, T]. In this analysis, the oldest divergence, T, estimate is for the South African and Melanesian population pair, dated to ~116 ka BP when assuming a constant inter-generational time of 28 years. Notably, the divergence of Australo-Melanesians from the African populations is earlier than the divergence of the South, Central, or East Asian populations, consistent with previous analyses (McEvoy et al. 2011). The second analysis, relying on hypothetical "archaeological divergence" estimates and their dependency on the genomic estimates of effective population size, N_e, also results in support for the same multiple dispersals and southern route model. In this latter analysis, the point of emphasis is on the timing of the dispersals rather than the geographical routes of dispersal. The best model is one of an initial dispersal at 130 and a later dispersal at 50 ka BP. This scenario best follows proposals of early occupation of the Levant and the Arabian Peninsula by anatomically modern humans (Stringer 2000; Walter et al. 2000; Petraglia et al. 2010; Armitage et al. 2011). Importantly, the best-supported model considers occupation of Southeast Asia and Australasia to be between 45-50 ka BP.

The overarching implication of this study is that the dispersal pattern of modern humans from Africa has shaped the genomic and phenotypic variation of extant populations. Methodologically, this study productively uses two lines of evidence in tandem. The supporting information elaborates on this beyond the test of dispersal models. Of note, the Aeta/Agta "Negrito" population from the Philippines is inferred to be descended from both first and second dispersal ancestors, consistent with previous analyses (Rasmussen et al. 2011). This is determined by two contrasting but reconcilable results. On the one hand, the

Aeta/Agta cluster closer to South, Central, and East Asian populations in both principal component analysis (PCA) and discriminant analysis of PCs (DAPC). On the other hand, the Aeta/Agta form a basal branch with Australo-Melanesians in a maximum-likelihood phylogenetic tree. In the best-supported tree, gene flow is inferred from the sampled Japanese population to the Aeta/Agta using a TreeMix analysis (Pickrell and Pritchard 2012). The PCA and DAPC results are relatively consistent when using either the genomic or cranial phenotype data. Future work should also employ the methods of the TreeMix analysis to cranial phenotype data, as it could provide a powerful tool for inference of gene flow. In all analyses, Australo-Melanesians are considered relatively isolated populations and are interpreted to descend from the first dispersal.

The original raw dataset used in this study was published as part of supplementary information and is available on-line at the *Proceedings of the National Academy of Sciences USA* journal website. Following the publication of this study, the computational methods employed therein resulted in two publications on population genetics software and programming code (Benazzo et al. 2015; Mezzavilla and Ghirotto 2015).

3.4 Appendix III: Ancestor-descendant models of fossil and extant modern human populations support multiple dispersals from Africa and a southern route into Asia

Having received support for a multiple dispersals scenario using biological datasets from extant and recent human populations, the next logical step is to validate these results using fossil data. In testing the same models as in the previous study and applying comparable methods, the multiple dispersals and southern route model again receives the best support. The Herto-Qafzeh-Skhul paleo-deme, representing the cranial phenotypic variation of Middle-Late Pleistocene anatomically modern humans in Africa and the Levant, can be considered ancestral to descendants of the first dispersal. Consistent with the previous study, only Australo-Melanesians are modelled as descendants of the first dispersal. All other populations can be considered to be descended from the second dispersal, here represented by an ancestral Hofmeyr-Nazlet Khater paleo-deme.

Using cranial data alone limits the number of fossils that can be included in hypothetical ancestral paleo-demes. Future work should seek to use a quantitative genetics analytical framework using other skeletal elements. By including fossils between the critical time period of 50-130 ka, it would be possible to test alternative temporal models of dispersal.

Likewise, as the fossil record for Southeast Asia grows, it will be desirable to use only fossil data in a similar study design. As high quality genomes of ancient specimens becomes available, it will eventually be possible to test these models using fossil and ancient DNA in tandem in a similar way to the previous study.

3.5 Appendix IV: An early expansion into Southwest Asia and a delayed expansion into Eurasia can reconcile conflicting out-of-Africa models

While the previous studies provide robust support for an out-of-Africa expansion that entailed two dispersals, such scenario remains highly contested. This review critically appraises the on-going debate and includes discussion of the two previous studies, as well as of other relevant studies published after the completion of the dispersal models tests in this dissertation. New tests of the dispersal models, which entail either early, Middle Pleistocene occupation of Southeast Asia or occupation of South India prior to the Toba eruption >75 ka BP, are both rejected when using the genomic data of the second study (Appendix II). Interestingly, early occupation of South Asia is supported, albeit weakly, with the cranial phenotype data. Such a result may be consistent with the hypothesis that some South and Southeast Asian populations may retain the signal of an early dispersal route (e.g. Petraglia et al. 2010; Ghirotto et al. 2011), but further work is needed to clarify this.

Overall, the best way to reconcile the current lines of archaeological, paleontological, genomic, and climatological lines of evidence is to consider an early expansion of anatomically modern humans into Southwestern Asia as early as the terminal Middle Pleistocene. Currently, evidence of this is unequivocal in the Levant, as represented by the Qafzeh-Skhul paleo-deme, and supported for the Arabian Peninsula by growing archaeological evidence. Populations of anatomically modern humans may have expanded further east in the early Pleistocene, but the current evidence suggests that these would most likely be extinct lineages, contributing nothing or little to extant populations. If, on the other hand, the current fossil evidence for anatomically modern humans in East Asia is discarded, then an early expansion may have remained restricted to Southwestern Asia. These populations (i.e. in the Levant and the Arabian Peninsula) could have maintained some level of contact with African populations, perhaps in a long process of divergence between African and non-African populations (Scally and Durbin 2012). From this region, populations would have successfully expanded only later in two waves into Eurasia, representing a delayed expansion (Xing et al.

2010a; Xing et al. 2010b). In such a model, Southwest Asia plays a greater role in recent human evolution than previously considered.

The debate on the out-of-Africa event is far from over and continued field work will shed light on what is likely a complex, nuanced process. Nevertheless, this dissertation has productively used two lines of evidence in tandem, under a common quantitative, evolutionary framework. As data accumulates, it will be possible to employ population approaches within a paleopopulation genetics framework (Wall and Slatkin 2012), on the one hand, and a paleo-deme approach (Howell 1999), on the other. Such an approach is desirable in order to resolve conflicting models generated from any single line of evidence and will thus enhance the reconstruction of the human past.

3.6 Appendix V: Vocabulary language data may reflect recent population history

Having *(i*) explored the relationship of neutral genomic loci and cranial shape loci and (*ii*) using these two lines of evidence to test competing dispersal models, a logical next step is to delve further into phenotypic space. Linguistic phenotype, as measured by variation in vocabulary, is shown in this study to correlate most to facial phenotype. Indeed, this association is shown to be greater than for the neurocranium or the temporal bone. While variation in facial shape has a significant correlation with neutral genetic variation, as shown in the first study, it may reflect more recent population history than the temporal bone (Appendix I). From an evolutionary-developmental perspective, it was hypothesized in the first study of this dissertation (Appendix I) that the face may evolve at a faster rate than the temporal bone. The results of this study fit well with that hypothesis, as vocabulary has been shown to change faster than other aspects of language, such as grammatical structure. Further work is necessary to support these associations, ideally with populations where both vocabulary and grammatical language information is available, as well as genomic and environmental data. Nevertheless, this study is an interesting approach for addressing the association of a phenotype that is unregulated by genomic variation (language) to one that is partly regulated by it (cranial shape). It paves the way for a comprehensive phenomic research program in the anthropological sciences, taking forth the challenge of the new synthesis.

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Appendix I

"The reduction of the biological system to mutable hereditary information… leaves out a feature which is essential for any theory which is to be applicable to biology as a whole. We need a hereditary system which does not merely contain information, but which…leads to the production of a phenotype…. It is the phenotype which acts on the environment…and it is on phenotypes that the environment exerts its natural selective forces."

Conrad Hal Waddington (1968: 525)

Waddington CH. 1968. Towards a theoretical biology. Nature 218(5141):525-527.

Genomic validation of the differential preservation of population history in modern human cranial anatomy

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ABSTRACT

In modern humans, the significant correlation between neutral genetic loci and cranial anatomy suggests that the cranium preserves a population history signature. However, there is disagreement on whether certain parts of the cranium preserve it to a greater degree than other parts. It is also unclear how different quantitative measures of phenotype affect the association of genetic variation and anatomy. Here, we revisit these matters by testing the correlation of genetic distances and various phenotypic distances of ten modern human populations. Geometric morphometric shape data from the cranium of N=224 individuals are used to calculate phenotypic P_{ST}, Procrustes, and Mahalanobis distances. We calculate their correlation to neutral genetic distances, F_{ST}, derived from single nucleotide polymorphisms (SNPs). We subset the cranial data into landmark configurations that include the neurocranium, the face, and the temporal bone, in order to evaluate if these different cranial regions are differentially correlated to neutral genetic variation. Our results show that both P_{ST} and Mahalanobis distances are appropriate for comparison with F_{ST}. They also indicate that overall cranial shape is significantly correlated with neutral genetic variation. Of the component parts examined, the temporal bone is the most significantly correlated, to a greater degree when considering the time in which populations diverged. Our results reconcile some of the discrepant conclusions drawn from previous studies. They suggest that while the cranium, as a whole, can be used to reconstruct modern human population history, the temporal bone tracks it at a higher fidelity and at more profound time depth.

Molecular and morphological data are essential for reconstructing phylogeny across taxa and population history within a species. While these lines of evidence can be used in tandem, they sometimes lead to conflicting results (Collard and Wood 2000; Edwards 2009). For this reason, identifying whether some anatomical regions are more informative of population history and phylogeny than other anatomical parts is a matter of ongoing inquiry, particularly for the primate cranium (e.g. Hlusko 2004; Harvati and Weaver 2006b; Cardini and Elton 2008; von Cramon-Taubadel and Smith 2012). This endeavor is pragmatic in a paleontological and archaeological context, where poor conservation may preclude the study of complete fossils or skeletons or the extraction of endogenous DNA. For modern humans, there is wide consensus that cranial form as a whole can be informative of population history and that, at a global scale, population differentiation has occurred to a considerable degree under neutrality (Relethford 2004a, b; Roseman 2004; Harvati and Weaver 2006a, b; Manica et al. 2007; Roseman and Weaver 2007; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009, 2010; Hubbe et al. 2009; Smith 2009; von Cramon-Taubadel 2009a, b, 2011). These assertions are strongly supported by studies that quantified the correlation of biological distances between populations, derived independently from anatomical and neutral genetic markers (Roseman 2004; Harvati and Weaver 2006a, b; Smith 2009; von Cramon-Taubadel 2009a, b, 2011; Reyes-Centeno et al. 2013).

From these findings, there is agreement on the significant correlation between neutral genetic distances and phenotypic distances derived from the whole cranium and the temporal bone. While some studies (Harvati and Weaver 2006a; von Cramon-Taubadel 2009a; Reyes-Centeno et al. 2013) found a stronger correlation for the temporal bone than the whole cranium or its other component parts, Smith (2009) found that the whole cranium and the basicranium had a stronger correlation to neutral genetic distances than the temporal bone. On the observation that shape variation in the temporal bone was most pronounced between African and non-African populations, Harvati (2002) and Harvati and Weaver (2006b) hypothesized that temporal bones conserve a population history signal of deep population divergence. At the same time, von Cramon-Taubadel (2009a, b, 2011), using adult specimens, found that while the temporal bone had the highest absolute correlation with neutral genetic loci, neither it nor the basicranium could be statistically considered to preserve a better population history signal than the whole cranium or than some other bones or cranial segments. In another point of disagreement, Harvati & Weaver (2006a, b) and von Cramon-

Taubadel (2009b, 2011) found a significant correlation between neutral genetic loci and neurocranial shape, while Smith (2009) did not. Lastly, while some studies (Harvati and Weaver 2006a, b; Reyes-Centeno et al. 2013) found no significant correlation for facial shape and neutral genetic variation, others have (Roseman 2004; Smith 2009; von Cramon-Taubadel 2009b, 2011), particularly for the upper face.

Some of the discrepancies in accumulating studies of modern human cranial phenotypic variation and neutral genetic variation might be a consequence of methodological differences. Firstly, most studies have quantified cranial shape with the use of landmark data, while Roseman (2004) used linear craniometric variables. Thus far, most studies have relied on protein markers or genomic microsatellites, which are DNA fragments containing short, tandemly repeated (STR) sequences. As previously noted (Weaver et al. 2008), microsatellites are comparable to linear craniometric variables because their variation is associated with an increase or decrease in length. Yet, rather than pairing STR data with linear craniometric measurements, most studies pair STRs with cranial shape variables that measure the variation of landmark configurations following standardization with Procrustes superimposition (Gower 1975; Rohlf and Slice 1990). Inconsistent conclusions in linear versus landmark-based studies may therefore stem from an improper pairing of genomic and anatomical loci. Secondly, some studies (Roseman 2004; Smith 2009; von Cramon-Taubadel 2009a, b, 2011; Reyes-Centeno et al. 2014) have calculated distance measures using explicit evolutionary models, following a quantitative genetics framework (Relethford and Blangero 1990; Relethford et al. 1997). In this context, population distances from anatomical data are represented by pairwise P_{ST} values (or its analogue, Q_{ST}: Spitze 1993), representing the apportionment of morphological variation between populations (Roseman and Weaver 2007). They are analogous to F_{ST} in population genetics, which is the fixation (F) index comparing the subset ($_S$) genetic diversity within populations to the total ($_T$) genetic diversity of all sampled populations (reviewed in: Holsinger and Weir 2009). As an alternative to this model-bound approach, other studies (Harvati and Weaver 2006a, b; Smith et al. 2007, 2013; Reyes-Centeno et al. 2013) have used model-free methods, representing population relationships via Mahalanobis and Procrustes distance measures. Whereas P_{ST}, F_{ST}, and Mahalanobis distances are measures of dissimilarity, relying on the variance-covariance structure of the datasets, Procrustes distances refer to the distance between landmark configurations (i.e. the square root of the summed squared distances between homologous landmarks). In population studies, pairwise Procrustes

distances are derived from the mean landmark configuration of populations, following Procrustes superimposition of all samples. Thirdly, sampled populations have differed in all studies, with imperfect matching of genetic and cranial populations. Lastly, other methodological decisions, such as the number and definition of landmarks chosen to represent the cranium or its component parts, also differ.

Given these discrepancies, in this study we revisit the correlation of neutral genetic loci and anatomical loci of the cranium following the landmark configurations used by Harvati & Weaver (2006a, b). We use genetic distances calculated from single nucleotide polymorphisms (SNPs)—genomic loci that vary as a result of substitutions, insertions, or deletions at a single base. Two advantages of using SNPs are that many more loci can be sampled in comparison to microsatellites and more precise estimates of population divergence time and effective population size, N_e, can be calculated. The latter can be incorporated in the calculation of P_{ST} (Relethford et al. 1997; Reyes-Centeno et al. 2014). We predicted that by doing so, we would find a higher correlation to F_{ST}, in comparison to the model-free Mahalanobis and Procrustes distances. Practically, SNP databases are increasingly growing such that proper pairing can be made with cranial populations. In addition to our primary objectives, we also sought to test the hypothesis that the temporal bone reflects deep population history in modern humans (Harvati and Weaver 2006b). Since SNPs are thought to evolve at a slower rate than microsatellites, such that changes in in SNPs occur less frequently than changes in STR sequences (Colonna et al. 2010), we predicted that the correlation between neutral genetic variation of SNPs and phenotypic shape variation of the temporal bone would be stronger than for other cranial regions or for the whole cranium. Additionally, we hypothesized that by explicitly including independent information on when populations diverged, such a correlation would increase.

MATERIALS AND METHODS

Our cranial dataset consisted of a subset of specimens used in Reyes-Centeno et al. (2014), from modern human Holocene collections housed at the Musée de l'Homme, National Museum of Natural History (Paris, France). *N*=224 crania (Table 1) were previously selected on the basis of adult status and the absence of bone pathology, balancing population samples by sex to the extent possible. These samples represent 10 ethno-linguistically defined populations from Africa, Asia, Australia, and Melanesia (Reyes-Centeno et al. 2014: Table S3).

Cranial anatomical landmarks were collected by H.R.-C. in the form of three-dimensional coordinate data using a MicroScribe G2X desktop digitizer. Landmark measurement error was tested by digitizing a specimen ten times across the span of a week. Error ranged from 0.183-2.175 millimeters (mm) or 0.147-4.892%. In the few cases where the specimen state of preservation precluded data collection, missing landmarks were estimated by reflected relabeling of the bilateral homologue (Mardia et al. 2000) using the Morpheus software (Slice 1994–1999). We generated four datasets, following Harvati & Weaver (2006a). The first was a landmark configuration that captured the anatomy of the whole cranium (32 landmarks). The other three encompassed its component parts: the right temporal bone (13 landmarks), the neurocranium (8 landmarks), and the face (13 landmarks). A generalized Procrustes analysis (GPA: Gower 1975; Rohlf and Slice 1990) was conducted separately for each dataset. Following GPA, we performed a principal component analysis (PCA). Both the GPA and PCA procedures were performed in the MorphoJ software (Klingenberg 2011). We used PC scores to arrive at pairwise P_{ST} values using the RMET 5.0 software (Relethford et al. 1997), producing distance matrices for each landmark configuration that we could then compare to the genetic F_{ST} distance matrix previously reported for the populations sampled here, generated from 3,345 SNPs (Reyes-Centeno et al. 2014: Table 2). Pairwise P_{ST} values were corrected for population sample size bias (Relethford et al. 1997). We also included in the calculation of P_{ST} estimates of N_e, as reported in Reyes-Centeno et al. (2014). We assumed full heritability (h^2) in these estimates and note that while h^2 would affect the absolute P_{ST} values, its effect pairwise is proportional, such that changes in the resulting P_{ST} matrices do not affect its comparison to the F_{ST} matrix. In order to compare the model-bound and model-free approaches, we calculated Procrustes distances in the MorphoJ software and Mahalanobis distances in the XLSTAT commercial software (Addinsoft SARL). Following Harvati & Weaver (2006a, b), we selected the PCs that accounted for approximately 90% of combined variation when calculating F_{ST} and Mahalanobis distances. For all landmark configurations, we calculated the correlation values between all phenotypic distances via Mantel tests (Mantel 1967). Then, we compared genetic distances (F_{ST}) independently against all phenotypic distances (P_{ST}, Procrustes, Mahalanobis) and visualized their association in a regression plot, generated in XLSTAT. Next, we used the divergence time between populations, T, in order to conduct a partial Mantel test (Smouse et al. 1986) using the XLSTAT software. In this case, the correlation of F_{ST} and phenotypic distance (P_{ST}, Procrustes, or Mahalanobis distance) was

calculated while holding *T* constant. *T* values were in units of generations, as reported in Reyes-Centeno et al. (2014: Table S1). For all Mantel tests, correlation significance was determined after 10,000 permutations of the matrix values and with application of a Bonferroni correction for multiple model testing ($\alpha=0.05/x$, where *x* is the number of landmark configurations being compared, or $\alpha=0.0125$). Finally, in the cases were F_{ST} and P_{ST} were found to have a significant correlation after Bonferroni correction, we used a Dow-Cheverud test (Dow and Cheverud 1985) to assess whether P_{ST} of one landmark configuration could statistically be considered to be more correlated with F_{ST} than another landmark configuration.

Table 1. Populations and sample size

Population	***N***
Australia	20
Central Asia	24
East Africa	23
Japan	31
Melanesia	17
North India	15
Papua New Guinea	29
Philippines	21
South Africa	20
South India	24
Total	224

RESULTS

In calculating the correlation between the pairwise values obtained from the different phenotypic distance measures, all were found to be strongly correlated and highly significant (Table 2). The strongest correlation was between P_{ST} and Mahalanobis distances, with correlation values exceeding 95% for all landmark configurations. Correlation between P_{ST} and Procrustes distances ranged from ~60-82%, while that between Mahalanobis and Procrustes distances ranged from ~72-82%.

Table 2. Correlation of phenotypic distances[1]

Mantel Test	**Whole Cranium**	**Temporal Bone**	**Neurocranium**	**Face**
***P*$_{st}$-Mahalanobis**	0.984 (<0.0001)	0.977 (<0.0001)	0.994 (<0.0001)	0.978 (<0.0001)
***P*$_{st}$-Procrustes**	0.856 (<0.0001)	0.780 (<0.0001)	0.908 (<0.0001)	0.849 (<0.0001)
Mahalanobis-Procrustes	0.904 (<0.0001)	0.847 (<0.0001)	0.902 (<0.0001)	0.902 (<0.0001)

[1]Pearson correlation coefficient (*r*) and two-tailed significance *p* (in parenthesis) values after 10k permutations.

When considering the direct relationship between F_{ST} and P_{ST} values, only Mantel test results for the neurocranium configuration were non-significant (Table 3). Figure 1 shows the regression plots of F_{ST} and P_{ST} for all landmark configurations. Neutral genetic variation, as calculated from SNPs, could explain approximately 27%, 19%, and 31% of shape variation in the whole cranium, the face, and the temporal bone, respectively (R^2 values in Fig. 1). For the

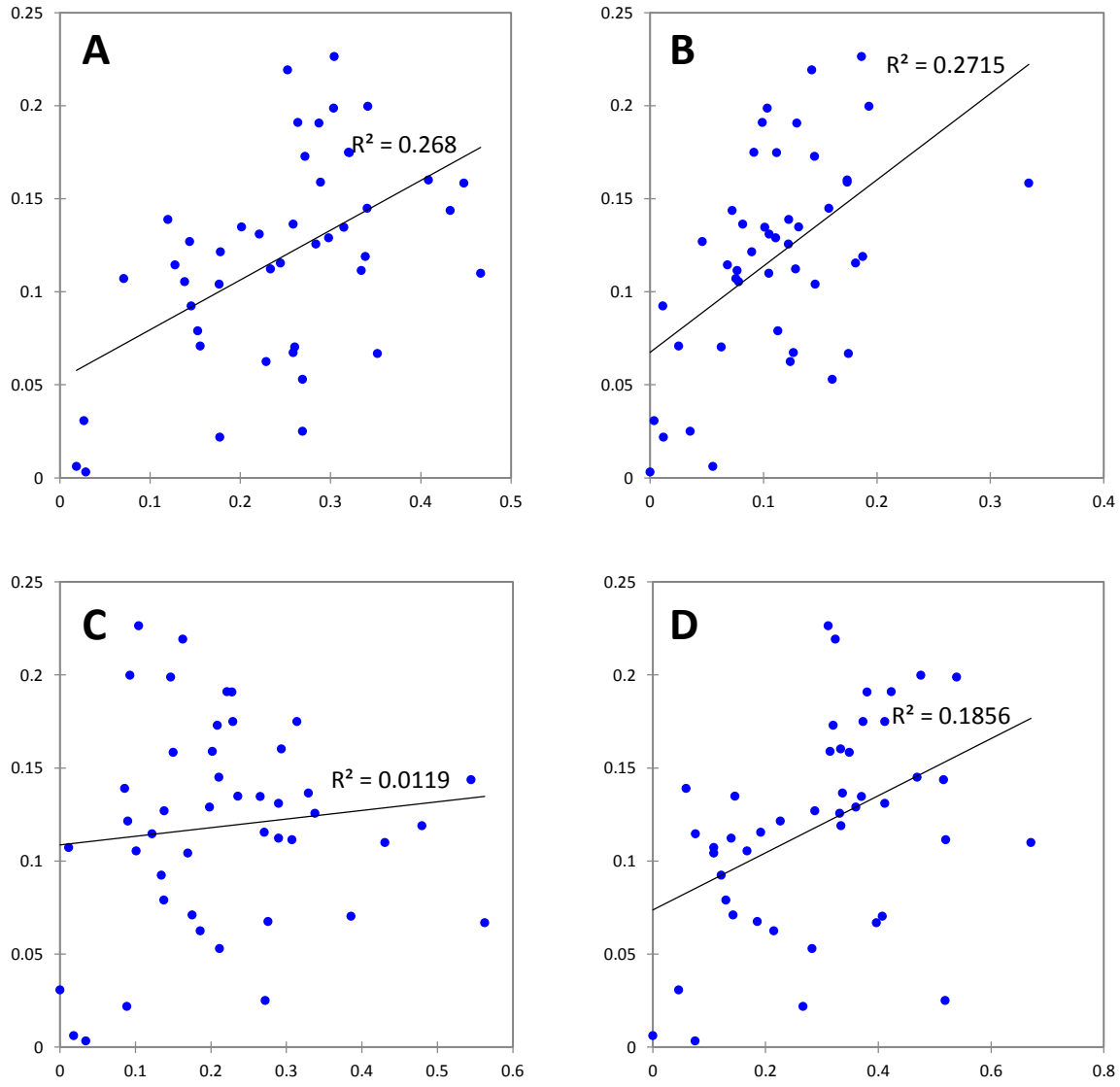

Figure 1. Regression of pairwise F_{ST} and P_{ST} values. P_{st} on horizontal axis; F_{ST} on vertical axis. P_{ST} is derived from the following landmark configurations: (A) the whole cranium, 32 landmarks; (B) the right temporal bone, 13 landmarks; (C) the neurocranium, 8 landmarks; and (D) the face, 13 landmarks. Note outlier in (B), corresponding to paired East Africa and Philippines populations.

temporal bone, this relationship is after the removal of an outlier value for the East Africa and Philippines pair, where P_{ST} values are larger than expected under a proportional F_{ST}-P_{ST} relationship, as shown in Figure 1b and as previously noted (Reyes-Centeno et al. 2014). With

inclusion of the outlier pair, the temporal bone and whole cranium have similar correlation values, r=0.521 and r=0.518, respectively. Considering the relationship between F_{ST} and model-free phenotypic distances, the temporal bone has a significant correlation for both Mahalanobis and Procrustes distances. Mahalanobis distances for the whole cranium configuration also have a significant correlation with F_{ST}, but Procrustes distances do not after considering the Bonferroni correction. Absolute correlation values were highest for the temporal bone and p-values were lower, regardless of the type of phenotypic distance used. Figures 2 and 3 show the regression plots for F_{ST} against Mahalanobis and Procrustes distances, respectively. All Dow-Cheverud test results were non-significant.

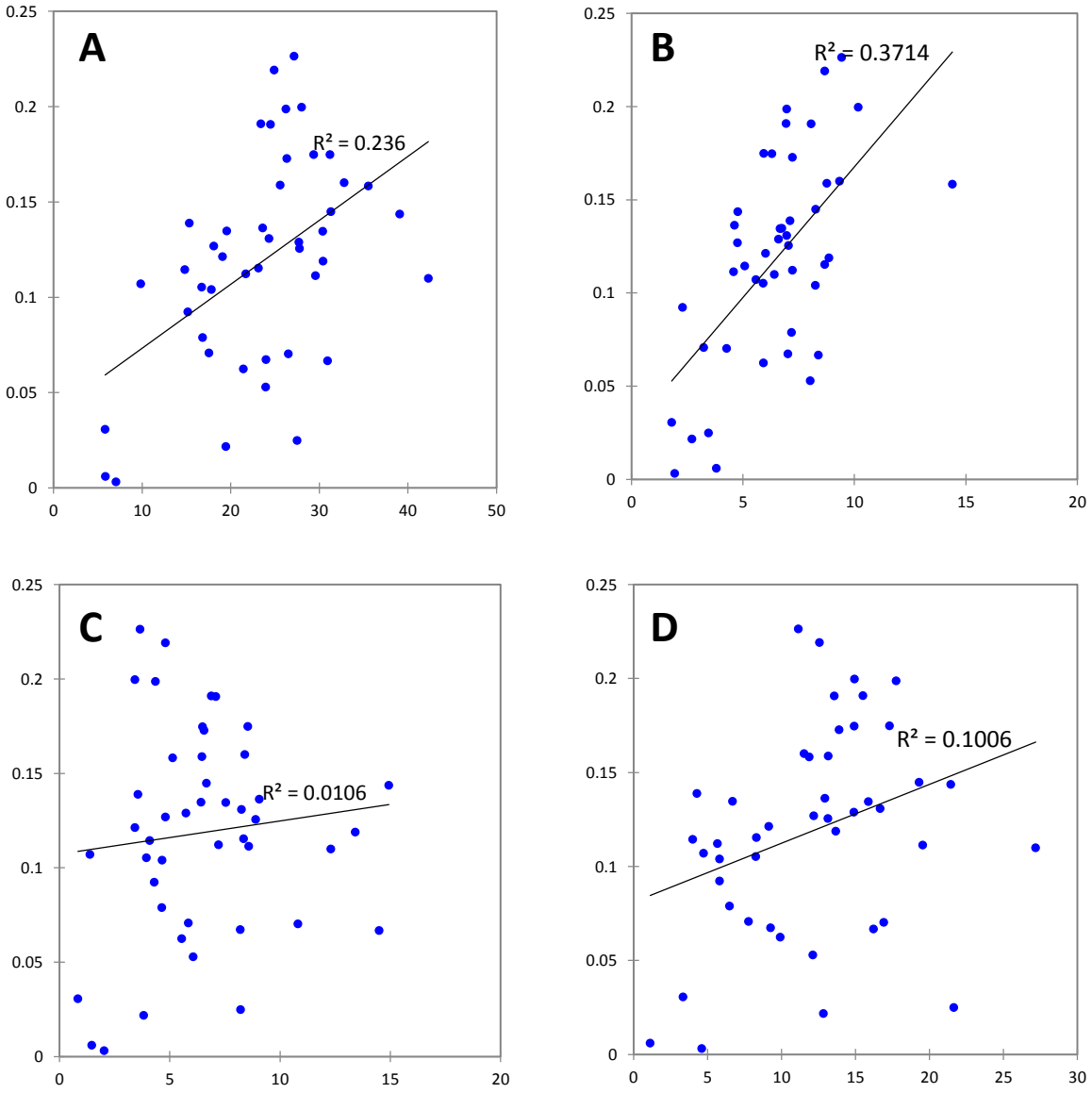

Figure 2. Regression of pairwise F_{ST} and Mahalanobis distance values. Mahalanobis values on horizontal axis; F_{ST} on vertical axis. Landmark configurations A-D as in Fig. 1. Note outlier in (B), corresponding to paired East Africa and Philippines populations.

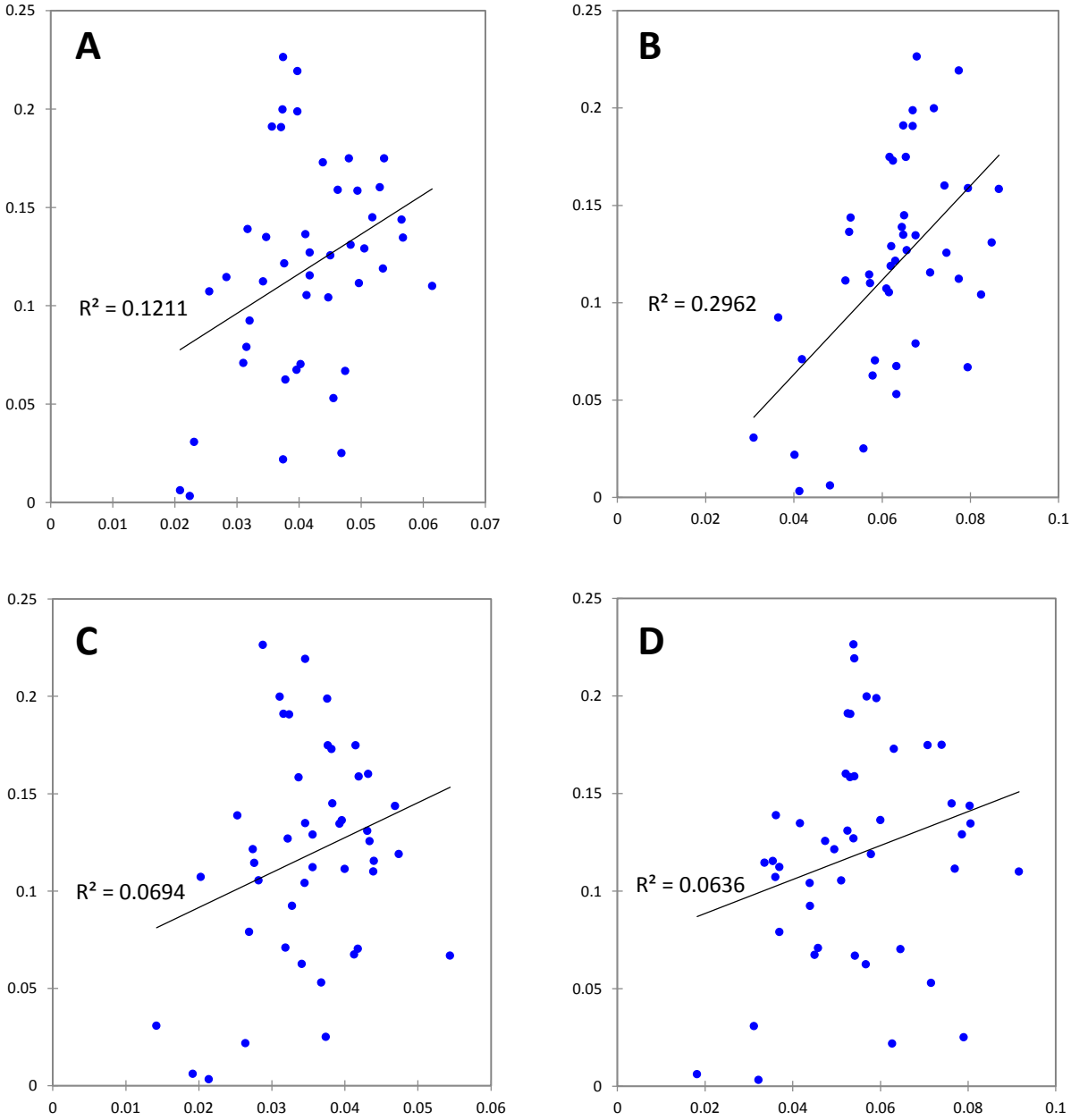

Figure 3. Regression of pairwise F_{ST} and Procrustes distance values. Procrustes values on horizontal axis; F_{ST} on vertical axis. Landmark configurations A-D as in Fig. 1.

In the partial Mantel tests (Table 3), the correlation of F_{ST} and P_{ST} values, when controlling for divergence time *T*, were significant for the temporal bone and the whole cranium. For the model-free comparisons, only Mahalanobis distances derived from the temporal bone configuration were significantly correlated with F_{ST} following Bonferroni correction. Again, Dow-Cheverud tests were non-significant. Correlation and *p*- values were stronger for the temporal bone. For both simple and partial Mantel tests, the correlation of F_{ST} and phenotypic distances was weaker for Procrustes distances than for P_{ST} or Mahalanobis

distances. The exception to this was for the neurocranium configuration, where the correlation of F_{ST} and Procrustes distances was higher and more significant than for P_{ST} or Mahalanobis distances.

Table 3. F_{ST} correlation with phenotypic distances[1]

Mantel Test	Whole Cranium	Temporal Bone	Neurocranium	Face
F_{st}-P_{st}	**0.518 (0.0003)**	**0.555 (<0.0001)**[2]	0.109 (0.486)	**0.431 (0.004)**
F_{st}-Mahalanobis	**0.486 (0.001)**	**0.645 (<0.0001)**[2]	0.103 (0.491)	0.317 (0.035)
F_{st}-Procrustes	0.348 (0.021)	**0.544 (0.0003)**	0.264 (0.081)	0.252 (0.097)
F_{st}-P_{st}, T	**0.391 (0.007)**	**0.591 (<0.0001)**[2]	0.251 (0.103)	0.154 (0.315)
F_{st}-Mahalanobis, T	0.334 (0.023)	**0.558 (<0.0001)**[2]	0.253 (0.094)	0.100 (0.510)
F_{st}-Procrustes, T	0.219 (0.151)	0.341 (0.019)	0.341 (0.024)	0.065 (0.673)

[1]Pearson correlation coefficient values (*r*) and two-tailed significance *p* (in parenthesis) values after 10k permutations; F_{ST}: genetic differentiation distances, P_{ST}: phenotypic differentiation distances, T: divergence time. Bold type indicates significance after Bonferroni correction (α=0.0125).

[2]after removal of outlier population pair (East Africa and Philippines)

DISCUSSION

In comparing the phenotypic distance values obtained from a model-bound, quantitative genetic approach with those calculated from model-free methods, we found that P_{ST} and Mahalanobis distances are most highly correlated. The correlations between P_{ST} and Procrustes distances, as well as between Procrustes and Mahalanobis distances, were substantially lower. Nevertheless, we found a higher Procrustes-Mahalanobis correlation than previously reported for the temporal bone (*r*=0.662 in Smith et al. 2007). The unequivocally strong correlation between P_{ST} and Mahalanobis distances is in part due to the similar way in which they are calculated, as noted in the introduction of this communication and in previous studies (Relethford 1991; Relethford and Harpending 1994). Contrary to our prediction, Mahalanobis and P_{ST} distances were similarly correlated to F_{ST}, even at the inclusion of population-specific N_e, suggesting that model-free Mahalanobis distances are an appropriate proxy for model-bound P_{ST} distances of cranial phenotype in modern human populations. We note that no data reduction procedure was employed for the resulting Procrustes distances, in comparison to using PC scores that explained 90% of shape variation when calculating P_{ST} and Mahalanobis distances. Likewise, no correction for sampling bias was made in the calculation of Procrustes distances. Nevertheless, the effect that phenotypic distance choice

has on the comparison with a genetic dissimilarity matrix like F_{ST} became evident in the remainder of our results, discussed below.

Of the landmark configurations explored here, both the temporal bone and whole cranium are significantly correlated with SNPs. Our results are most comparable to the studies by Harvati and Weaver (2006a, b) since we sampled the same landmarks and examined the same cranial configurations. In contrast to our results, Harvati and Weaver (2006a, b) found a significant correlation between neutral genetic distances and phenotypic distances of neurocranial shape. In agreement with our results, Smith (2009) found no significant correlation of neutral genetic variation and neurocranial shape variation. Smith considered that landmark choice could account for the discrepancy with Harvati & Weaver's results. However, our results here show that landmark choice alone cannot explain the contrasting results. Agreement of our results with Smith's (2009) might be partly attributed to the fact that we sampled similar populations. Thus, neurocranial shape might be affected by a common non-stochastic process, such as climate, in at least a subset of the populations that both we and Smith sampled. Roseman (2004) considered the neurocranium to reflect natural selection, as variables encompassing this cranial region were significantly correlated with climate variables. Harvati & Weaver (2006a, b) also found that the neurocranium was correlated with latitude and with climate variables. That association was partly driven by the inclusion of a population that inhabited cold climates, where adaptation to such environment is thought to be reflected in cranial anatomy (Roseman 2004; Harvati and Weaver 2006a, b; Hubbe et al. 2009; Smith 2009; von Cramon-Taubadel 2009a). However, since we have not included populations from cold climates, further work is necessary to determine why the neurocranial shape in at least some of our populations depart from neutral expectations.

In previous studies using STRs, values for the correlation of neutral genetic distances and temporal bone phenotypic distances ranged from r=0.205 to r=0.88 (Harvati and Weaver 2006a, b; Smith et al. 2007, 2013; Smith 2009; von Cramon-Taubadel 2009a). Our correlation values using SNPs are close to the midpoint of this range, suggesting that both STRs and SNPs are appropriate for comparison with landmark anatomical loci. Nevertheless, the prediction that we would find a higher correlation for the temporal bone was met in our results. Moreover, the use of SNPs allowed us to incorporate independent estimates of population T in partial Mantel correlations, which permitted testing of the previous proposal that the temporal bone tracks older events in modern human population history (Harvati and Weaver

2006b). Our results provide some support to this hypothesis. On the one hand, Dow-Cheverud tests were non-significant, suggesting that we cannot statistically affirm that the temporal bone reflects population history to a greater degree than another cranial segment or the cranium as a whole. This result is in agreement with the strong covariation between different cranial units in modern humans (Martínez-Abadías et al. 2012) and a pattern of integration that appears to be conserved across hominins (Singh et al. 2012). On the other hand, absolute F_{ST}-P_{ST} correlation values were higher for the temporal bone and improved when controlling for *T*, consistent with our predictions. It is worth noting that a proper comparison of the temporal bone and whole cranium configurations is inadequate, as landmarks of the former are included in the latter. Furthermore, in visualizing the regression of F_{ST} and P_{ST} values (Fig. 1), as well as that of F_{ST} and Mahalanobis or Procrustes distances (Fig. 2 and Fig. 3, respectively), it is clear that the temporal bone configuration follows a more linear pattern and therefore conforms better to neutral evolutionary expectations. In addition, Smith (2009) interpreted the high correlation for the basicranium, of which the temporal bone is a part, to its ossification in early ontogeny, making it less prone to natural selection or epigenetic effects during an individual's lifetime. Indeed, Smith et al. (2013) found that temporal bone shape is correlated with neutral genetic markers from early ontogenetic stages across populations.

Significance of the direct F_{ST}-P_{ST} correlation for the face is in agreement with some previous studies (Smith 2009; von Cramon-Taubadel 2009b, 2011) but differs from others (Harvati and Weaver 2006a; Reyes-Centeno et al. 2013). While the F_{ST}-P_{ST} correlation for the facial configuration was significant, both the correlation value and the regression plots suggest that a neutral evolutionary process explains facial anatomy to a lesser degree. This seemingly discrepant result can be reconciled with previous studies reporting a significant correlation with neutral genetic variation for the upper face and a significant correlation with climate variables for the lower face (Smith 2009; von Cramon-Taubadel 2009a). The fact that the correlation significance was lost when controlling for *T* in our results suggests that facial anatomy may also reflect more recent population affinities rather than deep population divergence. In parallel to differential rates of change for different genomic systems (Colonna et al. 2010), cranial anatomy may also evolve at differential rates, with the face evolving faster than the temporal bone, for example.

While Mahalanobis distances appear to be adequate proxies for P_{ST}, evolutionary inferences drawn from Procrustes distances must be made with caution. In our results, this is

evident in the weaker *r*- and *p*- values for Procrustes distances (Table 3). This was also clear when introducing the *T* variable, where Procrustes results were non-significant for all landmark configurations following Bonferroni correction. Moreover, the higher *r*- and *p*- values for the Procrustes distances of the neurocranium configuration, relative to the *r*- and *p*- values for P_{ST} or Mahalanobis distances, are likely spurious and not easily interpretable in a biological or evolutionary context. At the same time, the pattern of a stronger correlation for the temporal bone, followed by the whole cranium, was still evident when using Procrustes distances. We note that the regression of F_{ST} and Procrustes distances for the temporal bone did not produce the outlier pair (Fig. 3). This is because Procrustes distances do not capture the pronounced phenotypic variation of the outlier pair as is the case for Mahalanobis and P_{ST} calculations, which consider the apportionment of variance between all populations. In all, our study indicates that results from Mantel tests using a Procrustes distance matrix for comparison with a dissimilarity matrix such as F_{ST} should be interpreted with caution, although they may ultimately convey the same general pattern as P_{ST} and Mahalanobis distances. Since regression approaches (e.g. Mantel and Dow-Cheverud tests) are increasingly used with skeletal phenotype data for testing hypotheses that concern modern human origins, dispersal, and differentiation (Pinhasi and von Cramon-Taubadel 2009; Hubbe et al. 2010; von Cramon-Taubadel and Pinhasi 2011; Reyes-Centeno et al. 2014; Reyes-Centeno et al. Under Review), such future studies should quantify population distances with P_{ST} or Mahalanobis distances.

Finally, our results have implications on the use of cranial morphology in the reconstruction of modern human population history. While the temporal bone has been suggested to be particularly useful for phylogenetic reconstruction of hominoids (Lockwood et al. 2002, 2004), it appears that it is not a better indicator of phylogeny when compared to other cranial parts (von Cramon-Taubadel and Smith 2012). Removing the modern human sample increases the correlation of molecular genetic and phenotypic distances in hominoids (von Cramon-Taubadel and Smith 2012), suggesting that the utility of the temporal bone may be limited at an intra-generic or intra-specific taxonomic level and thus unique to humans. This might be related to autapomorphies in the human temporal bone (Harvati 2003; Tattersall and Schwartz 2008), many of which are captured by the landmarks we sampled. Our partial Mantel results nonetheless suggest that that temporal bone shape can serve to reconstruct population history at profound time depths in modern humans. We caution that our results are not directly comparable to some studies of linear measurements, where both

components of the face and the neurocranium have been inferred to retain a population history signal (Manica et al. 2007; Hubbe et al. 2009; Betti et al. 2010). Both the methods and anatomical information captured in those studies differ from ours. Likewise, because those studies have not included direct correlations with genomic data, further work will serve to clarify the degree to which facial and neurocranial variables reflect population history in modern humans.

In future studies, work on the temporal bone should attempt to assess the impact of landmark selection in its correlation to neutral genetic variation. For example, while most ossification of the temporal bone occurs pre-natally, somatic growth and pneumatization accounts for most post-natal changes in shape, particularly for the mastoid region (Dahm et al. 1993; Nemzek et al. 1996; Hill 2011). Testing the association of neutral loci and morphology in an ontogenetic framework (e.g. Smith et al. 2013) for other cranial regions will also be useful in further validating the cranium's differential preservation of population history. More broadly, it would be of interest to sample cranial populations for which both STR and SNP data are available. This would allow for a direct comparison of the effect that genomic marker choice has on resulting genetic distances and their correlation to phenotypic distances. Indeed, F_{ST} values differ when using either microsatellite or SNP loci, even when these are sampled from the same populations (reviewed in: Holsinger and Weir 2009). Since microsatellites evolve at a faster rate than SNPs, using both markers for the same populations would permit inference on the hypothesis that certain parts of the cranium evolve at a faster or slower rate than others. Further parallel work with other primate taxa is necessary to adapt this knowledge to interpretations of the primate fossil record. With sufficient recovery of ancient DNA, it will eventually be possible to incorporate fossil genomes and phenotypes in evaluating their association at a greater spatio-temporal context.

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Appendix II

"When the [phylogenetic] tree is projected on a world map…, it shows the interesting feature that it follows what might have been some reasonable routes of migration."

Luigi Luca Cavalli-Sforza (1966:375)

Cavalli-Sforza LL. 1966. Population structure and human evolution. Proceedings of the Royal Society of London B: Biological Sciences 164(995):362-379.

Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia

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ABSTRACT

Despite broad consensus on Africa as the main place of origins for anatomically modern humans, their dispersal pattern out of the continent continues to be intensely debated. In extant human populations, the observation of decreasing genetic and phenotypic diversity at increasing distances from Sub-Saharan Africa has been interpreted as evidence for a single dispersal, accompanied by a series of founder effects. In such a scenario, modern human genetic and phenotypic variation was primarily generated through successive population bottlenecks and drift during a rapid worldwide expansion out of Africa in the Late Pleistocene. However, recent genetic studies, as well as accumulating archaeological and paleoanthropological evidence, challenge this parsimonious model. They suggest instead a "southern route" dispersal into Asia as early as the late Middle Pleistocene, followed by a separate dispersal into northern Eurasia. Here we test these competing out-of-Africa scenarios by modeling hypothetical geographical migration routes and assessing their correlation with neutral population differentiation, as measured by genetic polymorphisms and cranial shape variables of modern human populations from Africa and Asia. We show that both lines of evidence support a multiple dispersals model in which Australo-Melanesian populations are relatively isolated descendants of an early dispersal, while other Asian populations are descended from, or highly admixed with, members of a subsequent migration event.

Paleontological and genetic data indicate a common ancestral population of modern humans residing in Africa between ~100-200 thousand years ago (ka) (White et al. 2003; McDougall et al. 2005; Fu et al. 2013; Poznik et al. 2013). The timing and pattern of the modern human African diaspora continues to be strongly debated. Competing hypotheses center on either a single Late Pleistocene dispersal into Eurasia between ~50-75ka or multiple dispersals beginning as early as the Middle Pleistocene ~130ka (Petraglia et al. 2010; Rasmussen et al. 2011; Oppenheimer 2012; Mellars et al. 2013). The observed pattern of decreasing genetic (Ramachandran et al. 2005; Liu et al. 2006) and cranial (Manica et al. 2007) diversity at increasing distances from Sub-Saharan Africa has been interpreted as evidence for a single dispersal, characterized by a series of founder effects during global expansion. In its simplest form, a single dispersal scenario follows a series of founder events in an eastward expansion (EE) model that conforms to terrestrial routes mostly along a latitudinal axis across Asia (Liu et al. 2006; Ramachandran and Rosenberg 2011).

Another interpretation consistent with decreasing biological diversity from Africa is to consider multiple dispersals (MD) out of the continent. In an MD model, an initial dispersal between ~50-100ka occurs primarily along a coastal route through the southern Arabian Peninsula and is followed by a second dispersal through the Levant at ~50ka and into northern Eurasia (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). This model proposes that extant, isolated populations in Asia could retain the biological signal of the initial, southern route dispersal. Such hypothetical, “relic” populations could include Australians, Melanesians, Papuans, Dravidian speakers of South Asia, and short-statured “Negrito” populations of Southeast Asia. A recent genetic study proposed that living Australians are direct descendants of the southern route dispersal, while Papuans, Melanesians, and Philippine Aeta “Negrito” populations also retain a signal of the southern route, but one which is obscured due to admixture with members of the second dispersal (Rasmussen et al. 2011). In this model of multiple dispersals with isolation (MDI), a southern route dispersal out of Africa commences between ~62-75ka and is followed by a second dispersal between ~25-38ka. An alternative chronology for the MDI model posits a southern route dispersal as early as the late Middle Pleistocene ~130ka (MDI-MP), rather than the Late Pleistocene (MDI-LP), and is based primarily on archaeological evidence in the Arabian Peninsula (Petraglia et al. 2010; Armitage et al. 2011).

Growing consensus on the southern route dispersal has been strengthened by the study of single nucleotide polymorphisms (SNPs) in hypothetical relic populations (Ghirotto et al. 2011a; Rasmussen et al. 2011; Reich et al. 2011; Pugach et al. 2013). However, whether this reflects evidence of multiple dispersals from Africa continues to be debated (Rasmussen et al. 2011; Reich et al. 2011). A reconciling view, therefore, has been that a single dispersal from Africa might have taken place in the Late Pleistocene ~75ka, followed by divergence into separate migration waves outside the continent, likely in Southwest Asia (Oppenheimer 2012). Like the MD and MDI models, migration into Southeast Asia is via a "beachcomber" single dispersal (BSD) route along the coast. Unlike the EE model, the BSD model implies substantial migration along a longitudinal axis in East Asia.

Since temporal and spatial dimensions are explicit in these competing out-of-Africa models, distinguishing them can be achieved by assessing the correlation of predicted spatial and temporal distances and observed neutral biological distances between modern human populations. Such biogeographical approach accounts for the primary drivers of recent human evolution: migration, mutation, and drift. We employed this test for ten populations sampled from Africa and Asia using genetic and cranial phenotype data (Table 1). We limited our phenotype analyses to the temporal bone, as it has been shown to conserve modern human population history at higher fidelity than other parts of the cranium, from an early ontogenetic stage, and in a largely neutral manner (Harvati and Weaver 2006; Smith et al. 2013). For both lines of evidence, we used the same quantitative evolutionary framework to assess biological distances between our sampled populations (Roseman and Weaver 2007).

Table 1. Populations, Sample Size, and Geography

Population		Genetics *N*	Cranial Phenotype *N*	Geographical Coordinates	
				Latitude	Longitude
AU	Australia	12	20	-33.89	151.24
CA	Central Asia	56	25	43.29	68.26
EA	East Africa	66	25	9.02	38.74
JP	Japan	107	31	35.66	139.82
ME	Melanesia	30	17	-9.42	159.94
NE	Philippines	16	23	14.6	120.98
NG	New Guinea	10	31	-9.48	147.19
NI	North India	61	15	28.63	77.2
SA	South Africa	215	20	9.02	38.74
SI	South India	141	26	6.93	79.86

RESULTS

We used two analytical approaches in determining the fit between inter-population biological differentiation and the out-of-Africa dispersal models. First, we used partial Mantel tests (Legendre 2000; Pinhasi and von Cramon-Taubadel 2009) to determine the correlation of population differentiation and geographical distances between populations along hypothetical dispersal routes, controlling for population divergence times in each case. Second, we considered the temporal information contained within each of the competing out-of-Africa models in order to validate our partial Mantel results and, in the case of the MDI model, distinguish the chronology of the southern route dispersal, commencing either in the late Middle Pleistocene (MDI-MP) or in the Late Pleistocene (MDI-LP).

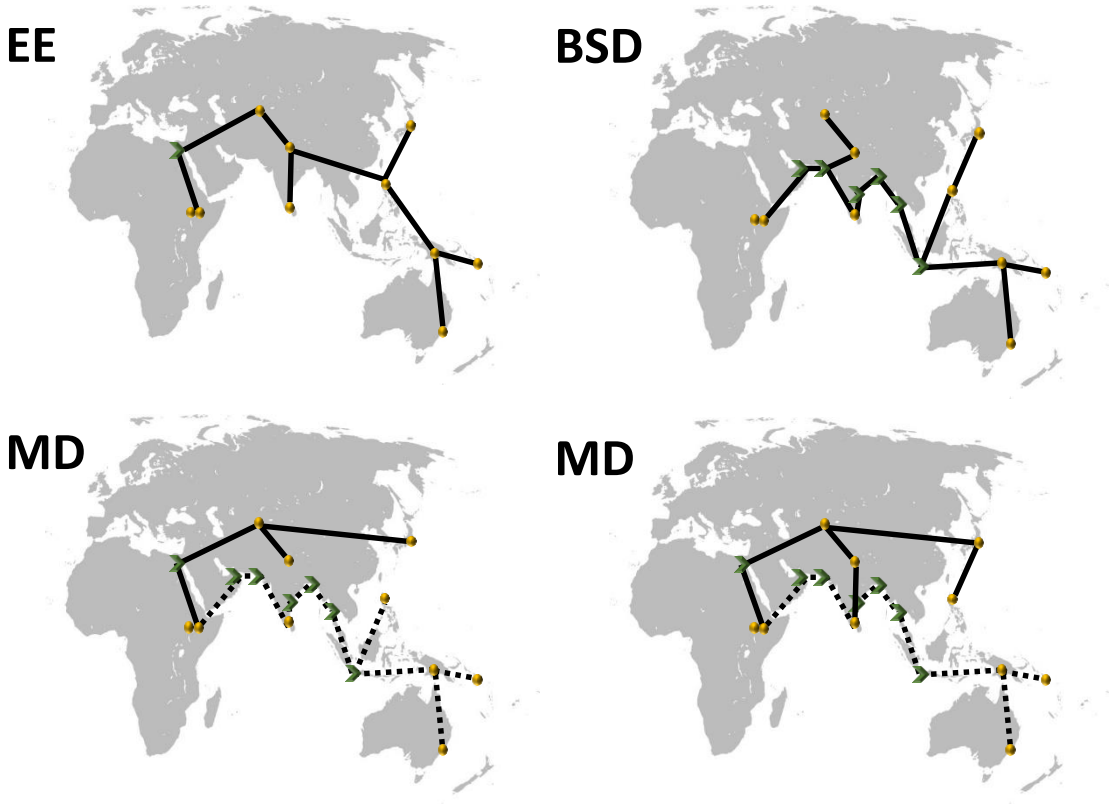

Figure 1. Out-of-Africa dispersal models. Spheres are approximate centroids of populations sampled (Table 1), connecting lines are dispersal routes, and arrows are geographical waypoints (Table S4). The eastward expansion (EE) model connects populations primarily along a latitudinal axis (5, 19). The beachcomber single dispersal (BSD) model connects populations primarily along a coastal route (3). The multiple dispersals model (MD) connects hypothetical relic populations along a southern route (dotted lines) and north Eurasians along a northern route (15). The multiple dispersals with isolation (MDI) model assumes that only Australo-Melanesian populations retain a strong southern route biological signal (7). For simplicity, a Holocene map outline is shown.

In our first analysis, genetic distances, F_{st}, and cranial phenotypic distances, P_{st}, between populations were calculated using SNP data and three-dimensional anatomical landmark data,

respectively (Table 2). Geographical distances, *G*, were calculated as geodesic distances between populations along hypothetical dispersal routes (Fig. 1). Temporal distances between populations were calculated from the genomic data, based on levels of linkage disequilibrium, in order to assess when population pairs diverged in time (Table S1). Independently for F_{st} and P_{st}, we assessed their pairwise correlation with *G* while holding divergence time, *T*, constant. This approach has the effect of controlling for drift due to the fact that populations separated at distinct points in time and space. Therefore the partial Mantel test results indicate which out-of-Africa model best explains population differentiation when considering both spatial and temporal dimensions. The MDI model best explained both genetic (F_{st}) and phenotypic (P_{st}) differentiation (Table 3). In fact, for the phenotype dataset, only the MDI model test results were statistically significant. In the case of the genetic dataset, the control and MDI models were significant after Bonferroni correction for multiple model tests, although the MDI correlation coefficient was almost twice as large as that of the control model. A Dow-Cheverud test (Pinhasi and von Cramon-Taubadel 2009; Hubbe et al. 2010) indeed differentiates MDI as a better model against the control (r=0.588, p=<0.0001).

Table 2. Genetic & Phenotypic Distances[1]

	AU	CA	EA	JP	ME	NE	NG	NI	SA	SI
AU	0	0.372231	0.557596	0.322725	0.365393	0.674131	0.142495	0.354671	0.35569	0.400061
CA	0.1099	0	0.524056	0.099755	0.571562	0.516308	0.359326	0.166615	0.448843	0.220931
EA	0.1907	0.12894	0	0.572357	0.636501	*1.298547*	0.724035	0.379112	0.333683	0.495417
JP	0.14366	0.03067	0.17477	0	0.55383	0.476002	0.389483	0.200167	0.450304	0.293722
ME	0.07893	0.14487	0.22634	0.17281	0	0.737244	0.304302	0.515503	0.497316	0.40173
NE	0.11885	0.05288	0.15832	0.06243	0.1588	0	0.625152	0.585473	0.723552	0.581859
NG	0.09229	0.11133	0.19972	0.13632	0.10713	0.11536	0	0.371397	0.419062	0.432981
NI	0.10533	0.02177	0.12136	0.07084	0.13882	0.06732	0.11443	0	0.328728	0.088056
SA	0.19096	0.13456	0.00605	0.17484	0.21913	0.16006	0.19871	0.12691	0	0.393329
SI	0.10408	0.02495	0.12556	0.07025	0.13477	0.06676	0.1122	0.00316	0.13087	0

[1]Below diagonal: F_{st} values; above diagonal: P_{st} values (outlier value noted in italics; Fig. S1).

Table 3. Dispersal Models Test[1]

	Control	EE	BSD	MD	MDI
F_{st}	**0.405 (0.008)**	0.282 (0.085)	0.321 (0.035)	0.389 (0.013)	**0.782 (<0.0001)**
P_{st}[2]	0.138 (0.401)	0.040 (0.822)	0.142 (0.375)	0.184 (0.268)	**0.464 (0.008)**

[1]Partial Mantel test of population distances (F_{st}/P_{st}) and geodesic distances (*G*) for all dispersal models, while controlling for population divergence values (*T*). Values are Pearson correlation coefficient, *r*, rounded to the third digit and two-tailed probability, *p*, (in parenthesis) after 10k permutations. Bold type indicates significance after Bonferroni correction (α=.01).

[2]P_{st} correlations after removal of outlier EA-NE value (Table 2).

In our second analysis, we generated hypothetical divergence values, *C*, between populations, based on the chronology of dispersal for each model (Table 4). In contrast to our estimates of population divergence from the genomic data, the model chronology dates reflect estimates of modern human colonization within the geographical space of the populations we sampled. These dates contain inherent information about both time and space since they are primarily derived from archaeological, paleontological, and climatological records. Although this test is not explicit about dispersal routes, it serves to distinguish the out-of-Africa models based on the expected dates of colonization for a specific geographical region. Treating *C* as divergence values allowed us to exploit the relationship between population differentiation, divergence time, and effective population size, N_e (Holsinger and Weir 2009). We calculated N_e from the genomic data (Table S2) (Hayes et al. 2003) and, using *C*, constructed hypothetical F_{st} values to represent each out-of-Africa dispersal model. We then used a simple Mantel test to assess the fit between these hypothetical values and the empirical F_{st} and P_{st} values. We found that the MDI-MP model receives the best support (Table 5). Considering the Bonferroni correction for multiple model tests, results were only significant for the cranial phenotype dataset. Nevertheless, correlation and significance values were highest for the MDI-MP model in both biological datasets.

Table 4. Dispersal Models Chronology[1]

	AU	CA	EA	JP	ME	NE	NG	NI	SA	SI	Reference
EE	40	45	56	36	40	36	40	45	56	45	Liu *et al.* 2006
BSD	55	25	75	40	55	40	55	40	75	45	Oppenheimer 2012
MD	65	30	80	25	65	65	65	30	80	70	M. Lahr & Foley 1994
MDI-MP	50	45	130	40	50	40	50	45	130	45	Petraglia *et al.* 2010
MDI-LP	50	31.5	68.5	25	50	25	50	31.5	68.5	31.5	Rasmussen *et al.* 2011

[1]Based on approximations from the references provided, dates (~ka) are proposed times of dispersal and colonization within the geographical space of the sampled populations.

Table 5. Dispersal Models Chronology Test[1]

	EE	BSD	MD	MDI-LP	MDI-MP
F_{st}	-0.146 (0.337)	0.099 (0.524)	0.038 (0.820)	0.157 (0.307)	0.335 (0.022)
P_{st}[2]	0.176 (0.245)	0.260 (0.098)	0.237 (.029)	0.145 (0.409)	**0.463 (0.001)**

[1]Partial Mantel test of population distances (F_{st}/P_{st}) and geodesic distances (*G*) for all dispersal models, while controlling for population divergence values (*T*). Values are Pearson correlation coefficient, *r*, rounded to the third digit and two-tailed probability, *p*, (in parenthesis) after 10k permutations. Bold type indicates significance after Bonferroni correction (α=.01).

[2]P_{st} correlations after removal of outlier EA-NE value (Table 2).

DISCUSSION

The test of current competing out-of-Africa models shows unambiguous support for a multiple dispersals model in which Australians, Papuans, and Melanesians remain relatively isolated after an early dispersal from Africa via a southern route. Although some degree of Holocene admixture between our sampled Indian and Australian populations has been previously proposed (Pugach et al. 2013), our results are generally consistent with the view that extant Australians are descended from a relatively isolated lineage that first occupied that continent ~50ka (Rasmussen et al. 2011). They differ from previous findings in that our dispersal chronology test suggests an initial African dispersal closer to the Middle-Late Pleistocene boundary. This is consistent with archaeological evidence for modern human occupation in the southern Arabian Peninsula at ~125ka (Petraglia et al. 2010; Armitage et al. 2011). This date is in intriguingly closer correspondence with the genetic divergence estimates for our sampled populations, with a calendar date of divergence between Melanesians and South Africans at ~116ka, for example (Table S1). No modern human fossils have been discovered in the southern Arabian Peninsula, but lithic artefacts show affinities with African assemblages, including those discovered alongside the fossil remains at Herto, Ethiopia, dated between ~154-160ka (Clark et al. 2003; White et al. 2003). Importantly, the geological age of these specimens falls within the recent estimates for the common ancestor of all modern human populations (Fu et al. 2013; Poznik et al. 2013). This implies that an initial dispersal occurred not long after modern human origins in Africa, rather than much later, as an EE or BSD model would predict. The environmental and geographical viability for the MDI-MP model has been confirmed with a recent synthesis of available Middle-Late Pleistocene climate proxy data for Africa (Blome et al. 2012). Likewise, spatially explicit simulations developed from climate and microsatellite genetic data are in agreement with a southern route dispersal and earlier dates of Eurasian occupation than previously hypothesized (Eriksson et al. 2012). Moreover, it has been proposed that severe East African droughts occurring between 135-75ka may have prompted human population fragmentation and bottlenecks (Scholz et al. 2007), also possibly resulting in dispersals out of the continent. The modern human fossil series of Qafzeh and Skhul from the Levant, dated between ~90-120ka, could therefore correspond to this initial dispersal. Although often considered to represent a short-lived extension of African ecosystems rather than evidence of a long-range dispersal into Eurasia (Klein 2000), in comparative craniometric studies, the Levantine series and other early modern

humans from Africa have consistently closer affinity to recent Australians than to other modern human populations (White et al. 2003; Grine et al. 2007; Gunz et al. 2009; Harvati et al. 2011).

Presently, clear evidence of modern human occupation eastward of the Arabian Peninsula during the early Late Pleistocene is lacking. Occupation of Australia is documented by the human paleontological record at ~50ka and in continental Southeast Asia at a maximum date of ~63ka (Rasmussen et al. 2011; Demeter et al. 2012). Specimens before this time period are fragmentary and taxonomically ambiguous but have, in some cases, been claimed to represent anatomically modern humans (Liu et al. 2010; Mijares et al. 2010; Petraglia et al. 2010; Demeter et al. 2012; Oppenheimer 2012). The MDI-MP model tested here suggests that while Southeast Asia may have been populated by modern humans, replacement of these descendants from subsequent migrants may obscure a southern route biological signal in extant populations of that region (Petraglia et al. 2010). Our data set conforms to this hypothesis in that neither the genetic nor the cranial phenotype dataset from our sampled populations separate the Indo-European and Dravidian speakers from India, as might be expected if the latter where relic descendants of the southern route dispersal (Supporting Information, *The "Negrito" Hypothesis*). Instead, both Indian samples exhibit closer genetic and phenotypic affinity to the hypothetical second dispersal descendants (the Japanese, Aeta/Agta, and Central Asian populations). Sampling of other isolated, relic populations will serve to further support this hypothesis (Ghirotto et al. 2011a; Rasmussen et al. 2011).

While the models tested do not explicitly account for archaic admixture, the continued validation of the southern route dispersal and support for the MDI-MP model have important implications for understanding the degree, timing, and location of such events. Presently, the favored explanation for genetic resemblance between Neanderthals and non-African modern human populations is a hypothetical admixture event in the Middle East (Green et al. 2010). Likewise, shared polymorphisms between Denisovans and certain relic descendants of a southern route dispersal are explained by admixture in Southeast Asia (Reich et al. 2011). Identifying the presence of Neanderthal and Denisovan occupation along the southern route geographical space and within the Late Pleistocene temporal boundary is therefore crucial. The paleontological and archaeological records thus far remain elusive. An important consideration, therefore, is the persistence of population substructure in Africa (Green et al. 2010; Ghirotto et al. 2011a; Ghirotto et al. 2011b; Eriksson and Manica 2012; Lowery et al.

2013), which has been inferred from the human paleontological record (Gunz et al. 2009; Harvati et al. 2011) and is concordant with climate fluctuations in the continent (Scholz et al. 2007; Blome et al. 2012).

Population substructure implies that differential lineage assortment could be pronounced if populations in Africa remained spatially and temporally separated, affecting the subsequent diversity that is exported outside of the continent, as in an MDI-MP scenario. Genetically, polymorphisms within a parental population are randomly distributed into daughter lineages during speciation. In the recent human lineage, modern humans, Neanderthals, and Denisovans can be considered the daughter lineages of a common parental ancestor. Therefore, expression of shared genetic polymorphisms with Neanderthals and Denisovans in certain extant populations would be the consequence of biogeographical contingency and drift instead of, or in addition to, admixture with other hominins (Ghirotto et al. 2011a, b; Eriksson and Manica 2012; Lowery et al. 2013). In a similar vein, expression of a plesiomorphic skeletal phenotype in extant and extinct populations has been interpreted as evidence for admixture with, or "assimilation" of, other hominin populations (Smith et al. 1989). Instead, population substructure implies that such expression reflects the retention of traits inherited from the parental population and could be more prominent in descendants of the southern route dispersal, who are chronologically closer to the parental ancestor. These findings do not imply that dispersing modern people from Africa did not interbreed with other hominin populations but suggest that, at present, other hypotheses also appear to be compatible with the biological evidence.

CONCLUSIONS

Considering two independent biological datasets, applying a common quantitative evolutionary framework, and using a biogeographical approach, we have tested the primary hypotheses for the modern human out-of-Africa event. Our results are unambiguous in their support of multiple dispersals into Eurasia, with Australians, Papuans, and Melanesians retaining the signal of a southern route dispersal that commenced closer to the temporal boundary of the Middle-Late Pleistocene. Furthermore, these results suggest that models of ancient admixture events with other hominin populations should enclose the South Asian, southern route geographical space and a Late Pleistocene time frame—areas that have been largely understudied and where neither Neanderthal nor Denisovan occupation has been

confirmed by the fossil record. This study suggests that ancient population substructure, in addition or as an alternative to hominin interbreeding, may contribute to the observed pattern of resemblance between certain modern human populations and other hominins, ultimately generating the structure of extant modern human genetic and phenotypic diversity. Continued field work, alongside rapid advances in modern and ancient genome sequencing, will allow for greater resolution in modeling the spatial and temporal dimensions of modern human origins and dispersals.

MATERIALS AND METHODS

Genetic Data. We combined SNP data from published datasets for *N*=714 individuals and grouped the samples into ten ethnolinguistically and geographically related populations using the Greenberg language classification (Table 1, Table S3). Using the PLINK 1.07 software (Purcell et al. 2007), we selected only the autosomal SNPs with genotyping success rate > 98%, and minor allele frequency > 0.01. In order to optimize strand alignment, we also removed from the merged genotype data file the alleles carrying ambiguities in strand-flipping, namely A/T and C/G polymorphisms. Following these quality control procedures, 3345 SNPs were available for subsequent analysis. For measures of biological distances, we estimated the Weir-Cockerham F_{st} (Holsinger and Weir 2009) values between pairs of populations (Table 2). Each value represents the average of the pairwise F_{st} calculated for each SNP, over all SNPs in the dataset. F_{st} does not by itself provide information on the mechanisms involved in generating the differentiation between populations, namely parameters of demography, time, and space. Since our objective was to test spatial dispersal scenarios, a measure informative of both demography and time is required in order to assess the relationship between biological distance and geographical distance. Under neutrality, genetic differences between populations accumulate because of genetic drift, and so their extent, represented by F_{st}, is inversely proportional to N_e and directly proportional to the time, *T*, elapsed since their separation. Therefore, to estimate *T* from genetic differences between populations, independent estimates of N_e are needed. Levels of linkage disequilibrium (*LD*) also depend on N_e and on the recombination rate between the SNPs considered (Tenesa et al. 2007). However, *LD* between SNPs separated by large distances along the chromosome reflects relatively recent N_e whereas *LD* over short recombination distances depends on relatively ancient N_e (Hayes et al. 2003). Thus, we estimated *LD* independently in each population

considering the number of polymorphic markers available for that population, which depended on the sequencing platform in which the data was originally typed (Table S3). For example, ~54,000 SNPs were used for the Aeta/Agta population and ~600,000 SNPs were used for the Australian sample. We assigned to each SNP a genetic map position based on the HapMap2 (Release #22) recombination data. For each pair of SNPs separated by less than 0.25 cM, we quantified *LD* as r^2_{LD} (Hill and Robertson 1968). All of the observed r^2_{LD} values were then binned into 50 recombination distance classes, from 0.005 to 0.25 cM, with incremental upper boundaries of 0.005 cM. Pairs of SNPs separated by less than 0.005 cM were not considered since at such short distances gene conversion may mimic the effects of recombination (Tenesa et al. 2007). We also adjusted the r^2_{LD} value for the sample size using $r^2_{LD} - \left(\frac{1}{n}\right)$ (Tenesa et al. 2007). We estimated N_e for each population in each recombination distance class as $Ne = \left(\frac{1}{4c}\right)\left[\frac{1}{r^2_{LD}} - 2\right]$, corresponding to the effective population size $\frac{1}{2}c$ generations ago, where *c* is the distance between loci, expressed in Morgans (Sved 1971; McVean 2002; Hayes et al. 2003). Finally, the long-term N_e for each population was calculated as the harmonic mean of N_e over all recombination distance classes up to 0.25 cM. At this point, based on the independently-estimated values of N_e (Table S2), we calculated the separation time between populations as $T = \ln(1 - Fst)/\ln\left(1 - \left(\frac{1}{2Ne}\right)\right)$ (Holsinger and Weir 2009), expressed in generations (Table S1). All procedures were performed with the *NeON* and *4P* software packages developed by the Barbujani lab and available on-line at (http://www.unife.it/dipartimento/biologia-evoluzione/ricerca/evoluzione-e-genetica/software). Because our objective was to test competing dispersal models, we did not include parameters of migration or admixture events in these calculations.

***Cranial Phenotype Data*.** We matched the sampled genetic populations with *N*=233 modern human (Holocene) crania (Table 1), balancing population samples by sex to the extent possible. Crania, housed at the Musée de l'Homme, National Museum of Natural History (Paris, France), were selected on the basis of adult ontogeny and the absence of bone pathology. Congruence with the genetic populations was assessed firstly by ethno-linguistic affiliation and secondly by geographical provenance (Table S3). Following Harvati & Weaver (2006), a total of thirteen anatomical landmarks were collected by H.R.-C. for the right-side temporal bone of each specimen. Landmarks were collected in the form of three-dimensional

coordinate data using a MicroScribe G2X desktop digitizer. Landmark measurement error was tested by digitizing a specimen ten times across the span of a week and ranged from 0.25-1.157mm, or 0.3-1.35%. All specimens were subjected to generalized Procrustes analysis, which superimposes the specimens following a least-squares procedure that rotates and translates the specimen landmark configurations and scales them to unit centroid size (Harvati and Weaver 2006; Gunz et al. 2009; Harvati et al. 2011; Smith et al. 2013). Because the number of variables (a total of 39 Procrustes shape variables per specimen) exceeded the number of specimens per population, we performed a principal component analysis (PCA) using the MorphoJ 1.05 software (Klingenberg 2011) and used PC scores to arrive at pairwise P_{st}. By convention, seven degrees of freedom are lost following Procrustes superimposition in three dimensions, accounting for scaling and for translation and rotation along each axis; therefore, a total of 32 PCs were used for arriving at P_{st}. We included in the calculation of P_{st} the parameters of N_e (Table S2) derived from the genetic data, as well as the cranial trait heritability value h^2=0.23 ascertained for the basicranium in a modern human population (Martínez-Abadías et al. 2009). P_{st} calculations were made in the RMET 5.0 software and corrected for sampling bias (Relethford et al. 1997).

Geographical Data. Geodesic distances, *G*, were calculated using the PASSaGE 2 software (Rosenberg and Anderson 2011), which assumes a spherical terrestrial shape and a radius of 6379.336847 kilometers (km). Latitude and longitude coordinates (Table 1) are an approximate centroid for each population, although we placed both African samples at Addis Ababa, Ethiopia in order to avoid assumptions about internal migrations within the continent. Our control model was calculated using the pairwise geodesic distances between populations, without consideration for geographical barriers (Hubbe et al. 2010). Waypoints were used in the other models in order to represent the complex geography of hypothetical dispersal routes (Fig. 1, Table S4). The EE model connects populations by geographical proximity and primarily along a latitudinal axis (Liu et al. 2006; Ramachandran and Rosenberg 2011), with Cairo as a waypoint into Eurasia. The BSD model follows the migration pattern proposed by Oppenheimer (2012), following a migration into Eurasia via the southern Arabian Peninsula. A broad MD model represents the hypothesis that Dravidian-speaking Indians, Philippine Aeta/Agta “Negritos”, Papuans, Melanesians, and Australians are relic southern route descendants, whereas Indo-European-speaking Indians, Central Asians and Japanese are

descendants of the second dispersal along a northern inland migration route through the Levant (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). The MDI model assumes the same geographical dispersal scenario as the MD model but considers only Australians, Papuans, and Melanesians as southern route dispersal descendants (Rasmussen et al. 2011) (Supporting Information, *The "Negrito" Hypothesis*, Figs. S1-4, Table S5).

***Chronological Data and Hypothetical* F_{st}.** Per dispersal model, hypothetical divergence values, *C*, between populations were determined by averaging the estimated dates of expected colonization in their indigenous region (Table 4). For example, the hypothetical divergence between Australians and Central Asians was at 42.5ka under the EE model or 47.5ka under the MDI-MP model. We treated these as *T* in order to take advantage of the known relationship between population differentiation and N_e. Using the N_e values derived from the genomic data, we then calculated hypothetical F_{st} values as $Fst = 1 - (1 - (\frac{1}{2Ne}))^C$.

Mantel Tests. When distance matrices (as opposed to paired observations) are considered, the significance of their association can only be evaluated by comparison with an empirical null distribution, i.e. by Mantel tests. Simple Mantel tests were used to explore the correlation of the F_{st} and P_{st} values, as they are expected to be proportional under neutrality and thus display a linear correlation (Roseman and Weaver 2007). The phenotypic distance between the Aeta/Agta (NE) and East African (EA) populations was a clear outlier in our dataset, greater than expected in an otherwise linear relationship between F_{st} and P_{st} values (Table 2, Fig. S1). This demonstrates that these populations are the most phenotypically differentiated when considering the apportionment of variance between populations, and proportionally greater than their genetic differentiation. Given the statistical framework of our study, i.e. Pearson product-moment correlations, we removed this outlier from subsequent analyses. Simple Mantel tests were also used in our second analysis in order to assess the correlation between the hypothetical F_{st} values and the F_{st} or P_{st} values empirically derived from our datasets.

Partial Mantel correlations, estimated from the residuals of a previous correlation, allow one to keep constant the effects of a third matrix over the matrices being compared (Legendre 2000). The partial Mantel test (Table 3) assessed the correlation of the pairwise biological population differentiation values (F_{st} or P_{st}) against the dispersal models (*G*), while controlling for population divergence values (*T*). To assess whether one model could be

favored over another when more than one competing model was correlated significantly after Bonferroni correction for multiple model tests, we conducted a Dow-Cheverud test (Pinhasi and von Cramon-Taubadel 2009; Hubbe et al. 2010). In all cases, we ran 10k permutations to assess correlation significance. The population differentiation matrix (F_{st} or P_{st}) was permuted prior to the regression with *T*. This method is preferred over permuting the rows and columns of the residual matrices (Legendre 2000). Calculations were made in the PASSaGE 2 software (Rosenberg and Anderson 2011).

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SUPPORTING INFORMATION

The "Negrito" Hypothesis

The ethnographic term "Negrito" broadly refers to Southeast Asian populations exhibiting a phenotype of short stature, dark skin color, and tufted hair and implies a common origin hypothesis (Endicott 2013). Alongside Australians, Papuans, Melanesians, and Dravidian speaking Indian populations, the "Negrito" have been hypothesized to be isolated, "relic" descendants of a first dispersal out of Africa and into Asia (Mirazón Lahr 1996). Following a biogeographical approach, the designation of "relic" is in reference to the ecological context of populations that have become isolated as a result of occupying geographical refugia or exploiting specific ecological niches. To date, the most comprehensive genetic study exploring diversity of modern human populations in Asia sampled seven "Negrito" populations, including the Agta, Aeta, and Iraya from the northern Philippines; the Mamanwa and Ati from Southern Philippines; and the Jehai and Kensiu from Malaysia (HUGO Pan-Asian SNP Consortium 2009). This study found that "Negrito" population affinities are with geographically proximate populations rather than with other "Negrito" groups. The study therefore challenges a simple common origin hypothesis for the "Negrito" and implies other evolutionary mechanisms accounting for their common phenotype. Nonetheless, the Mamanwa's ancient association with Australians and highland Melanesians has been interpreted as evidence for an early, southern route dispersal into Southeast Asia (Pugach et al. 2013). Likewise, the Aeta remain candidate descendants of a first dispersal within the MDI model, alongside Melanesians and Papuans (Rasmussen et al. 2011).

To assess affinities of our Aeta/Agta sample, as well as our Papuan and Melanesian samples, we conducted a principal component analysis (PCA) using the *SNPRelate* R package (Zheng et al. 2012) and a discriminant analysis of principal components (DAPC) using the *adegenet* R package (Jombart et al. 2010). We used the same data and groupings as in the main text (Cavalli-Sforza 2005; HUGO Pan-Asian SNP Consortium 2009; Reich et al. 2009; Xing et al. 2009, 2010; Bryc et al. 2010; Reich et al. 2011; Pugach et al. 2013) (Table 1, Table S3). DAPC is a multivariate method, free of assumptions about Hardy-Weinberg equilibrium or linkage disequilibrium. It has been shown to generally perform better than the STRUCTURE method (Pritchard et al. 2000) and is also analogous to an ADMIXTURE method (Alexander et al. 2009) in that a number, *K*, of clusters can be specified in order to assess population

structure. We identified the best supported grouping of individuals running a *K*-means clustering of principal components (Liu and Zhao 2006) and used a Bayesian Information Criterion (BIC) approach to assess the best supported number of clusters. For the genetic dataset, we found *K*=5 to be the best supported model (Fig. S2a) and therefore used this in the DAPC. While results were less clear for the cranial phenotype dataset, with BIC results approximately equivalent for *K*=5-8 clusters (Fig. S2b), we also used *K*=5 as the best supported model. For the genetic dataset, the DAPC along the first two axes revealed three major clusters within the five supported by the *K=5* model (Fig. S3a). They included (a) AU-NG-ME; (b) ((JP-NE)-CA-(NI-SI)); and (c) EA-SA. This clustering pattern is also observed along the first two PCs in a standard PCA (Fig. S3b). The Aeta/Agta were not classified into the AU-NG-ME cluster (Table S5), as might be expected if they shared an ancient association with those populations in a similar fashion as the Mamanwa. Instead, the Aeta/Agta classified primarily with the Japanese and Central Asians. As foreseen by the BIC results of the cranial phenotype data, classification was much more mixed in this case, with individuals classified across less coherent clusters (Table S5). Nevertheless, in the clusters where the Aeta/Agta were classified the most, Japanese and Central Asians were also strongly represented.

To more robustly assess the association of our Aeta/Agta sample, we conducted a TreeMix analysis (Pickrell and Pritchard 2012) on the genetic data. The TreeMix method relaxes the assumptions of branching models of biological evolution, incorporating the possibility that populations did not remain isolated after their separation. Accordingly, evolutionary trees are constructed considering the possibility of gene flow between populations after their split. A maximum-likelihood tree was initially inferred from allele frequencies, with migration events added to populations that showed a poor fit to this tree. We modeled several scenarios allowing a number of migration events from 0 to 10, until (a) 99% of the variance in relatedness was explained and (b) further migration events did not significantly increase the variance explained by the model. The trees were forced to have a root in Africa. Interestingly, the topography of the maximum-likelihood tree places the Aeta/Agta in a branch with Australians, Papuans, and Melanesians (Fig. S4a). It also reveals a strong likelihood of admixture between Japanese (JP) and Aeta/Agta (NE), with an inferred migration from the former to the latter.

Following these exploratory analyses, we placed Papuans and Melanesians as descendants of the first dispersal and Agta/Aeta as descendants of the second dispersal for

the MDI model. Because we grouped the Aeta and Agta as one population, our results are not directly comparable to those of Rasmussen et al. (2011). However, we similarly interpret these analyses to suggest that the Aeta/Agta might have descended from an early southern route dispersal, but have been strongly admixed with a subsequent dispersal. Since living Aeta/Agta speak an Austric language and given the inferred migration from Japan, such admixture might largely be consequent of the Holocene Austronesian expansion of mainland Asian populations into the Pacific (Endicott 2013).

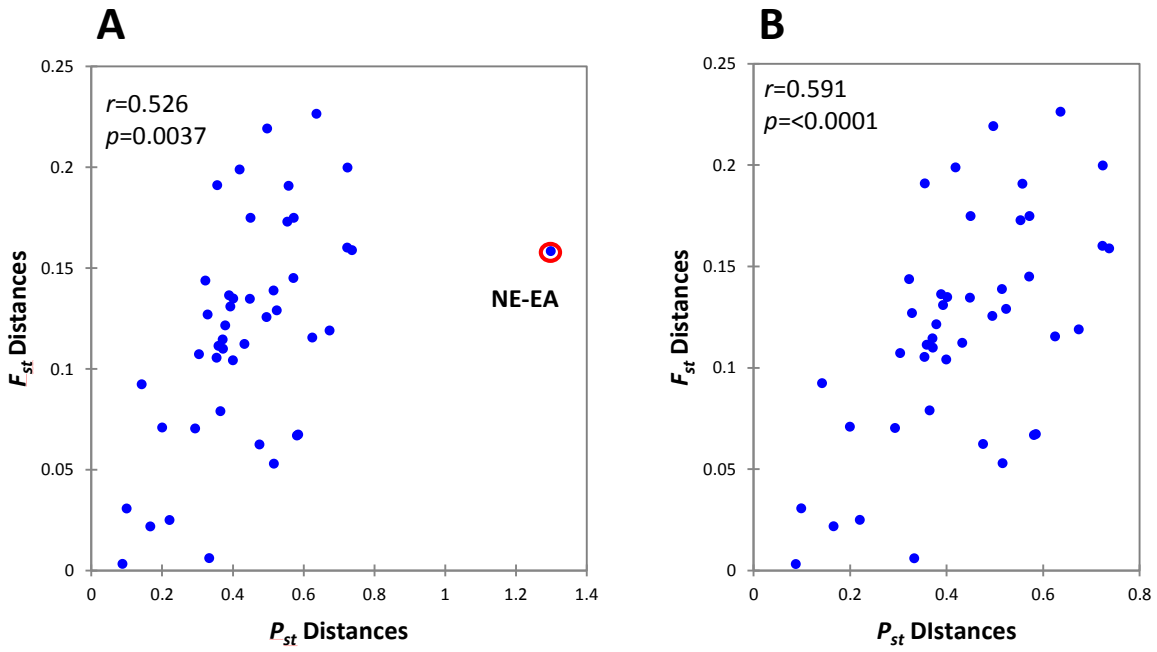

Figure S1. F_{st}-P_{st} Correlation. (A) Regression of F_{st} and P_{st} values, with presence of outlier (EA-NE population pair) highlighted. (B) Regression of F_{st} and P_{st} values after removal of outlier. Reported values are Pearson correlation, *r*, and two-tailed probability, *p,* after 10k permutations.

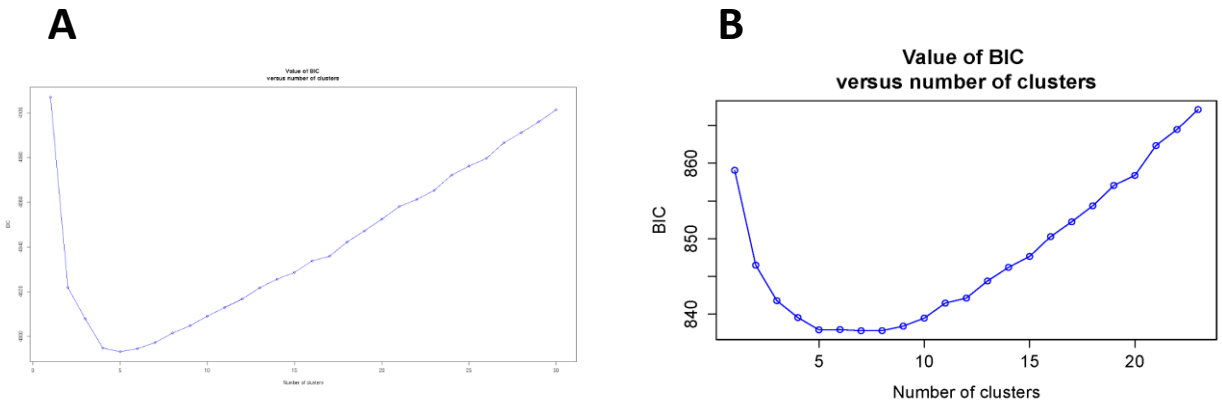

Figure S2. Bayesian Information Criteria (BIC) of *K* Clusters for genetic (A) and cranial phenotype (B) datasets.

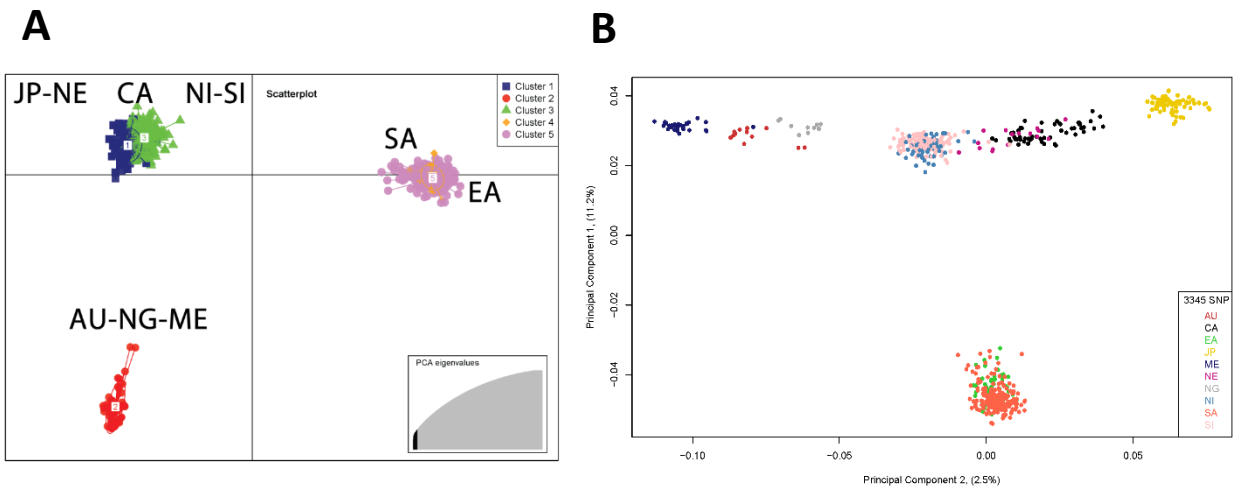

Figure S3. Genetic DAPC & PCA Scatterplots. (A) *K*=5 DAPC scatterplot along the first two axes. (B) PCA of SNP genetic data along the first two axes, capturing ~13.7% of total variance.

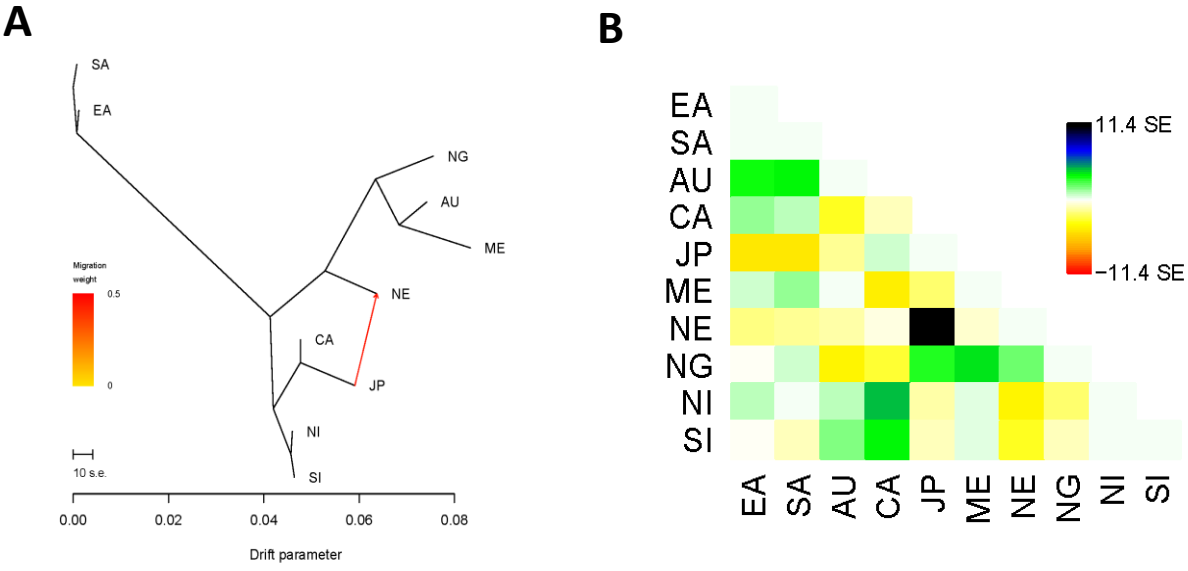

Figure S4. TreeMix Analysis. (A) Maximum-likelihood tree of population affinity. Red arrow indicates migration event and directionality. (B) Residual values from the tree. Values above zero indicate pairs of populations that are candidates for admixture events.

Table S1. Population Divergence Values[1]

	AU	CA	EA	JP	ME	NE	NG	NI	SA	SI
AU	0	35339	100422	45489	19359	25110	19645	41286	106548	32642
CA	1262.1	0	70440	10248	42428	12718	28151	8949	77815	8406
EA	3586.5	2515.7	0	96054	113476	69835	91255	74738	4306	67586
JP	1624.6	366	3430.5	0	49496	14431	33457	29123	101514	23486
ME	691.4	1515.3	4052.7	1767.7	0	28711	19314	50590	116348	38301
NE	896.8	454.2	2494.1	515.4	1025.4	0	16355	21011	75592	15725
NG	701.6	1005.4	3259.1	1194.9	689.8	584.1	0	37176	96986	27608
NI	1474.5	319.6	2669.2	1040.1	1806.8	750.4	1327.7	0	82225	1266
SA	3805.3	2779.1	153.8	3625.5	4155.3	2699.7	3463.8	2936.6	0	74609
SI	1165.8	300.2	2413.8	838.8	1367.9	561.6	986	45.2	2664.6	0

[1]below diagonal: generations (*T*); above diagonal: *T* expressed in calendar years, assuming generations of 28 years and rounded to the nearest whole number.

Table S2. Effective Population Size (N_e)

Population	**N_e 95% Confidence Interval[2]**	**N_e**
AU	3920-10212	4784
CA	5596-6594	6057
EA	11285-13535	12167
JP	4830-6404	5692
ME	2872-4075	3626
NE	1511-3055	2304
NG	2031-2856	2462
NI	6036-9163	8464
SA	11256-13800	13174
SI	5533-6309	5824

[2]These values, rounded to the nearest whole number, were erroneously omitted in the publication (Reyes-Centeno H *et al*. 2014. Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. *Proceedings of the National Academy of Sciences of the United States of America* 111(20):7248-7253) and are thus uniquely reported in this dissertation.

Table S3. Genetic and cranial samples

	Cranial subpopulations	**Genetic subpopulations**	**Language family**[1]	**Genetic data (References)**
AU	Australian	Australian	Australian	Pugach *et al.* 2013
CA	Dungan, Kalmyk, Tarantchi, Uyghur	Kyrgystani, Uyghur	Dene-Caucasian, Eurasiatic	Cavalli-Sforza 2005; HUGO Pan-Asian SNP Consortium 2009; Xing *et al.* 2010
EA	Afar-Danakil, Amhara, Bouma, Glaba, Habesha, Igai, Karo, Koukou, Nyangatom, Pouma, Turkana	Alur, Bulala, Hausa, Kaba, Mada	Afro-Asiatic, Nilo-Saharan	Xing *et al.* 2009, 2010 ; Bryc *et al.* 2010
JP	Japanese	Japanese	Eurasiatic	Cavalli-Sforza 2005; HUGO Pan-Asian SNP Consortium 2009; Xing *et al.* 2009, 2010
ME	Solomon & Vanuatu Islanders	Papua New Guinea highlands	Indo-Pacific	Cavalli-Sforza 2005; Reich *et al.* 2011; Pugach *et al.* 2013
NE	Aeta, Agta	Aeta, Agta	Austric	HUGO Pan-Asian SNP Consortium 2009
NG	Papua New Guinea, Torres Strait Islanders	Papua New Guinea “lowlands” (Bougainville)	Indo-Pacific	Cavalli-Sforza 2005; HUGO Pan-Asian SNP Consortium 2009
NI	Bengali	Bhil, Kashmiri Pandit, Lodi, Meghawal, Sahariya, Satnami, Srivastava, Tharu, Vaish	Indo-European	Reich *et al.*. 2011; Pugach *et al.* 2013
SA	Khoi, Malabar, Nama, San, Sotho, Tswana, Xhosa, Zulu	Bambara, Bamoun, Bantu, Dogon, Fang, Hema, Kongo, !Kung, Luhya, Mbuti Pygmy, Nguni, Pedi, San, Sotho/Tswana, Xhosa	Khoisan, Niger-Kordofanian	Xing *et al.* 2009, 2010 ; Bryc *et al.* 2010
SI	Maravar, Tamil	Chenchu, Dalit, Hallaki, Irula, Kamsali, Kurumba, Madiga, Mala, Naidu, Velama, Vysya	Dravidian	HUGO Pan-Asian SNP Consortium 2009; Xing *et al.* 2009, 2010; Reich *et al.* 2011; Pugach *et al.* 2013

[1]Language families as defined by J. Greenberg (Cavalli-Sforza and Feldman 2003).

Table S4. Geographical Waypoints Used in Dispersal Models

Waypoints[1]	**Geographic Coordinates**	
	Latitude	**Longitude**
Bangkok	13.73	100.52
Cairo	30.06	31.24
Chennai	13.06	80.24
Colombo	6.93	79.86
Dhaka	23.71	90.41
Dubai	25.27	55.31
Jakarta	-6.21	106.84
Karachi	24.89	67.03

[1]Locations correspond to Fig. 1 of main text

Table S5. DAPC Classification[1]

	DAPC Cluster									
	1		**2**		**3**		**4**		**5**	
	Genetics	**Phenotype**	**Genetics**	**Phenotype**	**Genetics**	**Phenotype**	**Genetics**	**Phenotype**	**Genetics**	**Phenotype**
AU	**0**	**1** (5%)	**12** (100%)	**11** (55%)	**0**	**6** (30%)	**0**	**0**	**0**	**2** (10%)
CA	**25** (45%)	**7** (28%)	**0**	**2** (8%)	**31** (55%)	**10** (40%)	**0**	**3** (12%)	**0**	**3** (12%)
EA	**0**	**1** (4%)	**0**	**2** (8%)	**0**	**3** (12%)	**0**	**7** (28%)	**66** (100%)	**12** (48%)
JP	**107** (100%)	**12** (39%)	**0**	**4** (13%)	**0**	**8** (26%)	**0**	**5** (16%)	**0**	**2** (6%)
ME	**0**	**0**	**30** (100%)	**3** (18%)	**0**	**2** (12%)	**0**	**8** (47%)	**0**	**4** (23%)
NE	**15** (94%)	**9** (39%)	**0**	**0**	**1** (6%)	**13** (56%)	**0**	**0**	**0**	**1** (4%)
NG	**0**	**4** (13%)	**10** (100%)	**15** (48%)	**0**	**4** (13%)	**0**	**5** (16%)	**0**	**3** (10%)
NI	**0**	**5** (33%)	**0**	**1** (7%)	**61** (100%)	**3** (20%)	**0**	**3** (20%)	**0**	**3** (20%)
SA	**0**	**1** (5%)	**0**	**2** (10%)	**0**	**6** (30%)	**41** (19%)	**1** (5%)	**174** (81%)	**10** (50%)
SI	**0**	**10** (38%)	**0**	**0**	**141** (100%)	**3** (12%)	**0**	**8** (31%)	**0**	**5** (19%)

[1]Classification number and rate (in parenthesis, approximate percent of total)

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Appendix III

“ …it is likely that East Africa and the Horn were crucial connecting links between the subcontinent, northern Africa, and the eruption of anatomically Modern peoples into Eurasia. Besides the overland route to western Asia over the Isthmus of Suez, the Straits of Bab-el Mandeb would have been another point of dispersal into western Asia that should not be forgotten. ”

J. Desmond Clark (1988: 300)

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Testing modern human out-of-Africa dispersal models and implications for modern human origins

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ABSTRACT

The modern human expansion process out of Africa has important implications for understanding the genetic and phenotypic structure of extant populations. While intensely debated, the primary hypotheses focus on either a single dispersal or multiple dispersals out of the continent. Here, we use the human fossil record from Africa and the Levant, as well as an exceptionally large dataset of Holocene human crania sampled from Asia, to model ancestor-descendant relationships along hypothetical dispersal routes. We test the spatial and temporal predictions of competing out-of-Africa models by assessing the correlation of geographical distances between populations and measures of population differentiation derived from quantitative cranial phenotype data. Our results support a model in which extant Australo-Melanesians are descendants of an initial dispersal out of Africa by early anatomically modern humans, while all other populations are descendants of a later migration wave. Our results have implications for understanding the complexity of modern human origins and diversity.

For most of the late twentieth century, discussion on human evolution and modern human origins, or anthropogeny (Varki et al. 2008), focused on validating or falsifying the polarizing models of either multiregional evolution or African origins and replacement of other hominins. Consensus on Africa as the primary birthplace for modern humans has emerged from paleontological and genetic evidence, placing the common ancestral population between approximately 100-200 thousand years ago (~ka) (White et al. 2003; McDougall et al. 2005; Fu et al. 2013b; Poznik et al. 2013; Scozzari et al. 2014). At the same time, hominin interbreeding has been proposed in order to explain the genetic affinities between extant and extinct hominin populations (Green et al. 2010; Reich et al. 2010; Hammer et al. 2011; Reich et al. 2011; Mendez et al. 2013; Prüfer et al. 2014; Sankararaman et al. 2014; Sigma Type 2 Diabetes Consortium 2014; Vernot and Akey 2014). Similarly, a revival of the "assimilation" hypothesis in human paleontology (Smith et al. 1989; Smith et al. 2005) has encouraged continued assessment of taxonomically ambiguous fossils as descendants of hominin interbreeding events (Liu et al. 2010; Rogers Ackermann 2010). As a result, the anthropogeny discussion has shifted toward assessing the degree, timing, and location of admixture between hominin populations (Sankararaman et al. 2012; Cooper and Stringer 2013; Sankararaman et al. 2014). However, an alternative view is that genetic and phenotypic resemblance between extant and extinct populations is a consequence of deep population substructure in Africa, as well as drift following the out-of-Africa expansion (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996; Green et al. 2010; Blum and Jakobsson 2011; Ghirotto et al. 2011; Eriksson and Manica 2012; Lowery et al. 2013; Eriksson and Manica 2014; Reyes-Centeno et al. 2014). In this view, the context of the geographical and temporal niches occupied by recent hominins can explain, at least in part, the resemblance between Holocene populations and some Pleistocene hominins. This view suggests that genetic and phenotypic plesiomorphic traits in certain extant populations reflect differential diversity exported outside of Africa, particularly if the dispersal pattern out of the continent consists of multiple exits.

Given these competing views, understanding the spatial and temporal distribution of hominin populations in the Middle-Late Pleistocene is necessary for developing a coherent anthropogeny theory. Here, we review competing out-of-Africa dispersal hypotheses previously proposed from multidisciplinary evidence. We then design a test for assessing their spatio-temporal predictions using measures of cranial diversity between extant human populations and Pleistocene anatomically modern human (AMH) populations, or 'palaeo-

demes' (Howell 1999). Using a large craniometric dataset, we test the expected relationship of hypothetical ancestral palaeo-demes from Africa and the Levant and descendant Holocene populations from Asia, as compared to hypothetical geographical routes of dispersal predicted under different out-of-Africa models.

The serial founder effect and eastward expansion hypothesis

Support for the origins of AMHs in Africa and their expansion out of that continent comes from the consistent observation that genetic (Eller 1999; Harpending and Rogers 2000; Prugnolle et al. 2005; Ramachandran et al. 2005; Liu et al. 2006; Li et al. 2008; Deshpande et al. 2009), linguistic (Atkinson 2011), and cranial phenotypic (Manica et al. 2007; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009) diversity decreases with increasing distances from Sub-Saharan Africa. This pattern—referred to as a cascading bottleneck (Harpending and Rogers 2000) or serial founder (Ramachandran et al. 2005) effect— is usually interpreted to represent a single dispersal event, with an iterative loss of diversity during modern human expansion caused by small bottlenecks following each successive founding process. Biological diversity decreases primarily along a latitudinal axis in Eurasia, consistent with a series of short, simple terrestrial migration routes, avoiding major geographic barriers (Liu et al. 2006; Ramachandran and Rosenberg 2011). This eastward expansion (EE) scenario also results in increasing rates of population differentiation and genetic linkage disequilibrium with increasing distances from Africa (Ramachandran et al. 2005; Jakobsson et al. 2008). The EE hypothesis is compatible with a scenario in which expanding modern humans admixed with other hominin populations, but where their genetic contributions would have had to be small (DeGiorgio et al. 2009).

The multiple dispersals and southern route hypothesis

An alternative hypothesis that is also consistent with decreasing diversity from Africa is a multiple dispersals (MD) scenario, whereby modern humans expanded out of the continent at different timescales and via distinct geographical routes (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). The MD hypothesis was derived primarily from comparative craniometric studies and associations with the available paleo-environmental record. It predicts that a first, opportunistic dispersal between 50-100 ka involved a rapid migration primarily along a coastal route, through the southern Arabian Peninsula, reaching Southeast

Asia at roughly the same time that a second dispersal through the Levant prompted colonization of the rest of Eurasia between ~40-50 ka. Isolated populations throughout Southeast Asia are proposed to retain the signal of the initial "southern route" dispersal, while others are palimpsests of the two dispersals. Hypothetical "relic" populations include Australians, Melanesians, Papuans, Dravidian speakers of South Asia, and short-statured "Negrito" populations of Southeast Asian islands, such as the Andaman Islanders of the Bay of Bengal and the Aeta/Agta of the Philippines. Following a biogeographical approach, the designation of relics is in reference to the ecological context of populations that have become isolated as a result of occupying geographical refugia or exploiting specific ecological niches. The MD scenario predicts that these populations retain plesiomorphic traits because they diverged first from a structured ancestral African population, have remained isolated from subsequent population expansions, and consisted of smaller population sizes. A multiple dispersals scenario has been questioned on the basis of autosomal genetic data (Wollstein et al. 2010; Reich et al. 2011), but a southern route been supported by some recent genomic studies sampling proposed relic populations (Ghirotto et al. 2011; Rasmussen et al. 2011; Reich et al. 2011; Pugach et al. 2013; Reyes-Centeno et al. 2014).

The multiple dispersals with isolation hypothesis

In an amendment to the MD hypothesis, the multiple dispersals with isolation (MDI) scenario suggests that Australians are the only isolated descendants of the southern route dispersal, while Papuans, Melanesians, and possibly the Aeta "Negrito" from the Philippines retain a southern route genetic signal that is detectable, but obscured due to admixture with members of the second dispersal (Rasmussen et al. 2011). An isolation scenario for Australo-Melanesians is consistent with uni-parental (mitochondrial and non-recombining Y-chromosome DNA) and genome-wide data, although gene flow from outside the region during historical times is still detectable at low levels in Northern Australia (Hudjashov et al. 2007; Pugach et al. 2013). The chronological separation between the dispersals is considered to be relatively short, with the first commencing between ~75-62 ka, as inferred from the divergence of Africans and Australians, and the second between ~38-25 ka, as inferred from the divergence of East Asians and Europeans. However, dates of divergence between Africans and Eurasians have been estimated as far back as ~140 ka (Gutenkunst et al. 2009), which is more in line with a southern route dispersal interpreted to have occurred as early as the late

Middle Pleistocene or during the last interglacial, between ~131-114 ka (Stringer 2000; Petraglia et al. 2010; Armitage et al. 2011; Boivin et al. 2013; Reyes-Centeno et al. 2014; Scozzari et al. 2014).

The single dispersal and beachcomber arc hypothesis

Given the discrepancies between the EE and MD/MDI hypotheses, a reconciling view is that of a single wave bifurcating outside of Africa, likely in southwest Asia (Mellars 2006; Oppenheimer 2012). This view is broadly similar to the EE hypothesis in that population divergence outside of Africa is largely due to the geographic barrier of the Himalaya mountain range, which obstructed migrations between northern and southern Asia. The EE scenario also acknowledges the importance of a coastal 'beachcomber arc' migration into Australia, along the Indian Ocean rim. Based primarily on uni-parental genetic evidence, this beachcomber single dispersal (BSD) hypothesis suggests a single out-of-Africa event at ~75 ka (Oppenheimer 2012) or less than ~65 ka (Mellars et al. 2013). Like the EE scenario, BSD considers a series of founding bottlenecks during this expansion. However, in contrast to the parsimonious latitudinal gene flow of EE, BSD implies substantial migration along a longitudinal axis. For example, in addition to a dispersal along the Indian Ocean rim, the 'beachcomber arc' also includes the eastern Pacific Ocean rim. Furthermore, it allows for migrations from southwest Asia back into Africa. Gene flow, therefore, is much more dynamic. The implication for biological diversity is that Eurasian populations differentiated in southwest Asia, and that extant North African and non-African populations reflect a subset of this diversity. As in the MD/MDI hypotheses, a behavioral implication is inherent in the BSD model, as the southern, coastal dispersal is largely the result of a shift towards marine resource exploitation, documented in the late Middle Pleistocene archaeological and paleontological records of Africa (Henshilwood and Marean 2003; Marean et al. 2007).

Testing modern human dispersal patterns

These different out-of-Africa dispersal hypotheses have been formally evaluated by some of us (Reyes-Centeno et al. 2014), testing the geographical and temporal predictions of each scenario against two independent biological datasets, namely genomic and cranial shape variables derived from modern human Holocene populations. Since spatial and temporal distances between populations are explicit in the dispersal scenarios, distinguishing between

competing hypotheses is achieved by assessing the correlation of spatio-temporal distances with neutral biological distances. This approach is founded on the assumption that the primary driver of recent human evolution is genetic drift (Rogers Ackermann and Cheverud 2004; Roseman and Weaver 2007; Weaver et al. 2007; Reyes-Centeno et al. 2014; Weaver 2014). In the absence of selection and assuming a common ancestral origin, cranial phenotypic differentiation in modern human populations is expected to be proportional to the geographic proximity between them (Hubbe et al. 2010; Weaver 2014). Consensus has emerged on using cranial form as a proxy for identifying patterns of modern human population history and neutral diversification (Relethford and Harpending 1994; Roseman 2004; Harvati and Weaver 2006a, b; Manica et al. 2007; Betti et al. 2009; Hubbe et al. 2009; Smith 2009; von Cramon-Taubadel 2009; Smith et al. 2013). Only a limited number of populations and certain cranial regions have been shown to be affected by non-stochastic evolutionary processes, such as climate-related effects on cranial phenotype. Previous work found greater support for the MDI hypothesis, supporting an initial dispersal scenario that occurred closer to the Middle-Late Pleistocene boundary (Reyes-Centeno et al. 2014). However, that study used Holocene modern human samples, relied on genetic divergence and hypothetical 'archaeological divergence' estimates to control for a temporal component in the models, and was limited to a sample size of ten populations. Another approach is to analyze Holocene and Pleistocene populations in tandem, such that the former can be considered descended from the latter. This approach has been employed with craniometric data for testing competing dispersal scenarios for the peopling of the Americas from Asia (Hubbe et al. 2010). Drawing from this method, the use of African and Levantine Pleistocene fossil palaeo-demes as ancestral to Holocene populations is used here to control for the temporal dimension of competing dispersal hypotheses following the proposal that the fossil record can serve to represent spatiotemporally bounded biological populations, or palaeo-demes (Howell 1999).

Single dispersal models such as EE and BSD predict continuity in the cranial phenotype of early AMHs and the later fossil populations in Africa. In this view, morphological diversity during the out of Africa event would reflect features primarily observed in a later Late Pleistocene palaeo-deme (LPPD). By contrast, multiple dispersal scenarios such as MD and MDI predict that isolated, relic descendants of the first dispersal would show closer affinity to the earliest AMHs while all other extant populations would show closer affinities to the LPPD.

In such a scenario, two ancestral palaeo-deme populations account for the diversity exported outside of Africa (Fig. 1b).

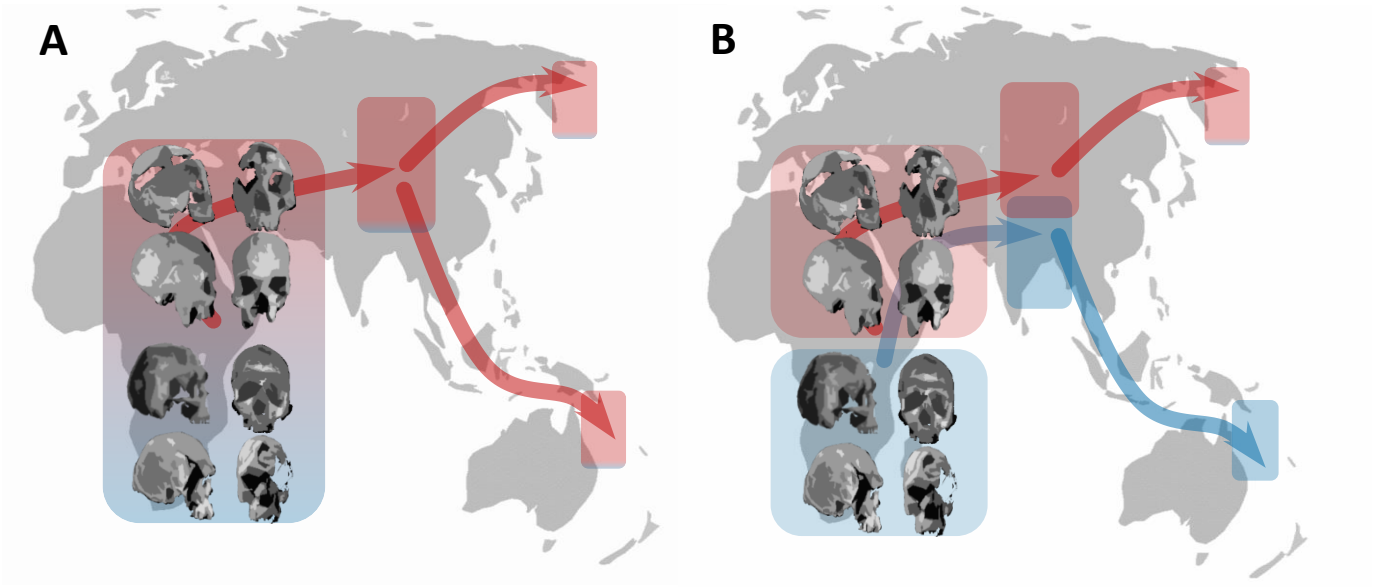

Figure 1. Study design. A schematic representation of the source population(s) in Africa under either a single dispersal (A) or multiple dispersals (B) hypothesis. In (A), continuity between early and later anatomically modern humans in Africa is expected, followed by eastward geographical continuity of Holocene populations, with decreasing diversity resulting from expansion. In (B), Middle-Late Pleistocene AMHs are expected to show affinities to descendants of an early southern route dispersal while Late Pleistocene modern humans are expected to show affinities to descendants of a second dispersal. Rectangles represent demes and their size indicates intra-population diversity. For simplicity, a Holocene map outline is shown. Fossil drawings adapted from the following sources (in order of appearance from top to bottom): Crevecoeur (2006: Nazlet Khater 2), Grine *et al.* (2007: Hofmeyr), Vandermeersch (1981: Qafzeh 6), White *et al.* (2003: Herto BOU-VP-16/1).

Because the competing scenarios suggest that AMH dispersal(s) occurred between ~135-25 ka, fossils within this time frame must be considered; however, the human fossil record from this period is scarce and fragmentary. In East Africa, the earliest relatively complete AMH adult crania is the Herto BOU-VP-16/1 specimen, dated to ~160 ka (White et al. 2003; McCarthy and Lucas 2014). In the Levant, the earliest AMH adult crania are at the Qafzeh and Skhul sites, dated to between ~135-80 ka (MacCurdy 1936; Vandermeersch 1981; Schwarcz et al. 1988; Grün et al. 2005). Since this region is often thought to represent an extension of African ecosystems (Howell 1999; Klein 2000), the Qafzeh/Skhul specimens can be included in a human origins palaeo-deme. Notably, some African specimens within or somewhat older than this time frame, such as Ngaloba LH-18 (Magori and Day 1983), Singa

(Stringer 1979; McDermott et al. 1996), the Jebel Irhoud specimens (Ennouchi 1962; Grün and Stringer 1991; Hublin 2001), are considered to represent early *Homo sapiens*, but retain some less modern elements in their cranial morphology (Stringer 1974; Gunz et al. 2009; Harvati et al. 2011). Consequently, these specimens are not representative of a hypothetical AMH origins palaeo-deme. Few adult crania from Africa or the Levant are known in the later part of the Late Pleistocene. The relatively complete specimens of Hofmeyr from South Africa (Grine et al. 2007) and the Nazlet Khater 2 specimen from Egypt (Crevecoeur et al. 2009) date to ~36 ka and ~38 ka, respectively, and have been attributed to populations ancestral to Upper Palaeolithic Eurasians. As such, they can be used to represent a LPPD.

MATERIALS AND METHODS

Samples. For the hypothetical palaeo-deme samples, we included six specimens belonging to the origins palaeo-deme or the LPPD (Table 1), maximizing the number of craniometric variables that could be collected across all samples and without imputing missing values. A total of twelve standard craniometric variables (Howells 1973; Bräuer 1988) were available for analysis (Table 2). Data for the Skhul and Qafzeh specimens were collected by C.S. (Stringer 1992). Published data were used for Herto BOU-VP-16/1 (White et al. 2003), Nazlet Khater 2 (Crevecoeur 2006; Crevecoeur et al. 2009), and the Hofmeyr specimen (Grine et al. 2007; Crevecoeur et al. 2009; Grine et al. 2010). For the Holocene sample, we used a subset of the craniometric dataset collected by T.H. (Hanihara 2006; Hubbe et al. 2009), totaling 2110 adult male individuals. The subset includes samples grouped according to the dispersal models tested here, comprising eighteen populations from Africa and Asia (Table 3).

Table 1. Fossil Pleistocene Cranial Sample

	Provenience	**Specimen**	**Geological Age** (~ka)
Origins paleo-deme	Ethiopia	Herto BOU-VP-16/1	160
	Palestine/Israel	Skhul 5	80-135
		Qafzeh 6	80-135
		Qafzeh 9	80-135
LPPD[1]	South Africa	Hofmeyr	36
	Egypt	Nazlet Khater 2	38

[1]Late Pleistocene Palaeo-deme (LPPD)

Table 2. Quantitative Cranial Variables: Linear Measurements

Bräuer (1988)	**Howells** (1973)	**Heritability** (h^2)		**Howells' Description**
		Martínez-Abadías (2009)	Carson (2006)	
M1	GOL	0.31	0.363	Maximum cranial length
M8	XCB	0.36	0.233	Maximum cranial breadth
M10	XFB	*n/a*	*n/a*	Maximum frontal breadth
M11b	AUB	0.40	0.397	Biauricular breadth
M19	MDH	*n/a*	*n/a*	Mastoid height
M29	FRC	0.11	0.144	Nasion-bregma chord
M30	PAC	0.06	0.307	Bregma-lambda chord
M43(1)	FMB	0.4	0	Bifrontal breadth
n/a	NPH	0.34	0.588	Nasion-prosthion height
M49a	DKB	0.33	0.170	Interorbital breadth
M52	OBH	*n/a*	0.478	Orbital height
M54	NLB	0.00	0.007	Nasal breadth
n/a	NLH	0.43	0.729	Nasal height

Table 3. Recent Holocene Cranial Sample

Abb.[1]	**Assigned Meta-Population**	**Geographic Provenance**[2]	**Assigned Geographic Locality**	**Geographic Coordinates**		**Sample Size *N***
				Lat.	**Long.**	
BENG	Bengal Bay	Andaman Islands	Dhaka	23.71	90.41	43
EGYP	Egypt	Egypt, Sudan	Cairo	30.06	31.24	413
ESIA	Indonesia	Indonesia	Jakarta	-6.21	106.84	146
INCH	Indochina	Laos, Myanmar, Thailand, Vietnam	Bangkok	13.73	100.52	132
JAPN	Japan	Japan	Tokyo	35.66	139.82	137
LVNT	Levant	Palestine, Israel	Jerusalem	31.77	35.22	85
MLAY	Malay Peninsula	Malaysia, Singapore	Kuala Lumpur	3.14	101.69	79
MNCH	Manchuria	China (Han), Korea	Shenyang	41.81	123.43	173
MONG	Mongolia	Mongolia	Ulaanbaatar	47.92	106.9	120
NAUS	Australia North	Torres Strait Islands, Queensland	Brisbane	-27.47	153.02	57
NIND	India North	N.E. India (Indo-European), Nepal, Tibet	New Delhi	28.63	77.2	129
NMEL	Melanesia North	New Britain, New Ireland, Solomon Islands	Honiara	-9.42	159.94	121
PAPU	Papua New Guinea	Papua New Guinea	Port Moresby	-9.48	147.19	110
PHIL	Philippines	Luzon Island (Agta/Aeta 'Negrito')	Manila	14.6	120.98	20
SAUS	South Australia	New South Wales, South Australia, Western Australia	Hobart	-42.88	147.32	116
SIND	South India	India (Dravidian)	Colombo	6.93	79.86	83
SMEL	South Melanesia	New Caledonia, New Hebrides	Noumea	-22.28	166.46	67
WASI	Western Asia	Afghanistan, N.W. India (Indo-European)	Kabul	34.52	69.17	79
					Total	**2110**

[1]Abbreviation

[2]Ethno-linguistic affiliation in parenthesis

We note that several studies have assessed the correlation of craniometric variables with climate parameters in order to infer environmental selection (Manica et al. 2007; Betti et al. 2009; Hubbe et al. 2009). Because distinct climate variables were used in those studies, results differ as to the degree to which climate affects each cranial measurement. In our analysis, we used only one variable (nasion-prosthion height, Table 2) that was consistently found to be under strong climate selection. However, this variable was also found to retain a strong global demographic signal by Manica and colleagues (2007) and to have a higher heritability value than the average of the variables sampled by Carson (2006).

Measure of population differentiation. Raw cranial measurements were size-standardized by dividing each measurement by the geometric mean of all measurements, per specimen (Darroch and Mosimann 1985; Jungers et al. 1995). These size-standardized variables were used to calculate biological distances between populations. For each analysis, we calculated the levels of phenotypic (morphological) differentiation, P_{st} (Roseman and Weaver 2007). We developed a matrix of pairwise P_{st} values representing phenotypic differentiation between populations. P_{st} follows the quantitative analytical framework of neutral genetic evolutionary theory and is analogous to the fixation index, F_{st}, in population genetics (Relethford and Blangero 1990; Holsinger and Weir 2009). It assumes an equal and additive model of inheritance of phenotypic traits, where phenotypic variances are proportional to genetic variances (Harpending and Ward 1982; Relethford and Harpending 1994). At least one of our sampled populations (Mongolians) are thought to be under strong climate selection and have been hypothesized to exhibit climate-adapted cranial morphology, therefore representing a deviation from neutrality (Hubbe et al. 2009). Because this runs contrary to the assumptions in our method, we recomputed P_{st} after removal of this population.

P_{st} acknowledges the fractional heritability of cranial traits and the added epigenetic effects on morphology. Currently, heritability estimates for cranial variables have only been ascertained in one population using two different approaches (Carson 2006; Martínez-Abadías et al. 2009). In these studies, estimates for each variable differ (reported in Table 2 for the variables used here), sometimes to a large degree (e.g. FMB h^2=0.4 or h^2=0). Given these discrepancies, as well as the fact that we used variables of unknown heritability and fossil populations for which no estimates are available, we use an approximate average value across

the known variables, h^2=0.3. Nonetheless, heritability corrections will not affect the relative relationship between the distances calculated since the corrections are proportional between population pairs. Lastly, we used a conservative approach assuming that population sizes are equal across all samples (Pinhasi and von Cramon-Taubadel 2009). P_{st} calculations were made in the RMET 5.0 software and corrected for sampling bias (Relethford et al. 1997). We note that uncorrected values do not affect the interpretations made from our analyses.

Modelling the out-of-Africa dispersal hypotheses. Out-of-Africa dispersal scenarios were modelled using geodesic distancebetween populations, *G*, along hypothetical dispersal routes (Fig. 2). Pairwise *G* was calculated using the PASSaGE software (Rosenberg and Anderson 2011), which assumes a spherical shape for the Earth and a radius of 6379.336847 kilometers. The null, control model is *G* calculated pairwise without regard to geographic barriers or continuity between palaeo-demes (Hubbe et al. 2010). Addis Ababa, Ethiopia (lat. 9.02, long. 38.74) was used as the location for the palaeo-demes in all models, in order to make our study methodologically comparable to previous work (e.g. Ramachandran et al. 2005; Ghirotto et al. 2011; Reyes-Centeno et al. 2014). Waypoints were used in order to capture the complex geography of coastal migration routes for the BSD, MD, and MDI scenarios. Waypoint latitude and longitude coordinates included the following: Dubai (25.27, 55.31), Karachi (24.89, 67.03), and Chennai (13.06, 80.24). We note that in the MD and MDI models, the geographical centroids of some populations were also used as waypoints. For example, Kuala Lumpur, which corresponds to the centroid of the Malaysian population, is also used as a waypoint for the southern route. This is because we sampled several populations from Southeast Asia living along a purported southern dispersal route (Indochina, Malaysia, Indonesia) but who are not considered isolated, relic populations in the MD or MDI models; therefore, we included them as descendants of the second dispersal but used the same geographical space to model the first dispersal. The evolutionary implication is that such populations are presumed to have replaced initial descendants of the first dispersal, or be highly admixed with them, obscuring a biological southern route signal. We also note that we have chosen modern points of reference (i.e. existing cities) for simplicity. Slight changes based on palaeo-environmental reconstructions are unlikely to significantly affect *G* at a continental scale. In order to compare the association of P_{st} and *G* when considering removal of the climate-adapted population, we maintained Ulaanbaatar, Mongolia as a waypoint between the Western Asian and Manchurian

populations for the EE, MD, and MDI models. The BSD model is not affected since Mongolia is a terminal node (i.e. connected by a migration route to only one other population). In all cases, therefore, *G* is unmodified when removing Mongolians.

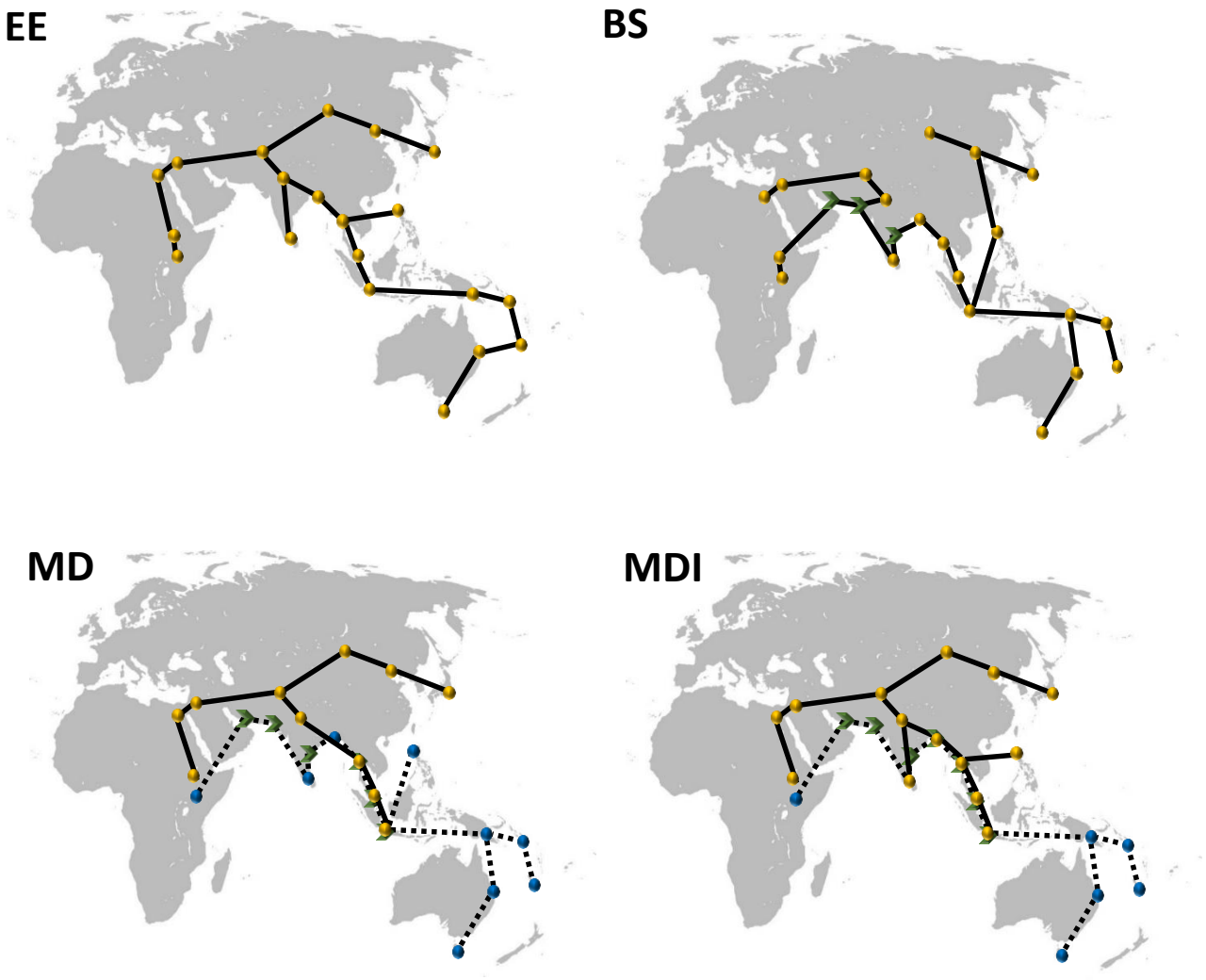

Figure 2. Out-of-Africa biogeographical models. Circles are approximate centroids of populations sampled (Table 1) and paleo-demes (Table 2), connecting lines are dispersal routes, and arrows are geographical waypoints. The eastward expansion (EE) model connects populations primarily along a latitudinal axis, avoiding geographic barriers. The 'beachcomber' single dispersal (BSD) model connects populations primarily along a coastal route. The multiple dispersals model (MD) connects hypothetical isolated, 'relic' populations (dark spheres) along a southern route (dotted lines). The multiple dispersals with isolation (MDI) model assumes that only Australo-Melanesian populations retain a strong southern route biological signal. For simplicity, a Holocene map outline is shown.

In the EE model, populations are connected by geographical proximity and primarily along a latitudinal axis, avoiding major geographic barriers (Liu et al. 2006; Ramachandran and Rosenberg 2011). This model assumes continuity between the palaeo-demes such that the origins palaeo-deme is ancestral to the LPPD and, in turn, only the LPPD is directly ancestral to

the Holocene populations (Fig. 2a). The implication is that morphological diversity in Asia would primarily be an export of the diversity of the LPPD. Following this same logic, populations in the BSD model are connected along a coastal 'beachcomber arc' route. Additionally, the Holocene Egyptian and Levantine populations are presumed to represent a migration back toward Africa, from southwest Asia. In the MD model, the origins palaeo-deme is ancestral to hypothetical relic populations along a southern, coastal dispersal route. Relic populations include Dravidian speakers from India, Andamanese Islanders from the Bay of Bengal, Philippine Aeta/Agta "Negritos," New Guinea Papuans, Melanesians, and Australians. The LPPD is ancestral to all other populations along an initial northern dispersal route. The MDI model follows the same approach as the MD model, but in this case only New Guinea Papuans, Melanesians, and Australians are considered isolated, southern route descendants of the origins palaeo-deme. We note that from both a genetic and morphological point of view, the Aeta/Agta have been found to have closer affinities to Northern and Eastern Asian groups than to Melanesians or Australians (Hanihara 1992, 2006; Rasmussen et al. 2011; Endicott 2013; Migliano et al. 2013; Reyes-Centeno et al. 2014), although they have been interpreted as representing a population that is highly admixed between the two dispersal groups (Rasmussen et al. 2011; Reyes-Centeno et al. 2014).

In order to connect the separate southern and northern ancestor-descendant series in the MD and MDI models, we use a similar approach to that employed in a recent test for multiple dispersals into the Americas (Hubbe et al. 2010). Our approach differs in that we include two hypothetical ancestral populations (the palaeo-demes) rather than one. In order to accommodate this, the northern and southern route descendants are connected by considering the distance of any given Holocene northern route population to the LPPD, plus the direct distance of LPPD to any given Holocene southern route population. The connection of a northern route Holocene population to the origins palaeo-deme would therefore be equal to its distance to the LPPD, plus the direct distance to the southern route population closest to Africa, plus the distance of this population to the origins palaeo-deme along the southern route. For example, in the MD model, the distance between the Western Asian population and the origins palaeo-deme would equal the distance of the Western Asian population centroid (Kabul) to the LPPD through Jerusalem and Cairo (along the northern route), plus the direct distance of LPPD to Dravidian-speaking Indians (the southern route population closest to Africa in this model), plus the distance of Dravidian Indians to the origins palaeo-deme

through the Karachi and Dubai waypoints (along the southern route). Thus, $G=(G_{WASI \rightarrow LVNT} + G_{LVNT \rightarrow EGYP} + G_{EGYP \rightarrow LPPD} + G_{LPPD \rightarrow SIND} + G_{SIND \rightarrow Karachi} + G_{Karachi \rightarrow Dubai} + G_{Dubai \rightarrow ORIG})$, or ~16719 km.

Statistical analyses. When using a pairwise distance approach, as employed here, assessing the association between two matrices is evaluated with Mantel tests, which compares their association to a null distribution. The method has been productively used for testing dispersal patterns of modern human populations (Pinhasi and von Cramon-Taubadel 2009; Hubbe et al. 2010; Hubbe et al. 2011). Pairwise population matrices were used to test for the correlation between pairwise P_{st} and G in a simple Mantel test (Mantel 1967). To test for significance (p-value), we ran 10k permutations of the matrix rows and columns. In all cases, we report the Pearson correlation coefficient (r) and two-tailed p-value of the permutation results. We accepted $\alpha=0.01$ as statistically significant results, corresponding to a Bonferroni correction for multiple model tests. In order to compare competing models, we applied a Dow-Cheverud test (Dow and Cheverud 1985). This analysis compares an observation matrix (in this case, pairwise P_{st} values) against two competing model matrices (in this case, pairwise G values for two given dispersal models). Thus, it is possible to assess whether one dispersal model correlates significantly better with morphological differentiation than another model.

RESULTS

The Mantel test correlation between pairwise P_{st} and G was significant for all dispersal models (Table 5). However, the correlation coefficient for the MDI model was more than twice the value of the model with the next highest coefficient. The MDI correlation coefficient was also higher after removal of the climate-adapted population, as expected if this population deviates from the assumption of our quantitative genetics analytical framework. Dow-

Table 5. Mantel test results[1]

Out-of-Africa Models	All populations	Select populations[2]
Control	0.265 (<0.0001)	0.251 (0.001)
EE	0.334 (< 0.0001)	0.311 (< 0.0001)
BSD	0.281 (< 0.0001)	0.223 (0.003)
MD	0.294 (0.001)	0.255 (0.001)
MDI	0.676 (<0.0001)	0.707 (<0.0001)

[1]Reported values are r Pearson correlation coefficient and two-tailed p-values after 10k permutations (in parenthesis). [2]After removal of climate-adapted population.

Cheverud tests revealed that all models fit the P_{st} values better than the control; however, only the MDI is significantly better (Table 6). Furthermore, MDI is significantly better than all other competing models (Table 7). These results were upheld when the Mongolian sample was removed. Thus, our test of out-of-Africa models supports a multiple dispersals scenario in which Australian, Papuan, and Melanesian populations descend from a southern route dispersal.

Table 6. Dow-Cheverud test: control against models[1]

Out-of-Africa Models	All populations	Select populations[2]
EE	-0.119 (0.103)	-0.102 (0.189)
BSD	-0.027 (0.699)	0.060 (0.444)
MD	-0.028 (0.698)	-0.003 (0.931)
MDI	-0.388 (< 0.0001)	-0.421 (< 0.0001)

[1]Reported values are *r* Pearson correlation coefficient and two-tailed *p*-values after 10k permutations (in parenthesis). Positive correlation values indicate that the control model is a better fit with P_{st} values than the competing model, while negative correlation values indicate that the alternative model is better. [2]After removal of climate-adapted population.

Table 7. Dow-Cheverud test: MDI against competing models[1]

Out-of-Africa Models	All Populations	Select Populations[2]
EE	0.362 (< 0.0001)	0.410 (< 0.0001)
BSD	0.336 (< 0.0001)	0.415 (< 0.0001)
MD	0.439 (< 0.0001)	0.507 (< 0.0001)

[1]Reported values are *r* Pearson correlation coefficient and two-tailed *p*-values after 10k permutations (in parenthesis). Positive correlation values indicate that the MDI model is a better fit with P_{st} values than the compared model, while negative correlation values indicate that the alternative model is better. [2]After removal of climate-adapted population.

When we analyzed our dataset by including only the more tightly spatio-temporally bound palaeo-deme of Qafzeh-Skhul, the MDI model was again supported, albeit with a slightly lower correlation coefficient (r=0.658, p=<0.0001; after removal of climate-adapted population: r=0.701, p=<0.0001). While the correlation differences are minimal, the lower value may be due to the fact this restricted origins palaeo-deme does not sample an actual ancestral African population. Nevertheless, Australians, Melanesians, and Papuans had the shortest distance to the origins palaeo-deme and the Qafzeh-Skhul palaeo-deme.

DISCUSSION

One or two dispersals?

In this study, we formalized the spatio-temporal predictions of four distinct modern human out-of-Africa hypotheses and compared them to distance measures derived from a large fossil and recent modern human comparative sample. Such an approach provides an independent method for testing hypotheses derived from the archaeological record or from molecular genetic evidence. It has the advantage that it can incorporate data from AHM Pleistocene palaeo-demes, which are not represented in current palaeogenetic work. Our results indicate that the MDI model is the strongest of the four scenarios examined. In this regard, our findings are consistent with previous morphological analyses of both metric and non-metric data from regional, as well as worldwide, cranial samples (Hanihara 2006; Stock et al. 2007; Hanihara et al. 2012); and with archaeological data that suggest an early modern human dispersal through the southern route (Armitage et al. 2011; Rose et al. 2011; Delagnes et al. 2013). Our results also agree with recent genome-wide analyses of human populations, including some sampling ancient genomes (Ghirotto et al. 2011; Rasmussen et al. 2011; Reyes-Centeno et al. 2014; Seguin-Orlando et al. 2014), which support multiple dispersals with an initial southern route migration. Finally, the results are compatible with paleoclimate reconstructions suggesting two broad windows of opportunity for dispersal out of the continent along a southern route, between ca. 140-115 ka and between ca. 80-65 ka (Blome et al., 2012; Rohling et al., 2013).

Nevertheless, our results conflict with uni-parental studies of extant modern humans, which propose a single dispersal as per the EE and BSD scenarios (e.g. Macaulay et al. 2005; Endicott et al. 2009; Fernandes et al. 2012; reviewed in: Oppenheimer 2012). A single dispersal is also supported by the finding that all non-African modern human populations share a similar percentage of autosomal DNA with extinct Pleistocene hominin (Neanderthal) populations (Green et al. 2010; Prüfer et al. 2014) since the most parsimonious explanation for the autosomal data posits a single admixture event in Southwest Asia at the initial phases of the modern human expansion out of Africa (Green et al. 2010). Different population sizes across Eurasia are thought to have resulted in slightly higher Neanderthal genetic contribution in East Asian populations (Prüfer et al. 2014; Sankararaman et al. 2014). The recent sequencing of

AMH genomes from Russia and China has shown similar or slightly stronger admixture signals than those preserved in living humans (Fu et al. 2014; Raghavan et al. 2014; Seguin-Orlando et al. 2014). These studies have also further constrained the timeframe for the proposed Neanderthal-modern human interbreeding event, which is now estimated to have occurred between ~60-50 ka when assuming a single admixture event (Fu et al., 2014; Seguin-Orlando et al., In Press). If these estimates are correct, they imply that the out-of-Africa expansion occurred once, shortly before ~60-50 ka (although see Seguin-Orlando et al. 2014, for support of an earlier migration of Australo-melanesian ancestors.).

At the core of these conficting findings is the question of how Australo-melanesians, if they are the descendants of an earlier dispersal, could inherit similar levels of Neanderthal admixture as all other non-Africans, and display the same derivation of uniparental markers as other non-Africans. A possible but untested answer regarding adxmiture proportions has been proposed by Weaver (2014), who suggested that this might be the result of interbreeding with Denisovans. Denisovans are close relatives of Neanderthals and have been proposed to have interbred with Australasians as well as Neanderthals (Reich et al. 2011; Skoglund and Jakobsson 2011; Prüfer et al. 2014). That admixture event was hypothesized to have occurred in Southeast Asia as modern humans expanded along the southern route (Reich et al. 2011), possibly across the Wallace Line in Southeast Asian islands (Cooper and Stringer 2013).

Early dispersal?

The most contentious issues in this debate are the timing of the dispersal or dispersals, how far the dispersals reached, and whether significant traces of the hypothesized early dispersal survive in extant populations. Support for an early Late Pleistocene dispersal comes from the sites of Jebel Faya, United Arab Emirates, and the Dohfar region, Oman. Dated to between ~100-130 ka, these have yielded lithic assemblages argued to have been made by AMHs (Armitage et al. 2011; Rose et al. 2011; Delagnes et al. 2013). However, no hominin remains have been found in association with these artefacts, prompting intense debate concerning the taxonomic status of their makers (Mellars et al. 2013). The Qafzeh and Skhul fossils from the Levant represent clear evidence of AMHs outside of the African continent in the early Late Pleistocene. Because the origins palaeo-deme in our analysis encompasses these specimens, our results are compatible with the view that they are related to the

ancestral population of Australians (Schillaci 2008; Petraglia et al. 2010). Indeed, in comparative craniometric studies early AMHs in general, and the Qafzeh-Skhul series in particular, consistently show morphological affinities with Oceanic populations, particularly Australians and Papuans (Stringer 1992; White et al. 2003; Grine et al. 2007; Schillaci 2008; Gunz et al. 2009; Harvati et al. 2011). While this result would seem to support an early Late Pleistocene initial dispersal, our current test of dispersal models cannot test for an alternative later initial dispersal because of the limitations of our fossil sample (see below).

Timeframes for the out-of-Africa dispersal are also proposed on the basis of divergence date estimates derived from various genetic loci. Parsimoniously, the divergence of Africans and non-Africans can be considered an upper limit for the out-of-Africa event (Green and Shapiro 2013). Such divergence dates depend largely on mutation rates, which have been intensely debated in the past (Roach et al. 2010; Scally and Durbin 2012; Poznik et al. 2013). Slow mutation rates yield older dates of divergence and fast mutation rates yield younger dates. For example, estimates from modern human genetic data have ranged between ~84-44 ka from mtDNA data (Macaulay et al. 2005; Endicott and Ho 2008; Endicott et al. 2009; Fernandes et al. 2012; Lippold et al. 2014); ~120-60 ka from Y-chromosome data (Lippold et al. 2014; Scozzari et al. 2014), and ~140-65 ka from nuclear data (Gutenkunst et al. 2009; Xing et al. 2010; Eriksson et al. 2012; Scally and Durbin 2012; Reyes-Centeno et al. 2014). Calibration with fossil genomes has now served to constrain these rates for the recent human lineage (Fu et al. 2013b, 2014; Rieux et al. 2014). The most recent calibrations have confirmed a relatively fast mutation rate for uni-parental genetic loci, dating the divergence of Africans and non-Africans to ~71 ka. Studies of modern human bacterial pathogens also suggest an initial southern route dispersal between ~55-75 ka (Moodley et al. 2009; Moodley et al. 2012). At the same time, calibration with the Ust'Ishim genome has also confirmed a slow nuclear mutation rate, thus implying older estimates of the dates of divergence (Fu et al., 2014).

In order to reconcile these contrasting estimates, a gradual divergence of Africans and non-Africans has been proposed, with ancestral populations in East Africa, South-western Asia, and possibly North Africa in intermittent contact with each other over an extended period of time between ~120-40 ka (Xing et al. 2010; Scally and Durbin 2012). In this view, uni-parental divergence estimates reflect the most recent divergence in a long process of population separation. This hypothesis is compatible with the recent proposal that the Qafzeh-Skhul series and the Middle Palaeolithic toolmakers of the Arabian Peninsula lithic

assemblages may correspond to a basal Eurasian population existing prior to ~40 ka (Fu et al. 2014; Lazaridis et al. 2014; but see Seguin-Orlando et al. 2014, for an alternative interpretation). While some fossil evidence has been used to propose an early late Pleistocene occupation of AMH in Indonesia and China (e.g. Storm et al. 2005; Westaway et al. 2007; Liu et al. 2010), most evidence suggests first modern human occupation of South East Asia between ~50-40 ka (Bowler et al. 2003; Barker et al. 2007; Higham et al. 2009; Demeter et al. 2012; Fu et al. 2013a).

Limitations

Our study is limited by several factors. Perhaps most importantly, it assumes that Holocene cranial phenotypic variation preserves a strong signal of ancient dispersal events rather than of more recent gene flow between populations. The observation that cranial phenotypic variance decreases as distance from Africa increases (Manica et al. 2007; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009), however, is not consistent with a significant influence of Holocene gene flow on the phenotypic structure of recent human populations. Not all available relevant early modern human specimens could be included in our palaeo-demes, due to their fragmentary preservation. The inclusion of less complete crania and other available skeletal elements from Middle-Late Pleistocene AMHs would help to more clearly assess the mode and tempo of the out-of-Africa modern human dispersal in future work. One or more of the AMH fossils included in our ancestral palaeo-demes may actually represent extinct lineages. Nonetheless, they likely closely resembled pene-contemporaneous ancestral populations. Finally, our fossil palaeo-deme samples, which date to ~160-80 ka (origins palaeo-deme) and ~37 ka (LPPD), constrain our ability to test alternative temporal frameworks for the out-of-Africa expansion. Our results indicate that multiple dispersal out of Africa occurred before ~37 ka and later than ~135-80 ka. Because of our sample composition, however, we are unable to further constrain the temporal frame of the dispersals, and cannot specifically consider the hypothesis that dispersal occurred between ~80-50 ka.

Our study also does not account for the effects that admixture between AMH and other hominins may have had on skeletal morphology. Such hybridization could potentially influence the structure of phenotypic variation in extant human groups, biasing our results. However, a large admixture effect is inconsistent with the observed pattern of decreasing

variance with increased distances from Africa (DeGiorgio et al. 2009), making it less likely that effects of admixture significantly influence our results. In addition, we take a conservative approach in assuming equal population sizes, but incorporating estimates of effective population size, inferred either from the archaeological record or calculated from genetic data, would refine P_{st} estimates (e.g. Reyes-Centeno et al., 2014). Finally, the objective of our study was to test competing out-of-Africa hypotheses derived from the literature, rather than to develop new models. Other dispersal scenarios, which were not considered here, are therefore possible.

CONCLUSIONS

Developing a coherent anthropogeny thesis and understanding the process of diversification of human populations from the late Middle Pleistocene up to the present requires a biogeographical approach, multidisciplinary lines of evidence, and a common evolutionary framework. In the absence of sufficient information, parsimonious models should be favored over models that are more complex. However, accumulating paleontological, archaeological, and genomics research may necessitate more complex scenarios for understanding the mode and tempo of the modern human expansion process out of Africa. There is growing recognition that some early modern human populations have little or no descendants today, while some extant populations partly derive from cryptic ancestors who have yet to be identified in the fossil record. In this study, we have used the largest modern human cranial dataset available in a quantitative genetics analytical framework. Our test for out-of-Africa models supports multiple dispersals from Africa and relatively sustained isolation of Australo-Melanesian populations. Although we are unable to refine the time-scales of those dispersals from our work, these dispersals took place between 37 and 135 ka. Ongoing research will serve to clarify how the out-of-Africa process has shaped the genetic and phenotypic diversity of extant populations.

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Appendix IV

"The global experiment of human evolution cannot be repeated in a laboratory. We must infer what happened from the one-time experimental results, fragmentary and scattered as they may be."

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Out of Africa and into Asia: Fossil and genetic evidence on modern human origins and dispersals

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ABSTRACT

Genetic and fossil evidence has accumulated in support of an African origin for modern humans. Despite this consensus, several questions remain with regard to the mode and tempo of dispersal out of the continent. Competing models contrast primarily by the number of dispersals, their geographic route, and the extent to which expanding modern humans interacted with other hominins. Central in this debate is whether Southeast Asia was occupied significantly earlier than Eurasia and, if so, whether the population ancestral to extant Southeast Asians and Australo-Melanesians was notably different from the ancestral population of extant Eurasians. Here, genetic and fossil evidence for the dispersal process out of Africa and into Asia is reviewed. A scenario that can resolve the current archaeological, genetic, and paleontological evidence is one which considers an initial expansion of anatomically modern humans into the Arabian Peninsula and the Levant during the terminal Middle Pleistocene, with continued exchange with Africans until the Late Pleistocene, when modern humans then dispersed into Australasia and Eurasia in two waves. Advances in population genomics and methods applying evolutionary theory to the fossil record will serve to further clarify modern human origins and the out-of-Africa process.

1. African origins of anatomically modern humans

Over the last decades, multidisciplinary lines of evidence have accumulated to support an African origin for anatomically modern humans (AMHs). Fossils recovered from East Africa are the first worldwide to exhibit a suite of modern anatomical traits akin to living and recent human populations. Exemplary fossils include the Middle Pleistocene Omo Kibish I (Butzer 1969; Day 1969; Leakey 1969) and the Herto BOU-VP-16/1 (Clark et al. 2003; White et al. 2003; McCarthy and Lucas 2014) specimens, both from Ethiopia. Cranial fragments from Aduma in the Middle Awash region of Ethiopia, dated to approximately 79-105 thousand years ago (~ka) (Haile-Selassie et al. 2004), suggest continuity of AMHs in East Africa into the Late Pleistocene. Prior to the discovery of the Middle Awash specimens and the radiometric dating of the Omo Kibish site (McDougall et al. 2005), early molecular genetic studies of mitochondrial DNA (mtDNA) also served to advance an African origins hypothesis (Brown 1980; Cann et al. 1987; Vigilant et al. 1991). Phylogenetically, mtDNA of extant individuals outside of Africa could be traced to deep-rooted African lineages. Broadly, these studies supported a common origin of extant human populations ~200 ka, in agreement with the paleontological evidence. Contemporaneously, craniometric studies, drawing from a long tradition of anthropometric research in anthropology, led to the similar proposal of a relatively recent, common origin for modern human populations (Howells 1973, 1989; Stringer and Andrews 1988; Stringer 1992). Subsequent molecular studies of the Y-chromosome corroborated this hypothesis (Thomson et al. 2000; Underhill et al. 2000) and analyses of nuclear DNA found that levels of intra-population diversity decreased as a function of geographic distance from Africa (Eller 1999; Harpending and Rogers 2000). This association was hypothesized to represent a demographic signal of the expansion process out of Africa, whereby expanding modern humans experienced “cascading bottlenecks” as they successively grew and spread across the world, iteratively founding new populations. Each founder population represented only a subset of the diversity from the former. More commonly referred to as the “serial founder effect” in subsequent studies, the negative relationship between intra-population diversity and geographic distance from Africa was confirmed with other genomic datasets (Prugnolle et al. 2005; Ramachandran et al. 2005; Liu et al. 2006; Li et al. 2008; Deshpande et al. 2009), as well as with dental and skeletal data (Manica et al. 2007; Hanihara 2008; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009; Betti et al. 2012) and even linguistic data (Atkinson 2011). Sub-Saharan Africa as a

hypothetical location of modern human origins has consistently been a better fit to the serial founder model, in line with the fossil record. Ongoing evidence from molecular and paleontological evidence is thus in broad agreement with an African origin for modern humans.

2. Out-of-Africa and into Asia: Genetic and fossil evidence

The dispersal process outside of Africa remains controversial, with different lines of evidence resulting in diverse and sometimes conflicting models for its mode and tempo. While most molecular genetic lines of evidence suggest that extant populations are descended from only one successful Late Pleistocene dispersal, archaeological and paleontological records lend support to an early Middle-Late Pleistocene expansion out of Africa (Klein 2000; Stringer 2000; Mellars 2006; Petraglia et al. 2010; Oppenheimer 2012a; Mellars et al. 2013). The fossil record inevitably suffers from sampling bias and the added uncertainty that some specimens may represent extinct lineages. On the other hand, the molecular genetic record has until recently been biased in sampling limited loci, with several assumptions of genomic evolutionary processes complicating historical inference. These lines of evidence are discussed in more detail below in order to place into context competing hypotheses of the modern human expansion process out of Africa and into Asia. Fig. 1 illustrates some of the key fossils discussed. The evidence from Southeast Asia and Australia is particularly important in assessing the mode and tempo of the out-of-Africa dispersal process, as some evidence of modern human occupation in this region appears to pre-date or be contemporaneous to the hypothetical single out-of-Africa event.

2.1 Fossil evidence

Outside of Africa, AMHs clearly inhabited the Levant region between 80-135 ka, as evidenced by the skeletal remains from the Qafzeh and Skhul sites (Vandermeersch 1981; Schwarcz et al. 1988; Grün and Stringer 1991; Grün et al. 2005). Indirect fossil evidence that could be associated to pene-contemporaneous AMHs in the region is the depletion of a giant clam species after ~125, as documented in the Gulf of Aqaba, attributed to systematic overharvesting (Richter et al. 2008). The lithic assemblages at Herto and Aduma (Clark et al. 2003; Yellen et al. 2005) have affinities to the later or pene-contemporaneous Red Sea assemblages at Asfet (Beyin 2013) and Abdur (Walter et al. 2000; Bruggemann et al. 2004;

Buffler et al. 2010) in Eritrea, as well as to those at Jubbah, Saudi Arabia (Petraglia et al. 2010) and Jebel Faya, United Arab Emirates (Armitage et al. 2011; Bretzke et al. 2013). Likewise, various "Nubian complex" lithic assemblages across the Arabian Peninsula exhibit affinities to their counterparts in Northeast Africa, dated to between ~128-74 ka (Rose et al. 2011). The late Nubian assemblage at Taramsa Hill, Egypt is associated with an AMH individual (Vermeersch et al. 1998). While affinities between these Middle Stone Age / Middle Paleolithic (MSA/MP) assemblages is complex—reflecting both common descent and local technological development (Groucutt and Petraglia 2012; Petraglia et al. 2012; Delagnes et al. 2013; Usik et al. 2013), it is reasonable to infer that the Arabian toolmakers were anatomically modern.

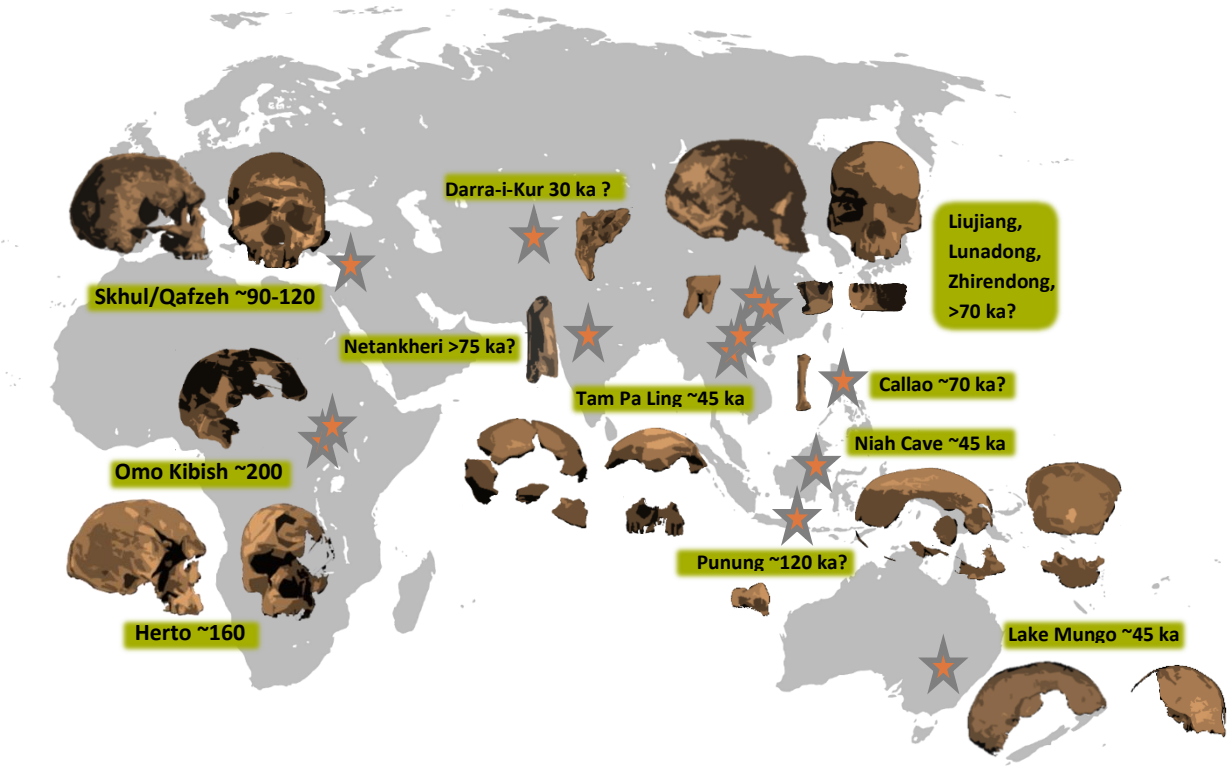

Figure 1. Anatomically modern human fossils from Africa, Asia, and Australia. Question marks indicate uncertainty in taxonomy, chronometric dating, or both. Drawings adapted from photographs in the following sources: (Liujiang: Woo 1959; Omo I: Day 1969; Darra-i-Kur: Angel 1972; Qafzeh 6: Vandermeersch 1981; Lake Mungo III: Thorne et al. 1999; Herto BOU-VP-16/1: White et al. 2003; Punung PU-198: Storm et al. 2005; Niah Cave "Deep Skull:" Barker et al. 2007; Zhirendong 3: Liu et al. 2010; Callao II-77-J3-7691: Mijares et al. 2010; Tam Pa Ling I: Demeter et al. 2012; Netankheri NTK-F-02-07: Sankhyan et al. 2012; Lunadong LN0030: Bae et al. 2014)

The continuity of AMHs in the Levant and the Arabian Peninsula after their Middle to early Late Pleistocene expansion is unclear. Neanderthals may have temporarily displaced the Qafzeh-Skhul population by ~65 ka, as suggested by the latter's presence in the nearby Amud and Kebara caves (Grün and Stringer 1991; Howell 1999; Klein 2009). The recently discovered calvaria from Manot Cave, Israel suggests that modern humans re-occupied the region by ~55 ka (Hershkovitz et al. 2015). Parsimoniously, this has implied two separate dispersal events from Africa. However, increasing paleoenvironmental data suggests that segments of the Arabian Peninsula remained habitable in the early Late Pleistocene (Parton et al. 2015; Parton et al., In Press), potentially playing a role in the movement of AMH populations and serving as refugia (Rose and Petraglia 2010). The Manot 1 specimen has various anatomical traits shared with later Upper Paleolithic specimens in Eurasia, as well as affinities to earlier AMHs from East Africa. At the same time, in overall neurocranial shape, its closest affinities are primarily to recent (Holocene) African individuals. The archaeological association of Manot 1 remains unclear, attributed to either the Middle or initial Upper Paleolithic assemblages found at the site.

Eastward of the Arabian Peninsula, the fossil record is sparse. The humerus fragment at Netankheri, India has been considered anatomically modern, dated stratigraphically to >75 ka, and associated with lithic remains that have both Middle and Upper Paleolithic characteristics (Sankhyan et al. 2012). Another MSA/MP assemblage in Jwalapuram, India also suggests precocious settlement by modern humans in the region (Petraglia et al. 2007; Clarkson et al. 2012). Although no human fossils have been recovered at this site, the Jwalapuram assemblage shows affinities to South African MSA toolkits associated with modern humans. Nevertheless, the taxonomic status of the lithic toolmakers is under strong scrutiny, with some scholars suggesting that the Jwalapuram industry could have been manufactured by Neanderthals or other Eurasian hominins (Mellars et al. 2013). The toolmakers of the lithic assemblages from Central Asia are likewise indeterminate, with sparse hominin remains that are sometimes taxonomically ambiguous (Glantz et al. 2008; Glantz 2011). Aside from the Netankheri humerus, anatomically modern specimens in the region are found substantially later. The temporal bone from the Darra-i-Kur cave in Afghanistan, associated with a MP assemblage, was discovered in a context dated to ~30 ka (Angel 1972; Dupree 1972). The fragmentary cranio-dental remains from the Fa Hien and

Batadomba caves in Sri Lanka date to between ~25-33 ka (Kennedy and Deraniyagala 1989; Kennedy 1999).

In continental Southeast Asia, the Tam Pa Ling specimen is the first clear example of AMHs in the region, derived from a geological context dated to ~46 ka (Demeter et al. 2012). The relatively complete cranium and partial skeleton of an AMH human from Liujiang, Southern China has been variably dated to between ~68-153ka or older (Woo 1959; Shen et al. 2002), with most scholars accepting the younger dates and additionally considering the possibility of interment from younger stratigraphic layers (Klein 2009; Oppenheimer 2012a). At the same time, the mandible from Zhirendong, China, retrieved from a context dated to >100ka (Jin et al. 2009; Liu et al. 2010), is considered anatomically modern. Several early Late Pleistocene hominin dental remains have been discovered across Southeast Asia, but their taxonomic attribution remains unresolved (Demeter et al. 2005; Bacon et al. 2015). Recently, the dental remains recovered at Luna Cave in Southern China, from a context dated to between ~70-126 ka, were attributed to AMHs (Bae et al. 2014). Other anatomically modern specimens from the region post-date Tam Pa Ling. For example, the cranio-dental fragments from Laibin, Southern China (Jia and Wu 1959; Shen et al. 2007) and the burials at Moh Khiew Cave, Thailand (Matsumura and Pookajorn 2005), derive from contexts dated to ~42 and ~26 ka, respectively.

In island Southeast Asia, the Niah Cave specimens are directly dated to between ~39-45 ka, with deeper archaeological layers suggesting a minimum time of occupation at ~45 ka (Barker et al. 2007; Higham et al. 2009). A hominin metatarsal fragment from Callao Cave, Philippines, from a context dated to ~67ka, appears to be at the margin of modern human morphological variation and may therefore represent another taxon (Mijares et al. 2010; Détroit et al. 2013). An isolated premolar discovered within the Indonesian Punung faunal assemblage, from a context dated to ~120 ka (Storm et al. 2005; Storm and de Vos 2006; Westaway et al. 2007), is considered anatomically modern. However, given the fact that the taxonomic and chronological association is based on a recent re-analysis from an early twentieth century discovery, most scholars consider the Punung assessment to be tentative (Barker et al. 2007; Oppenheimer 2012a; Bacon et al. 2015). Other modern specimens from a clear geological context post-date those found at Niah Cave. These include the specimens from Tabon Cave, Philippines, directly dated between ~16-31 ka (Dizon et al. 2002; Détroit et

al. 2004) and the material from Wajak, Indonesia recently re-dated to between ~28-37 ka (Storm et al. 2013).

The first anatomically modern fossil specimens from Australia are roughly contemporaneous to those at Niah Cave. The Lake Mungo III skeleton from Southeastern Australia is derived from a context dated to ~40 ka, with earlier occupation at the site implied by the presence of lithic artefacts retrieved from a lower layer dated to between ~46-50 ka (Bowler et al. 2003; Fitzsimmons et al. 2014). Sites from Southwestern and Northern Australia may precede this, suggesting human occupation between ~50-60 ka (Roberts et al. 1990; Roberts et al. 1994; Turney et al. 2001). These dates remain controversial and many scholars consider them to be tentative until further analysis (e.g. O'Connell and Allen 2015), but the most recent re-analysis of the Madjedbebe site in Northern Australia supports occupation of Australia before 50 ka (Clarkson et al. 2015). Further work is thus necessary to resolve this debate.

Overall, increasing evidence from the Levant and the Arabian Peninsula suggests that hominins inhabited the region as early as the terminal Middle Pleistocene and that AMHs were present either continuously throughout the Late Pleistocene or intermittently as a result of different expansions from Africa. Because the fossil record of South and Central Asia remains a large gap, further work in the region is necessary in order to determine the extent of AMH expansion and to identify what other hominins occupied the region. The fragmentary remains from Southern China, Callao, and Punung preliminarily suggest the former scenario, but their taxonomic status and dating must be resolved. Regardless of this possibility, the fossil evidence from Southeast Asia and Australia securely indicates modern human occupation in the region by ~50 ka, implying that any out-of-Africa scenario should predate this. Likewise, this region appears to have been occupied earlier than northern Eurasia because thus far modern human occupation in in Western Europe and Siberia is dated to ~45 ka (Benazzi et al. 2011; Fu et al. 2014).

2.2 Genetic evidence

As with early molecular genetic studies from the late twentieth century, contemporary studies of uni-parental loci (mitochondria and the non-recombining section of the Y-chromosome) continue to play a central role in inferring the time at which human ancestors lived and when lineages separated. Due to the fact that uni-parental loci can be traced

linearly, sampled individuals can be related to each other in a straight-forward, genealogical manner. Because genetic differences between any two individuals is associated to the number of mutations accumulated along their respective lineages since separation from a common ancestor, it is possible to estimate the time when these lineages diverged. The divergence of African haplogroups from those unique to non-Africans can be interpreted as estimates for the dispersal of modern humans out of Africa. Moreover, associating the geographical distribution of haplogroups relative to their time of divergence can aid in reconstructing human migrations (Underhill and Kivisild 2007). Such phylogeographic approaches have dominated interpretations of human origins and dispersal (e.g. Underhill et al. 2001; Macaulay et al. 2005; Endicott et al. 2009; Oppenheimer 2009, 2012a, b; Fernandes et al. 2012; Mellars et al. 2013). In most studies, interpretations parsimoniously assume a single exit out of Africa, with divergence estimates of Africans and non-Africans representing maximum dates (Fu et al. 2013; Green and Shapiro 2013). The inclusion of DNA retrieved from prehistoric specimens has added to the spatial and temporal resolution of these estimates (Fu et al. 2013; Rieux et al. 2014; Karmin et al. 2015). However, divergence dates have differed to a substantial degree because their calculations rely on parameters of mutation rate and generation times, among other assumptions. Some early uni-parental studies, for example, produced conflicting mtDNA dates that were substantially older than those derived from Y-chromosome data. Of these, some relied on fossil calibrations, such as the split of the chimpanzee and hominin lineage at 5 million years ago (e.g. Thomson et al. 2000) and others included archaeological calibrations (e.g. Stoneking et al. 1986; Cann et al. 1987). While these methods continue to be used (e.g. Xing et al. 2010b; Poznik et al. 2013), estimates of mutations accumulated in family pedigrees (Awadalla et al. 2010; Roach et al. 2010; Campbell et al. 2012; Helgason et al. 2015) and calibrations with ancient DNA of well-dated human fossils (Fu et al. 2013; Fu et al. 2014; Rieux et al. 2014; Karmin et al. 2015) have gained popularity in human evolutionary studies. The former are controversial because they suggests relatively slow mutation rates across the genome, imply early divergence of non-African populations, and pose the possibility of a premature dispersal from Africa, as early as the terminal Middle Pleistocene ~130 ka (Scally and Durbin 2012; Lippold et al. 2014). By contrast, relatively fast mutation rates, as those consistently observed for mitochondria, suggest a later divergence of non-Africans, implying a later dispersal out of Africa, between ~54–95 ka (Fu et al. 2013; Rieux et al. 2014). Irrespective of the mutation rate used, calendar year estimates

may also differ simply because of generation time assumptions. Since estimates of genetic divergence are retrieved as number of generations, these values must be multiplied by an estimate of intergenerational time in order to arrive at a calendar date. Intergenerational intervals have also been debated, in part because they differ across modern human populations and because it is unclear how they have changed across the hominoid evolutionary time scale (Tremblay and Vézina 2000; Fenner 2005; Langergraber et al. 2012).

Calibration with the full genome sequence of a Late Pleistocene modern human femur recovered at Ust'-Ishim, Russia has provided reasonable estimates for mutation rates over the last 45 thousand years, corresponding to the approximate time at which the Ust'-Ishim specimen inhabited Siberia (Fu et al. 2014). The estimates have reconciled differing mutation rates, revealing that mutations in mitochondria across this time period have been relatively fast, while those of the nucleus occur at a slower rate. This, unfortunately, continues to pose a problem when reconstructing the timing of migrations and divergence of populations. From a practical standpoint, sampling a limited number of genetic loci, such as mitochondira or the Y-chromosome, has been cost effective and essential in developing the methodological basis for molecular genetics research. From a theoretical outlook, however, there is reason to be cautious of inferences drawn solely from these loci. Due to the stochastic nature of genes, genealogies from a single locus do not necessarily provide a realistic representation of the history of populations (Underhill and Kivisild 2007; Balloux 2010; Wall and Slatkin 2012). For example, when considering migration, alleles from different populations may coalesce more recently than the time since the respective populations actually diverged (Rosenberg and Feldman 2002). Recent work comparing modern human Y-chromosome and mtDNA data has also revealed significant differences in the demographic history of populations, as inferred from these loci independently (Karmin et al. 2015). For these reasons, divergence dates for Africans and non-Africans derived exclusively from uni-parental data are more conservatively viewed as the time of last gene exchange between their ancestral populations, rather than a signal of an exclusive out-of-Africa event (Rieux et al. 2014; Karmin et al. 2015). It should perhaps not be surprising that different genomic regions evolve at different rates or that neither mutation rates nor generation times are stable across hominoid populations in an evolutionary timescale. Nonetheless, efforts to optimize an overall genomic mutation rate continue, with a value intermediate to the slow and fast rates most recently proposed for

recent humans (Lipson et al. 2015). The debate will likely persist until further calibrations with older fossil genomes are available.

In the interim, alternative approaches are advisable in order to circumvent the complexity associated with mutation rates and the molecular dating of key events in human evolution. Using the recombining regions of the nuclear genome (i.e. all chromosomes) for reconstructing migration patterns of modern human populations is methodologically more complex, as linear gene genealogies cannot be constructed in the same straight-forward manner as with uni-parental loci. Analysis of the non-random association of alleles at different genomic loci, a pattern known as linkage disequilibrium (LD), is one alternative for drawing inferences of the human past. In addition to the negative relationship between intra-population diversity and geographic distance from Africa, the serial founder model is further supported by the positive relationship between LD and geographic distances from Africa (Ramachandran et al. 2005; Jakobsson et al. 2008). LD can arise for a number of reasons, including mutations, genetic drift, natural selection, and admixture. The serial founder model suggests that the majority (~76-78%) of observed genetic variation in modern human populations is due to genetic drift (Ramachandran et al. 2005); by extension, LD patterns are primarily due to drift during human geographical expansion beyond Africa. Divergence time can be estimated from patterns of LD when assuming a rate of genetic recombination across the genome, in contrast to assumptions of the rate of mutation. In doing so, divergence time estimates of non-Africans are incompatible with a single out-of-Africa event because East Asian and Australo-Melanesian populations appear to have diverged earlier from Africans in comparison to other non-African populations (McEvoy et al. 2011; Reyes-Centeno et al. 2014). Evolutionary assumptions of LD are not trivial (Rogers 2014), but other methods that explicitly model ancestral relationships under recombination and mutation also suggest that a parsimonious divergence of African and non-African populations is incompatible with current genomic evidence (Li and Durbin 2011; Schiffels and Durbin 2014). Likewise, the sequence of a historical Australian genome suggests that the separation of this lineage was earlier relative to the other Eurasian populations, suggesting two major waves of migration into Eurasia and Australia (Rasmussen et al. 2011). Together, genome-wide approaches have served to revisit hypotheses of multiple dispersals from Africa, including the “southern route” hypothesis that implicates an early colonization of Southeast Asia and Australia.

3. A southern route to Southeast Asia

At a time when the dominant hypothesis was a single out-of-Africa event at ~50 ka (Stringer and Andrews 1988; Klein 2000), initial reports of modern human occupation in Australia prior to 50 ka (Roberts et al. 1990; Roberts et al. 1994; Thorne et al. 1999; Turney et al. 2001) forced scholars to reconsider the mode and tempo out of Africa. The hypothesis of multiple dispersals from Africa and a southern route into Asia was proposed in order to both accommodate the earlier Australian dates and to explain the morphological affinities of extant Australians with recent and fossil populations from Africa and the Levant (Mirazón Lahr and Foley 1994; Mirazón Lahr 1996). Likewise, the absence of Upper Paleolithic assemblages in the early Australian sites suggested affinities to MSA/MP toolkits (Foley and Mirazón Lahr 1997). As such, the model predicted an early, rapid dispersal along a coastal route, reaching Southeast Asia and Australia roughly by the time a second dispersal through the Levant prompted colonization of the rest of Eurasia between ~40-50ka. Isolated populations throughout Southeast Asia were hypothesized to retain the signal of the initial southern route dispersal, while others would be a palimpsest of this and the subsequent northern route dispersal. Hypothesized isolated populations included Australians, Melanesians, Papuans, Dravidian speakers of South Asia, and short-statured "Negrito" populations throughout Southeast Asia, such as the Andaman Islanders of the Bay of Bengal and the Aeta and Agta of the Philippines, from which the Negrito term is derived (Endicott 2013). A wealth of subsequent molecular genetic studies ensued under this hypothetical framework, lending consistent support for the southern route model (Underhill et al. 2001; Macaulay et al. 2005; Moodley et al. 2009; Reich et al. 2011; Fernandes et al. 2012; Pugach et al. 2013). However, the multiple out-of-Africa dispersals component was not well supported when testing it against alternative single dispersal scenarios, implying that Eurasian populations differentiated outside of Africa (Wollstein et al. 2010). Thus a reconciling model of single dispersal from Africa between ~60-80 ka following a coastal "beachcomber arc" into Asia has gained popularity (Oppenheimer 2009, 2012a, b).

In another interpretation, the Australian dates were accommodated by an early Middle-Late Pleistocene coastal dispersal of anatomically modern humans expanding with a MSA/MP toolkit (Stringer 2000). The hypothesis, rooted on the evidence from the site of Abdur, was later reinforced with the various lithic assemblages attributed to AMH toolmakers in the Red Sea area and the Arabian Peninsula. From a paleontological perspective, this model

also explained the morphological affinities of recent and fossil Australians to the Skhul-Qafzeh paleo-deme (Stringer 1992; Schillaci 2008) and to early AMHs (White et al. 2003; Gunz et al. 2009). Adding to this hypothesis was the possibility that AMHs expanded eastward of the Arabian Peninsula, reaching India prior to the Toba volcanic eruption ~75 ka and surviving the disruptive event (Petraglia et al. 2007). Fundamentally, the pace of the first dispersal changed to suggest a more gradual expansion rather than a rapid event.

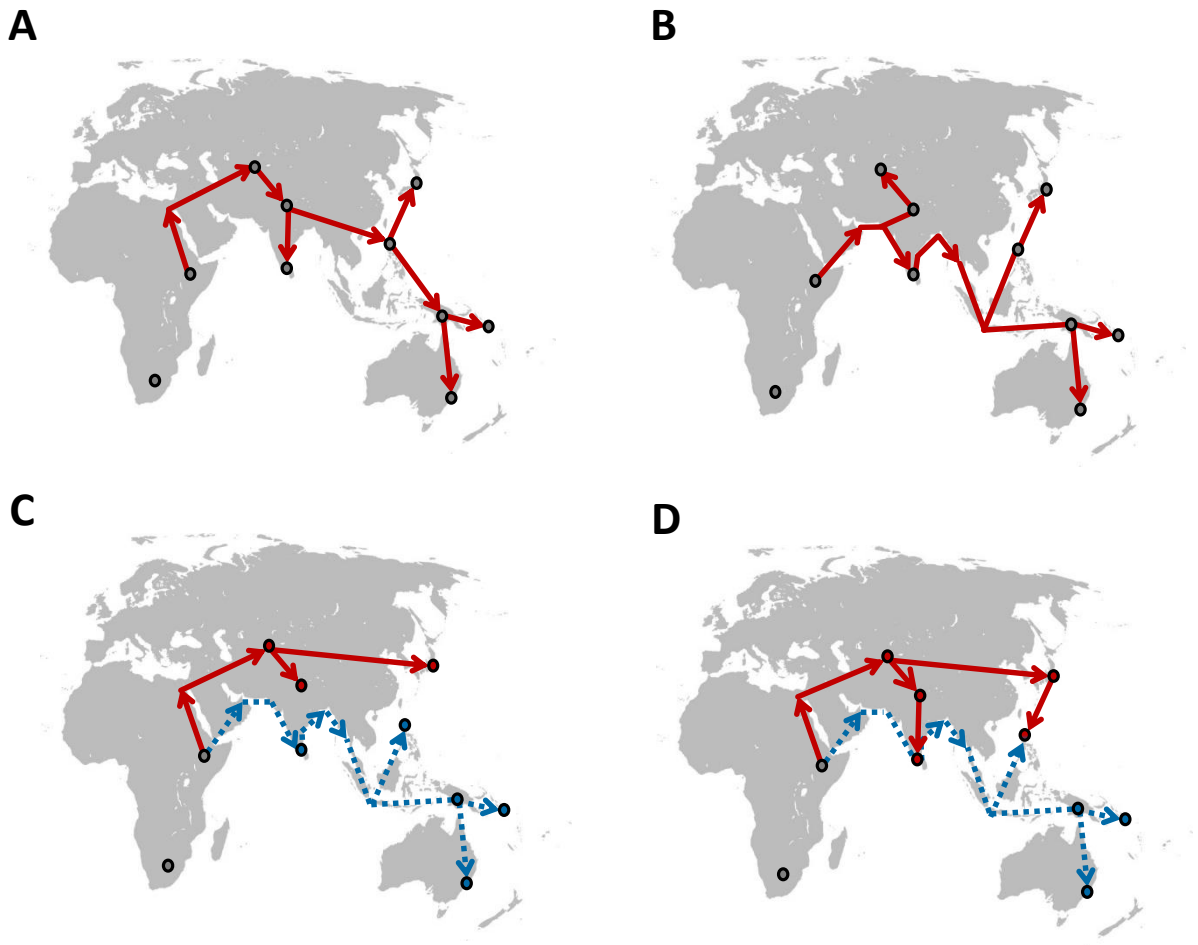

Figure 2. Schema of competing dispersal models. Models tested by Reyes-Centeno *et al.* (2014): (A) eastward expansion single dispersal; (B) "beachcomber" arc single dispersal; (C) multiple dispersals and a southern route; and (D) multiple dispersals and Austro-Melanesian isolation. Circles represent populations sampled; lines and arrows represent dispersal routes.

These competing models (Figure 2) have recently been revisited and tested using a spatially and temporally explicit framework in analyses integrating genomic and cranial phenotype data of extant and fossil populations (Ghirotto et al. 2011; Reyes-Centeno et al. 2014; Reyes-Centeno et al., Accepted). Together, these studies suggest that a model of separate dispersals from Africa is in better agreement with the sampled genomic and

morphological data. A gradual initial dispersal commencing within East Africa closer to the Middle-Late Pleistocene boundary 130 ka, with occupation of Australasia between 45-50 ka, has been assessed as a better fit (Figure 2d; Reyes-Centeno et al. 2014). As such, it is possible that the Qafzeh-Skhul paleo-deme was a surviving lineage, rather than a short-lived expansion of African ecosystems, as has often been suggested (e.g. Klein 2000). Likewise, Australo-Melanesians, which diverged earlier from African populations than other Eurasians, are considered relatively isolated from subsequent dispersal events, in agreement with other genomic studies (Rasmussen et al. 2011; Pugach et al. 2013). Because the Aeta and Agta Negrito populations from the Philippines have some affinities to Australo-Melanesians, they are hypothesized to be admixed descendants of both southern and northern route ancestors (Rasmussen et al. 2011; Reyes-Centeno et al. 2014). Likewise, some populations from India could retain signals of the southern route ancestry (Ghirotto et al. 2011) and, indeed, exhibit high levels of genomic diversity—comparable to levels found only in Africa (Xing et al. 2010a). A weak southern route signal in extant South Asian populations may be due to a history of rapid demographic growth and internal population replacements (Petraglia et al. 2010). If the possibilities of occupation in India ~75 ka or in Punung ~120 ka are considered, only the former scenario is plausible when testing these models with craniometric data of modern human populations (Table 1). However, a scenario in which India was occupied ~45 ka is in better agreement with both the genomic and cranial phenotype data (Table 1d), as previously reported (Reyes-Centeno et al. 2014).

Table 1. Dispersal models chronology test.

Dispersal Models[1]	Genetic Data[2]	Phenotype Data[2]
(A) Eastward Expansion	-0.146 (0.337)	0.176 (0.245)
(B) Beachcomber Arc	0.099 (0.524)	0.260 (0.098)
(C) Multiple Dispersals	0.038 (0.820)	0.237 (.029)
(D) Multiple Dispersals & Isolation	**0.335 (0.022)**	**0.463 (0.001)**
(E) Multiple Dispersals & Punung Occupation	0.228 (0.147)	0.178 (0.246)
(F) Multiple Dispersals & Jwalapuram Occupation	0.199 (0.191)	0.386 (0.010)

[1]A-D correspond to the models in Fig. 2. E: hypothetical occupation of Indonesia by anatomically modern humans (AMHs) by ~120 ka, as implied by the Punung premolar (Storm et al. 2005; Westaway et al. 2007). This scenario was modeled by assuming occupation of Melanesia and Australia by ~120 ka. F: hypothetical occupation of India by AMHs by ~75 ka, as implied by the Jwalapuram lithic assemblage (Petraglia et al. 2007).

[2]Results are correlation test of empirical inter-population genetic or phenotypic distances and hypothetical distances based on each dispersal chronology model. Values are Pearson correlation coefficient and permutation probability (in parenthesis). Bold type values indicate the best-supported model for each dataset. Methods and some results (a-d) are as reported in Reyes-Centeno *et al.* (2014).

Indeed, while an early Middle-Late Pleistocene dispersal scenario out-of-Africa is corroborated by some genomic, archaeological, and paleontological lines of evidence, the extent of this expansion eastward of the Arabian Peninsula or northward of the Levant is more contentious on genomic grounds. First, the amount of Neanderthal genetic material has been estimated to be the same in all non-African populations and to have introgressed at a single point in time and space, between 50-60 ka in the Middle East (Green et al. 2010; Fu et al. 2014). This suggests that all non-African populations split from Africans at a time post-dating introgression. It also implies that the divergence of Australo-Melanesians from Eurasians would post-date this event outside of Africa. However, both of these matters remain highly contested. Previously, the allegedly equal amount of Neanderthal genetic material across all non-African populations was taken to suggest a single dispersal out of Africa, even if it involved a southern route into Southeast Asia and Australia (Reich et al. 2011). Evidence has now accumulated to suggest that some non-African population have greater amount of Neanderthal genetic material than others, implying at least two separate admixture events (Currat and Excoffier 2011; Wall et al. 2013; Sigma Type 2 Diabetes Consortium 2014; Kim and Lohmueller 2015; Vernot and Akey 2015). Complicating matters, the time of introgression has been re-calculated with the intermediate mutation rate to between 35-49 ka (Lipson et al. 2015), and is otherwise seen as the last point of genic exchange between Neanderthals and modern humans rather than the only point of admixture (Sankararaman et al. 2012; Karmin et al. 2015). Perhaps more importantly, if the ancestors of Australo-Melanesians indeed made a steady, gradual migration into Southeast Asia, then their ancestral effective population size would either decline at an earlier time compared to other Eurasian populations or remain relatively stable. Current evidence, however, suggests that all non-African populations exhibit a similar decline in population size (Fu et al. 2014; Prüfer et al. 2014; Ilyas et al. 2015). Parsimoniously, this could imply that AMHs descended from a Middle-Late Pleistocene dispersal are extinct lineages, with no contribution to extant populations.

4. Reconciling the fossil and genetic lines of evidence

Accommodating the contribution of Middle-Late Pleistocene populations out of Africa into the lineages leading to extant human populations has resulted in complex evolutionary models. In one hypothesis, a gradual divergence model stipulates that the ancestors of African

and non-African populations maintained substantial gene exchange throughout the Middle-Late Pleistocene, possibly involving an intermediate population that included the lithic toolmakers of the Jwalapuram and Arabian Peninsula assemblages (Li and Durbin 2011; Scally and Durbin 2012; Schiffels and Durbin 2014). Under this scenario, the uni-parental evidence would reflect the last point of gene exchange between the ancestor of Africans and non-Africans, implying a long, drawn-out process of population divergence. In another hypothesis, a "delayed expansion" model proposes that the ancestral non-African population remained geographically restricted after the early Late Pleistocene divergence from African populations and prior to expansion into Eurasia (Xing et al. 2010a; Xing et al. 2010b). In this scenario, the intermediate non-African populations are thought to have resided in the Middle East and/or North Africa between ~40-88 ka. A delayed expansion model also appears to be compatible with recent Y-chromosome data, which reveals a large gap between the time when the African and non-African lineages diverged and when the latter differentiated (Karmin et al. 2015). Recently, the existence of a hypothetical basal Eurasian population was proposed in order to explain the variation of European populations spanning the Holocene (Lazaridis et al. 2014). This unsampled "ghost" population (Beerli 2004; Slatkin 2005) might be related to the Qafzeh/Skhul paleo-deme or the toolmakers of the Arabian Peninsula lithic assemblages (Lazaridis et al. 2014). A basal Eurasian population specifically attributed to known fossils or toolmakers remains more speculative, as adding more ancient genomes, such as those of Kostenki 14 and Ust'Ishim, invokes additional ghost populations and more complex scenarios (Haak et al., In Press). The above hypotheses are not necessarily mutually exclusive but further work is necessary to resolve them. While they are currently the best hypotheses reconciling the archaeological, paleontological, and genomic lines of evidence, none has explicitly incorporated data from Australo-Melanesian populations.

Figure 3a represents a plausible scenario compatible with the current archaeological, genetic, and paleontological lines of evidence, following scenarios described above. In such a model, the AMHs ancestral to non-Africans expanded into parts of the Arabian Peninsula and the Levant as early as the terminal Middle Pleistocene, perhaps in connection to deteriorating climatic conditions in East Africa (Scholz et al. 2007; Blome et al. 2012). Paleoclimate data from Africa suggests opportunities for dispersals via a northern route into the Levant broadly between ~140-75 ka and via a southern route into the southern Arabian Peninsula between ~145-115k and later between ~80-65 ka (Blome et al. 2012; Rohling et al. 2013). On the one

hand, interrupted opportunities of movement between the Red Sea might be most compatible with a delayed expansion model, where populations perhaps remained restricted to the Arabian Peninsula and the Levant. These populations then expanded in two waves, into Southeast Asia and Australia via a southern route and later into Eurasia, perhaps as competition with Neanderthals attenuated. Australo-Melanesians remained relatively isolated descendants of the first wave, while other populations are a palimpsest of the two. In this scenario, Southwest Asia plays a greater role in recent human evolution than is considered by most out-of-Africa models. At the same time, a gradual divergence model can be accommodated by continued gene flow along the northern route. Such a scenario skirts the evidence of AMHs east of the Arabian Peninsula prior to ~75 ka, considering these specimens extinct lineages, members of another hominin taxon, or minimally contributing to the ancestors of extant human populations.

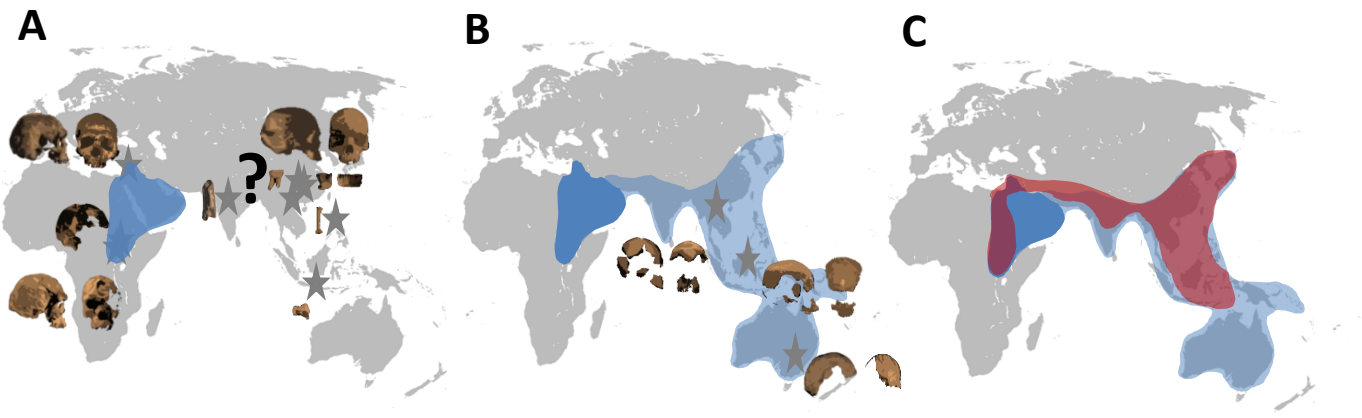

Figure 3. Schema of scenario reconciling current fossil and genomic evidence for the out-of-Africa process. First, (A) an early Middle-Late Pleistocene expansion of anatomically modern humans from East Africa and into the Levant and the Arabian Peninsula. Then, (B) modern humans expand into Southeast Asia along the southern route, reaching Australia ~50 ka. (C) A subsequent wave of dispersal along the northern route results in a palimpsest of populations across Southeast Asia, with Australo-Melanesians remaining relatively isolated.

In the original formulation of the southern route hypothesis (Mirazón Lahr and Foley 1994), passage from the horn of Africa into the southern Arabian Peninsula was preferential for the first dispersal because modern humans would have faced challenging desert conditions along the northern Levantine route between ~50-80 ka. However, if modern humans expanded earlier, the northern route could have also been used, as implied by the model described above (Fig. 3) and as might be suggested by the Qafzeh-Skhul paleo-deme. Previous studies (Ghirotto et al. 2011; Reyes-Centeno et al. 2014; Reyes-Centeno et al.,

Accepted) testing competing dispersal scenarios have modeled the southern route as a coastal dispersal along the Indian Ocean rim (Fig. 2), in keeping with a previous proposal of an Afro-Asian Middle Paleolithic expansion (Stringer 2000). Increasingly, the coastal component of the southern route is being amended to integrate riverine corridors (Field and Mirazón Lahr 2005; Field et al. 2007; Boivin et al. 2013). Therefore, the southern route model now hypothetically encompasses a broader geographical area that includes the Arabian Peninsula and the Levant, the space southeast of the Zagros and Himalayan mountain ranges, Southeast Asia, and Australasia. While the last decades have seen important progress in the amount of field work conducted in these regions, they remain a relatively large gap in the fossil record. Thus far, there is no clear evidence of Neanderthals or Denisovans occupying these regions in the Late Pleistocene, complicating our understanding of how modern humans may have interacted with these hominins during their expansion.

5. Modern human admixture with other hominins in Southeast Asia?

Current consensus indicates that as modern human populations expanded out of Africa, they interacted with other hominins, likely exchanging some level of genetic and cultural material. Some East Asian and Native American populations share a greater portion of genetic material with Neanderthals than other populations (Reich et al. 2010; Yang et al. 2012; Wall et al. 2013; Prüfer et al. 2014). Although it was previously hypothesized that demographic factors and natural selection could explain these differences (Sankararaman et al. 2014), it now appears that at least two admixture events between modern humans and Neanderthals must be invoked (Kim and Lohmueller 2015; Vernot and Akey 2015). Other scenarios are also possible, including continuous admixture events as modern humans dispersed into Eurasia (Currat and Excoffier 2011) or at least two admixture events with Neanderthals and with a related hominin following multiple dispersals into Asia (Weaver 2014). The latter view stems from the observation that populations throughout Southeast Asia and Australo-Melanesia share genetic material with a hominin of unknown taxonomy and related to the fossil discovered at Denisova Cave, Siberia (Reich et al. 2010; Reich et al. 2011; Skoglund and Jakobsson 2011; Meyer et al. 2012; Prüfer et al. 2014). Currently, Denisovans are known from a fossil molar, a phalanx, and the genomic profile of one individual (Reich et al. 2010). Initially, Denisovans were thought to occupy a wide home range spanning Siberia and Southeast Asia due to the fact that extant Australasian populations and

not extant Siberians share the most amount of DNA with them (Reich et al. 2011; Meyer et al. 2012). A single admixture event in Southeast Asia, as modern humans expanded along a southern route, was also hypothesized. Denisovans could have therefore inhabited island Southeast Asia, with admixture occurring beyond the Wallace line, east of Malaysia and Borneo (Cooper and Stringer 2013). However, because populations from continental Asia and the Americas also share a smaller proportion of genetic material with Denisovans (Skoglund and Jakobsson 2011; Huerta-Sánchez et al. 2014; Prüfer et al. 2014), multiple admixture events (Skoglund and Jakobsson 2011) or admixture within Eurasia (Huerta-Sánchez et al. 2014) has also been hypothesized, likely along the southern route (Rasmussen et al. 2011; Demeter et al. 2014). The higher amount of Denisovan DNA in Australasian populations east of the Wallace line could therefore be explained by their relative isolation: whereas they are descended from an initial dispersal event, continental Southeast Asians are a palimpsest of this and subsequent waves of expansion. Indeed, it has recently been proposed that Southeast Asian populations reflect the history of at least three major expansions spanning the Pleistocene and Holocene (Aghakhanian et al. 2015). Given the complexity of the competing admixture scenarios, the timing and location of introgression from Denisovans or other hominins into expanding modern humans remains unclear.

Uncertainty in the mechanisms of Denisovan introgression has also brought into question the degree of genetic material shared between extant Australo-Melanesians and other hominins (Rogers and Bohlender 2015). Estimates on the degree of this exchange is complicated by several factors and will likely change as more high quality genomic data of extant and extinct humans is generated. For example, while initial genomic estimates of Neanderthal material in non-African populations ranged from 1-4% (Green et al. 2010), values are now centered between this estimate (Prüfer et al. 2014), consistent with previous predictions of <2% (Currat and Excoffier 2011) and with the genomic patterns consequent of the serial founder effect (DeGiorgio et al. 2009). The degree of hominin genic exchange is particularly important for the hypothesis of multiple dispersals from Africa. Because estimates of population divergence can be inflated when hominin admixture is not taken into account, the separation of Africans and Australo-Melanesians could be roughly contemporaneous to the divergence of Africans and Eurasians (Alves et al. 2012). Simulation estimates accounting for hominin admixture (Alves et al. 2012), however, do not appear to sufficiently explain the LD-inferred divergence gap between Australo-Melanesians and

Eurasians from African populations. Another important parameter may be associated to population-specific mutation rates. Recently, the mutation rate in Australians was estimated to be higher than in other populations and may be attributed to the higher average age of fathers in this population (Lipson et al. 2015). This is because mutations in the germline occur at a greater rate in older fathers and are thus passed down to the next generation (Campbell et al. 2012; Kong et al. 2012; Helgason et al. 2015). Perhaps incorporating population-specific parameters of mutation rates and intergenerational times can serve to close this gap, but future work will serve to clarify this.

In keeping with the original proposal of the multiple dispersals and southern route model, it has been suggested that the genomic and morphological affinities of Australo-Melanesians to extinct hominins could also be a result of ancient population structure in Africa (Ghirotto et al. 2011; Lowery et al. 2013; Reyes-Centeno et al. 2014). Sustained population structure in Africa through the Late Pleistocene has been inferred from the human fossil record (Gunz et al. 2009), with the calvaria from Lukenya Hills, Kenya (KNM-LH 1: Tryon et al. 2015) and Iwo Eleru, Nigeria (Allsworth-Jones et al. 2010; Harvati et al. 2011) suggesting persistence of populations with plesiomorphic anatomy up to the terminal Pleistocene. Population structure is also invoked to explain some variation in Pleistocene lithic assemblages from North Africa (Scerri et al. 2014). Several genetic studies have suggested that long-term population structure is an unlikely scenario and cannot, by itself, explain genomic patterns of modern populations (Sankararaman et al. 2012; Yang et al. 2012; Wang et al. 2013; Prüfer et al. 2014) while others have shown that accounting for spatial structuring (Eriksson and Manica 2012, 2014) or considering a large ancestral populations in Africa (Blum and Jakobsson 2011) allows for this possibility. Nevertheless, what is clear is that African populations were already differentiated prior to dispersal out of Africa (Campbell and Tishkoff 2010). Understanding population structure within Africa is therefore critical because the genetic signals it leaves in extant populations can be erroneously interpreted as introgression from other hominins (Green et al. 2010; Blum and Jakobsson 2011; Eriksson and Manica 2012, 2014), particularly if the out-of-Africa event involved multiple dispersals by different populations.

Thus far, fossil evidence of Denisovans or Neanderthals along the southern route remains elusive. Candidate Denisovans in the fossil record include Narmada, Dali, Jinniushan, and Maba, as well as the more fragmentary remains from Xujiayao and Callao (Stringer 2012;

Cooper and Stringer 2013). Because these specimens span the Middle to Late Pleistocene, this hypothesis implies a long temporal range for the Denisovan lineage. From a morphological perspective, the fossil series discovered along the Solo River of Indonesia, including the Ngandong, Sambungmacan, and Ngawi specimens, have often been considered to show affinities to recent and fossil Australians and implied admixture between these lineages (e.g. Weidenreich 1943). However, while initial Late Pleistocene dates for these fossils suggested overlap between the Ngandong population and expanding modern humans (Yokoyama et al. 2008), more recent dates of the stratigraphic layers where these specimens were discovered suggest a much earlier Middle Pleistocene date (Indriati et al. 2011). Moreover, the Solo River fossil series does not show strong affinities to modern humans in overall cranial shape (Zeitoun et al. 2010). A complication in evaluating admixture from recent or fossil skeletons is that it remains unclear how skeletal phenotype changes after admixture events and how this phenotype may persist after several generations. Although primate hybrids might exhibit an intermediate overall morphology relative to the parental populations, more complex, unpredictable manifestations of phenotype might also be observed, particularly when genetic exchange is unbalanced between the different populations (Rogers Ackermann et al. 2006; Kelaita and Cortés-Ortiz 2013). The assimilation hypothesis in human paleontology (Smith et al. 1989; Smith et al. 2005) predicts that phenotypic changes would be significant enough to be detected in the skeletons of hybrid descendants, perhaps embedded in “anatomical details” (Smith et al. 2005, pp. 15) and non-metric traits (Rogers Ackermann et al. 2006; Rogers Ackermann 2010) rather than overall form. Ongoing research on hybridization in primate models (Rogers Ackermann et al. 2006; Rogers Ackermann 2010; Kelaita and Cortés-Ortiz 2013), as well as in admixed modern human populations from disparate geographical regions (Martínez-Abadías et al. 2006), will provide important insights into the patterns of morphological change after admixture events.

While it should not necessarily be surprising to find hominin hybrids in the fossil record, it remains to be seen how such individuals can be related to extant human populations. In other words, hominin hybrids may not have left descendants into future generations or be related to extant populations. In Pleistocene individuals, the presence of unusually long genetic sequence segments shared with Neanderthals has thus far provided the most robust evidence for admixture between modern humans and Neanderthals (Ust'Ishim: Fu et al. 2014; Kostenki 14: Seguin-Orlando et al. 2014). However, whereas the

Ust'Ishim individual is considered to represent an extinct lineage (Fu et al. 2014), Kostenki 14 is more likely ancestral to extant Europeans (Seguin-Orlando et al. 2014; Haak et al., In Press). Ancient DNA from Southeast Asian Pleistocene fossils is currently lacking and will be critical in evaluating potential hybridization events in the region. Proper interpretations of admixture and dispersal in Southeast Asia will require analogous efforts from the African evidence.

6. New perspectives and future directions

For the last 15 years, the serial founder model in human evolutionary genetics has served as the foundation for understanding the expansion of modern humans from Africa. Since its proposal, various nuanced scenarios compatible with the primary predictions of the serial founder effect have been explored. For example, simulations involving gene flow between the different modern human founder populations, as well as minimal admixture between modern humans and other hominins, could be included in explaining the patterns of extant population diversity and LD (DeGiorgio et al. 2009; Deshpande et al. 2009). Recently, simulations that emphasize recent admixture between populations rather than successive bottlenecks since the Pleistocene, have also been shown to produced patterns predicted by the serial founder model, perhaps in combination with natural selection and limited bottlenecks (Pickrell and Reich 2014). In essence, the role of admixture and natural selection are central to this new paradigm, in contrast to the role of genetic drift, although they obviously are not mutually exclusive. Indeed, a wealth of studies in human evolutionary genomics have now focused on the extent of admixture following population divergence, since historical and pre-historical gene flow between populations influences the structure of extant human populations. Classical approaches assuming linear branching models of biological evolution have increasingly been amended by methods that incorporate the possibility of gene flow between populations (e.g. Pickrell and Pritchard 2012).

A model of pervasive admixture has important implications for how anthropologists and geneticists use and interpret data from extant human populations. If recent admixture and natural selection play a central role, then extant human populations may be poor proxies for understanding the expansion of modern humans out of Africa (Pickrell and Reich 2014). In other words, populations in any geographic region today may not descend from those that first occupied that space. By this logic, however, extant African populations would also be poor proxies for ancestors of that continent and for the ancestors of non-Africans. As extant

African genomes are used to make inferences of recent human evolution, sequencing a genome derived from a specimen ancestral to all modern human populations would inevitably result in revisions to current models. Notably, Pleistocene genomes from Africa or the southern route geographical space are thus far not available. Ongoing technological and methodological developments may make this possible in the future, as ancient DNA is increasingly retrieved from unexpectedly early or environmentally challenging contexts (Dabney et al. 2013; Orlando et al. 2013; Meyer et al. 2014; Schroeder et al. 2015). Ancient DNA is certainly a promising avenue for clarifying currently conflicting models of human evolution (Wall and Slatkin 2012; Pickrell and Reich 2014). Nevertheless, including fossils with skeletal data of extant human populations will also continue to be important for developing a coherent theory of modern human origins and dispersal (e.g. Pinhasi and von Cramon-Taubadel 2009; Hubbe et al. 2010; Reyes-Centeno et al., Accepted). Comparative morphological approaches have been useful in paleoanthropology, but the discipline will excel further by continuing to develop methods founded in evolutionary theory, such as has been productively done in employing quantitative genetic approaches (Relethford 2007; Roseman and Weaver 2007; von Cramon-Taubadel 2014; Weaver 2014). For both human paleontology and genomics, population approaches (e.g. a paleo-deme (Howell 1999) framework on the one hand and paleopopulation genetics (Wall and Slatkin 2012) on the other) will be far more informative than data from single individuals and limited genetic or anatomical loci.

In understanding the dynamics of dispersal into Southeast Asia, future work should focus on disentangling the proportion of genomic material derived from other hominins and from different migration events throughout the Pleistocene and Holocene, including from the purported southern route ancestral population. Incorporating Australo-Melanesians is crucial for validating a southern route dispersal; as such, future studies should incorporate them and control for the genomic regions that they share with Denisovans. Perhaps most importantly, field work in Southeast Asia should intensify since this area is currently underrepresented in the fossil and archaeological records. Likewise, genomic studies of Denisovan introgression are likely to add more questions that will only be clarified with the paleontological and archaeological contexts. As more data becomes available, it should not be surprising that more complex scenarios will be necessary to explain the origin of modern humans and their worldwide colonization.

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Appendix V

"Organic evolution is not the only sort of evolution in the sense of a process of cumulative change. When a level of intelligence making symbolic speech possible was reached in an anthropoid line, a new evolutionary process emerged, enormously more rapid than organic evolution."

Sewall Wright (1950: 249)

Wright S. 1950. Genetical structure of populations. Nature 166(4215):247-249.

Tracking modern human population history from linguistic and cranial phenotype

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ABSTRACT

Languages and genes arguably follow parallel evolutionary trajectories, descending from a common source and subsequently differentiating. Despite agreement on tracing common ancestry within language families, it remains controversial whether individual languages can serve for this purpose. To address this question, we first evaluate the association between geographical and linguistic distances of vocabulary across 265 language families. We then assess the correlation between linguistic, geographic, and cranial distances among eleven populations from Africa, Asia, and Australia, taking advantage of the fact that population history is differentially reflected in human cranial anatomy. Whereas temporal bone shape reliably tracks deep population history and neutral genetic changes, facial shape is also strongly associated to environmental effects. Here, we show that linguistic variation strongly geographically patterned, even within widely dispersed groups. However, they are correlated predominantly with facial, rather than temporal bone, morphology. We therefore hypothesize that variation in vocabulary tracks relatively recent population history and may reflect factors other than common descent.

Early explorations on the association between languages and genes indicated that patterns of linguistic diversity paralleled those of genetic diversity. Most studies used pairwise distance measures of genetic and linguistic dissimilarity between populations in order to statistically compare the significance of their association (Derish and Sokal 1988; Sokal 1988; Sokal et al. 1988, 1989; Barbujani and Sokal 1990; Excoffier et al. 1991). Other work on the phylogenetic structure of genetic and linguistic data assessed similarities in the topology of generated trees (Cavalli-Sforza et al. 1988, 1992). In all, the general conclusion was that as modern human populations separated and became genetically differentiated, their languages followed a similar evolutionary trajectory. The call for a "new synthesis" (Renfrew 1991, 1992) was promptly issued, envisioning linguistic, genetic, and archaeological lines of evidence that would provide a coherent reconstruction of the human past. Contemporaneously, human paleontologists and geneticists advanced the hypothesis that extant modern human populations stem from a common ancestral population that inhabited Africa approximately 100-200 thousand years ago (~100-200 ka) (Cann et al. 1987; Stringer and Andrews 1988). Whereas the pioneering studies on the gene-language association tested hypotheses concerning the origins and dispersal of European peoples and languages within a historical time period (Sokal 1988; Sokal et al. 1988, 1989; Barbujani and Sokal 1990; Sokal et al. 1991, 1992), subsequent worldwide studies attempted to find an association into a pre-historical time depth. As with genes, it was hypothesized that languages spoken by extant African populations could hold traces of an ancestral "mother tongue," with Khoisan click languages (consisting of phonemes characterized by obstruent consonants) being the best candidates (Ruhlen 1991, 1994). Drawing from Darwin's idea of constructing a phylogeny of languages (Darwin 1859), the reasoning of this hypothesis was that if the evolutionary principle of common descent and modification could be applied to genes, then so, too, could it be drawn for languages. Here, we aim to revisit the question of how languages and inherited biological traits are associated, taking advantage of growing research showing that skeletal components of modern human crania differentially preserve population history. Thus, we seek to assess the association of cranial shape and language in order to understand to what extent language can be used to reconstruct population history.

For much of recent human evolution, genetic drift—changes that are due to stochastic rather than directed processes—is considered to be the primary mode by which hominin populations differentiated (Rogers Ackermann and Cheverud 2004; Weaver et al. 2007). In

modern humans, genetic diversity within populations has been found to decrease with increasing distances from Africa—a pattern that is attributed to a serial increase in genetic drift following an expansion out of the place of origin (Ramachandran et al. 2005). This pattern has also been observed for skeletal phenotype data (Manica et al. 2007; von Cramon-Taubadel and Lycett 2008; Betti et al. 2009, 2012, 2013) and, intriguingly, for phonemic language data (Atkinson 2011). The observed loss of phonemic diversity has suggested to some that language traits can be used to reconstruct deep population relationships. By this logic, the temporal depth of reconstruction would be at least as far back as the genetic divergence of Khoisan-speaking populations, ~40ka (Knight et al. 2003; Tishkoff et al. 2007), and possibly into the time of the common ancestral population (Atkinson 2011). However, most linguists view this possibility with great caution, in general favoring a more shallow, historical time depth due to the difficulty in distinguishing between common descent and other mechanisms, such as linguistic convergence, chance resemblances, word borrowing, and other non-stochastic processes (Comrie 2000).

Indeed, while genetic drift may be one of the primary evolutionary modes of differentiation in modern human populations, gene flow is an important factor that can act to reduce diversity among populations. Gene flow between populations increases their similarity via the exchange and mating of individuals. Similarly, active communication between speakers of different languages can lead to borrowing, ultimately making these languages appear more similar to each other. As such, it is not only the diversity within populations that must be examined, but also the diversity between populations. In addition to the negative correlation between intra-population diversity and increasing distances from Africa, a serial founder model also predicts a positive association between inter-population difference (biological distance) and geographical separation (geographical distance) (Ramachandran et al. 2005). Geographical distance is one of the main factors limiting gene flow, as populations close to each other are more likely to meet and exchange genes in comparison to populations far from each other. Furthermore, land-based geographical distances are more highly correlated with genetic distances—a result that considers oceans as barriers of movement and that is attributed to a model of the primary modes of dispersal from the African birthplace and into other parts of the world (Ramachandran et al. 2005). A positive, statistically significant relationship between land-based geographical distances and biological distances is consistently observed for genetic and skeletal data (Ramachandran et

al. 2005; Betti et al. 2010). Such a relationship is also expected among languages and dialects from the same language family (i.e. a group of languages whose common descent has been demonstrated conclusively by historical linguists). A recent study showing significant correlation between geographic distances and linguistic distances among language family categories (Belle and Barbujani 2007) relied on Ruhlen's controversial classification of linguistic phyla (Ruhlen 1991) rather than on raw variables of linguistic characteristics, such as phonemes, lexical similarity, or grammar. The question of whether vocabulary lists contain historical information beyond the limits of established language families, therefore, remains controversial.

Over the last decade, important progress has independently been made in both historical linguistics and skeletal shape analysis. In the latter case, advances have allowed for better quantification of variation between populations and species, proving useful in the assessment of phylogenetic affinities of previously contentious taxonomic categories (e.g. Harvati et al. 2004; Harvati and Weaver 2006b). Importantly, with the use of these methods, consensus has emerged on the differential preservation of population history in modern human cranial shape (Harvati and Weaver 2006a, b; Smith 2009; von Cramon-Taubadel 2009a, b, 2011; Reyes-Centeno et al. 2013; Smith et al. 2013). Whereas the temporal bone has consistently shown a significant correlation with neutral genetic markers, the facial region of the cranium shows a weaker correlation. In some studies (Harvati and Weaver 2006a, b; von Cramon-Taubadel 2009b, 2011), the neurocranium also shows a significant correlation with neutral genetic markers, but one that is weaker than that observed for the temporal bone. Moreover, the temporal bone is thought to reflect population affinities at a deep temporal scale while the neurocranium reflects more recent associations between populations (Harvati and Weaver 2006a, b). Thus, from a theoretical standpoint, cranial phenotypic data offers a unique way of calibrating to what extent language can track population history. Indeed, language can be considered an "extended phenotype" (Dawkins 1982), which, like the skeleton, is under influence of both heritable and non-heritable factors.

In historical linguistics, phylogenetic methods from computational biology are now widely used in testing competing models of the prehistoric origins and spread of languages within a language family (Gray and Jordan 2000; Gray and Atkinson 2003; Gray et al. 2009; Bouckaert et al. 2012). Comparisons of vocabulary lists across languages also suggest that deep historical signals can be detected (Pagel et al. 2013). These approaches are highly labor

intensive, require expert classification, and are currently available for only a handful of language families. However, using an exceptionally large database of vocabulary data covering about two thirds of extant worldwide languages (Wichmann et al. 2013), it has recently been shown that automated phylogenetic inference based on phonetic distances between words is in excellent agreement with expert classification (Jäger 2013). This automated approach may therefore allow for an accurate reconstruction of population history. Since genetic and skeletal phenotypic distances between populations are significantly correlated with geographical distances, a significant correlation between language and geography implies a linguistic spatial patterning that may be consistent with a serial founder model. In turn, correlation of linguistic distances to cranial phenotype distances can serve to infer the extent to which vocabulary data reflects population history.

RESULTS

Our first analysis quantified the association between geographical distances, *G*, and linguistic distance of *N*=265 language families, *F*. Using Mantel tests, we found the association to be significant ($p<0.0001$), irrespective of whether direct or land-based *G* were used (respectively, $r=0.292$ and $r=0.276$). Thus, geography explains ~8% of variance between language families worldwide. In order to relate this finding to a biological dataset, we sampled cranial shape data from eleven populations from Africa, Asia, and Australia (Fig. 1; Table 1). We computed the distances between their languages (*L*) and, in turn, evaluated their association with *G* and with biological distances. For *L,* we used the automated method following Jäger (2013; detailed in Materials and Methods section) and found that geography explains up to ~16% of variation ($r=0.402$, $p=0.003$ with land-based *G*). For biological distance, we calculated phenotypic distances (P_{st}) using cranial shape data. The P_{st} measure is analogous to the genetic distance measure F_{st}, acknowledging the effect that non-heritable factors may have on skeletal phenotypic variation (Roseman and Weaver 2007; Leinonen et al. 2013). Following Harvati and Weaver (2006a, b), we partitioned our cranial dataset into three component parts: the temporal bone, the face, and the neurocranium.

Figure 1. Populations used in study. Map showing geographic epicenter of cranial population samples (circles). Details of sample size, geographic locality, and ethnolinguistic affinities are in Table 1.

Table 1. Population Samples

Populations		**Subpopulations**	**Lat.**	**Long.**	***N* Crania**
AU	Australia	Australian	-33.89	151.24	26
CA	Central Asia	Uyghur, Dungan, Kalmyk, Tarantchi	43.29	68.26	30
EA	East Africa	Amhara, Karo, Habesha, Bouma, Glaba, Turkana, Igai, Koukou, Afar-Danakil, Nyangatom, Pouma	9.02	38.74	22
JP	Japan	Japanese	35.66	139.82	33
ME	Melanesia	Solomon & Vanuatu Islanders	-9.42	159.94	17
NC	New Caledonia	Kanala, Bouloupari, Gomen, Tuauru, Bonde, Ny, Kanala	-22.28	166.46	26
NE	Philippines	Aeta, Agta	14.6	120.98	19
NG	Papua New Guinea	Papua New Guinea, Torres Strait Islanders	-9.48	147.19	23
NI	North India	Bengali	28.63	77.2	15
SA	South Africa	Xhosa, Khoi, Nama, San, Sotho, Malabar, Zulu, Tswana	-26.2	28.05	20
SI	South India	Maravar, Tamil	6.93	79.86	34

Since the temporal bone is the better correlated to neutral genetic variation than other cranial regions, P_{st} values derived from it should correlate with *L* to a greater degree when vocabulary distances indeed parallel neutral genetic distances. Instead, we found that the face is most correlated to *L* (**Table 1**). The temporal bone, by contrast, had a substantially lower correlation. Indeed, a Dow-Cheverud test underscores the fact that facial shape is more strongly correlated to linguistic distances than either the neurocranium or the temporal bone (**Table 2**). At the same time, the neurocranium is not more strongly correlated to *L* than the temporal bone.

Table 1. Correlation of phenotypic and linguistic distances[1]

Distance measure	**Linguistic distance (*L*)**
Face P_{st}	$r = 0.545$, $p < 0.0001$
Neurocranium P_{st}	$r = 0.483$; $p = 0.0003$
Temporal bone P_{st}	$r = 0.324$; $p = 0.013$

[1] Correlation *r* is Spearman coefficient value. Significance *p* value (two-tailed) is after 10,000 permutations.

Table 2. Dow Cheverud tests[1]

Cranial Region	Face	Neurocranium	Temporal
Face			
Neurocranium	***r* = 0.287, *p* = 0.028**		
Temporal bone	***r* = 0.363, *p* = 0.009**	$r = 0.196$, $p = 0.158$	

[1]Positive *r* values indicate that the cranial segment listed in the column is more strongly correlated with language than the cranial segment listed in the row and vice versa for negative *r* values. Significance *p* value (two-tailed) is after 10,000 permutations. Bold type indicates significance at α=0.05.

In order to factor out the effect that geography has on both linguistic and phenotypic variation, we conducted a partial Mantel test between phenotypic, P_{st}, and linguistic distances, *L*, conditioned on land-based geographical distances, *G*. In doing so, the face remained the most highly correlated cranial segment (Table 3). Results for the neurocranium were similar, although they cannot be considered significant after Bonferroni correction. Partial correlation results for the temporal bone were non-significant.

Table 3. Partial correlation of phenotypic and linguistic distances, controlling for geography[1]

Distance measure	**Linguistic distance (*L*)**
Face P_{ST}	***r* = 0.395, *p* = 0.002**
Neurocranium P_{st}	$r = 0.329$; $p = 0.017$
Temporal bone P_{st}	$r = 0.127$; $p = 0.357$

[1]Correlation *r* is Spearman coefficient value. Significance *p* value (two-tailed) is after 10,000 permutations. Control for geography, *G*, is based land-based distances. Bold type indicates significance after Bonferroni correction (α=0.017).

DISCUSSION

The significant association we found between *G* and *F* is consistent with previous studies. The fact that our results were comparable to those reported by Belle and Barbujani (2007) also serves to validate the automated method for generating linguistics distances employed in this study. The positive association between geography and the two thirds of extant world languages represented by our dataset suggest a spatial patterning of vocabulary. The correlation between *G* and *L* for the eleven sampled populations was also significant, to an appreciably larger degree than the correlation between *G* and *F* when using land-based *G*. At face value, this suggests that the vocabulary of individual languages is more strongly geographically structured than the aggregate vocabulary of language families. However, this finding may be specific to our dataset, which sampled a substantial number of island populations where language structuring could be associated to ocean barriers. Thus, further work is necessary to clarify this pattern at global and regional levels.

While we found that the correlation between *L* and P_{st} was significant for all cranial segments examined, it was clear that the face has the strongest correlation to language. These are surprising results since a strong correlation between *L* and temporal bone P_{st} is expected if vocabulary and genetic diversity follow a parallel evolutionary trajectory that is primarily consequent of common descent. Previously, vocabulary data from well-studied language families, including Indo-European (Gray and Atkinson 2003; Bouckaert et al. 2012) and Austronesian (Gray and Jordan 2000; Gray et al. 2009), have been used for testing competing language dispersal scenarios, spanning a time depth into the early Holocene, ~9 ka. These results are in agreement with many archaeological and genetic lines of evidence for population dispersals. Comparisons of vocabulary lists across Eurasian languages have more recently attempted to extend this limit to the Pleistocene, as far back as ~14.5 ka (Pagel et al. 2013). It has previously been suggested that the temporal bone reflects population history since the divergence of African and Eurasian populations (Harvati and Weaver 2006b), which could be as early as the terminal Middle Pleistocene (Reyes-Centeno et al. 2014). Since we do not find a strong association between *L* and temporal bone P_{st}, our results do not support the use of vocabulary data to effectively reconstruct the human past as far back as the last common ancestor in Africa, as previously hypothesized for phonemes (Atkinson 2011). Our results, which derive from vocabulary data spanning three continents, thus suggest that

finding clear gene-language associations at a substantially greater spatial and temporal time depth may be elusive. Nevertheless, *L*'s spatial patterning, as well as its association with some aspects of cranial phenotype, suggests that vocabulary data retains a certain level of information regarding recent population history. Future work, particularly with advancements in dating techniques using linguistic data, may provide a better estimate for the temporal limits of vocabulary as a tool for reconstructing population history.

Beyond neutral evolutionary processes, it is necessary to consider other mechanisms that could have generated the observed pattern of vocabulary diversity present in today's languages. Early studies on the association of cranial segments and neutral genetic markers suggested that such differential correlations could reflect differences in skeletal development (Harvati and Weaver 2006a, b). Whereas the basicranium develops early in life, with some components almost fully formed in utero, other regions form later in life and are subject to epigenetic effects (Dahm et al. 1993; Nemzek et al. 1996; Hill 2011). Therefore, it was hypothesized that the cranium evolves at differential rate, with changes accumulating faster or slower in some parts compared to others. By this logic, the temporal bone would evolve at a slow rate and reflect deeper associations between populations while other parts of the cranium would evolve faster and reflect more recent population history. This evolutionary-developmental hypothesis has been tested recently for the temporal bone, where a significant correlation with neutral genetic markers exists beginning at an early ontogenetic stage and across populations (Smith et al. 2013). Differences in the evolutionary rate of change are also relevant for language since most linguists consider vocabulary to change in a highly dynamic manner (Comrie 2000). Within the framework of the evolutionary-developmental hypothesis and in the absence of selection, the language-face association might therefore be attributed to faster rates of change.

The rate of change of vocabularies is estimated to be between 3-4 times faster in comparison to changes in their grammar (Dyen et al. 1992). Although grammar data is not currently available for the populations we sampled, Colonna and colleagues (2010) have found a strong association between neutral genetic data and grammar data for a sample of ten populations across Europe, Africa, and Western Asia. Interestingly, they found a higher correlation between grammar and microsatellite sequences than between grammar and single nucleotide polymorphisms (SNPs). Microsatellites are DNA sequences containing short, tandemly repeated sequences (STRs) while SNPs are variants of a single base (substitution

mutations, insertions, or deletions). STRs evolve at a faster rate than SNPs such that changes in the STR genetic system occur more frequently than in the SNPs system. Thus, as previously hypothesized (Barbujani 1997; Belle and Barbujani 2007), the results from Colonna and colleagues (2010) suggest that grammatical rate of change is more comparable to the rate of change in microsatellites than in other genetic systems. A similar interpretation can be made here for cranial phenotype data where the discordance of cranial and linguistic phenotypic distances may be the result of different rates of evolutionary change. Other interpretations could relate to how both language and facial morphology are associated to a common, non-stochastic processes, such as climate. Indeed, climate variables have been found to also correlated with facial shape (Harvati and Weaver 2006a, b). In order to refine our interpretations, future work will require sampling populations for which environmental data is available, as well as both SNP and STR data.

Having already made substantial progress since the modern evolutionary synthesis (Huxley 1942) of the mid-twentieth century, the new synthesis (Renfrew 1991, 1992) at the end of the twentieth century aimed to create a general evolutionary framework (Wright 1950) for the diversification of languages and cultures. Incorporating this aspect of phenotype as part of the natural history of human populations is therefore an essential component of human evolutionary biology. Our study adds to the goals of the new synthesis by emphasizing the ability of incorporating a line of evidence—skeletal phenotype—shaped by both heritable and non-heritable factors, serving to calibrate the associations observed between genes and languages alone. Our study also outlines productive areas of future research within this multidisciplinary research program.

MATERIALS & METHODS

Cranial Phenotype data. Our data collection procedure follows the work by Harvati and Weaver (2006a, b). Sampled crania are from the Holocene modern human ethnographic and archaeological collections housed at the Musée de l'Homme, National Museum of Natural History (Paris, France). Crania were selected on the basis of adult ontogeny and the absence of bone pathology, balancing population samples by sex to the extent possible, for a total of *N*=265 (Table 1). For each specimen, a total of thirty-two anatomical landmarks—in the form of 3D coordinates—were collected by H.R.-C. using a MicroScribe G2X desktop digitizer.

Landmark measurement error was tested by digitizing a specimen ten times across the span of a week. Error ranged from 0.183-2.175 millimeters (mm) or 0.147-4.892%. In the few cases where cranial conservation precluded data collection, missing landmarks were estimated by reflected relabeling of the bilateral homologue (Mardia et al. 2000) using the Morpheus software (Slice 1994–1999). Specimens with missing data along the midline were not included. A generalized Procrustes analysis (GPA) was used to superimpose the raw coordinate data using the MorphoJ v1.05 software (Klingenberg 2011). Following GPA, three datasets were generated, represented the neurocranial (8 landmarks), facial (13 landmarks), and temporal bone (13 landmarks) segments of the cranium. Separating the dataset after GPA has the effect of considering the location of each segment relative to the others, ensuring the retention of positional information. We performed a principal component analysis (PCA) in order to determine which PC scores to use for calculating P_{st}. Currently, no consensus exists on the number of PC variables that should be included for arriving at population distances. Therefore, we chose a systematic, three-step "stopping rule" (Jackson 1993) approach to statistically assess which PCs to include. First, we performed 10000 bootstrap replicates on the shape variable data of each cranium. Second, the bootstrapped components were re-ordered and reversed in order to increase correspondence with the original, empirical axes (Peres-Neto et al. 2003). Third, we compared the 95% confidence interval of the bootstrapped eigenvalues with those expected under a random, hypothetical model (Jackson 1993). At this point, our stopping rule was to include the PCs before the first point in which the 95% eigenvalue confidence interval was below the hypothetical trendline generated from the random model. The PC selection procedure was carried out in PAST v2.17b (Hammer et al. 2001). We note that our PC selection method conforms to the common practice of excluding PCs that explain less than 1% of variance, as these components explain less of the variance than the original shape variables. Lastly, this PC selection approach is consistent with previous work showing that the number of PCs explaining a majority of variation is positively associated with the complexity of the cranial element, rather than the number of landmarks or total shape variables (von Cramon-Taubadel 2009a, 2011). Respectively for the face, neurocranium, and temporal bone, the approximate amount of cumulative variance (i.e. eigenvalue percent) explained by the selected PCs was 70%, 88%, and 89%. Finally, we used the selected PCs to calculate P_{st} using the RMET 5.0 software (Relethford et al. 1997). We followed the conservative approach of assuming that all populations had proportionally equal

demographic histories, i.e. population sizes. Because estimates of heritability differ and may be population specific (Carson 2006; Martínez-Abadías et al. 2009), we chose an approximation of heritability h^2=0.3 in all calculations. We note that while population size and heritability estimates affect absolute P_{st} values, all pairwise P_{st} changes are proportional and would therefore not affect subsequent matrix correlation analyses.

Language data. Linguistic distances (*L*) were computed from the Automated Similarity Judgment Program (ASJP) database (Wichmann et al. 2013). ASJP is organized into doculects, which are coherently documented language varieties that may include different variants of the same language. For example, doculects sampled for our Japanese population included varieties of Japanese spoken in Tokyo as well as that spoken in Kyoto. ASJP is a collection of core vocabulary lists from over 6,000 doculects, covering about two third of the world's extant languages. This database is confined to phonetic transcriptions and does not contain expert cognacy judgments. It has previously been shown that phylogenetic inference based on phonetic distances between ASJP word lists is in excellent agreement with expert classifications (Jäger 2013). The ASJP word list consists of words for 40 core concepts represented in each doculect. They are verbalized in all modern human languages, express the same meaning across languages, resistant to meaning changes or borrowing, and largely independent of culture (Holman et al. 2008). As such, distances derived from these can be considered neutral distances, making them comparable to distances derived from neutral genetic markers or their skeletal phenotypic correlates.

Distances between word lists were computed following the two-step procedure detailed by Jäger (2013). In the first step, similarity scores between individual words are determined using the Needleman-Wunsch algorithm (Needleman and Wunsch 1970) and empirically estimated weights. For example, the English, German, and Spanish words for "hand" (respectively, hand, Hand, and mano) are transcribed in the ASJP database as *hEnd*, *hant*, and *mano*. To estimate the similarity between the German word with the English and the Spanish word, the sound strings are pairwise aligned: *hEnd-hant* and *hEnd-mano*. This alignment corresponds to the Needleman-Wunsch algorithm (Needleman and Wunsch 1970), which is a bioinformatical standard method for aligning molecular sequences. Each pair of sounds is assigned a weight corresponding to the log-odds probability of the sounds being historically related versus the probability of being matched by chance (Jäger 2013). In the

German-English and German-Spanish example, both word pairs exhibit two matches and two mismatches. However, the mismatches (a-E and d-t) in the pair hant-hEnd reflect common sound changes while the mismatches (h-m and t-o) in hant-mano do not. This asymmetry is captured by the sum of the weights of the aligned sounds corresponding to the two alignments. For hant-hEnd, this sum is 4.80 while for hand-mano it is -11.85, so the former pair is a much better candidate for reflecting common descent than the latter. In the second step, the similarity between two doculects is quantified as the degree to which the distribution of string similarities between synonymous word pairs exceeds the distribution of string similarities between non-synonymous pairs. The distance between two doculects is defined as a linear function of the similarity with negative coefficient that has 0 and 1 as theoretical minimum and maximum, respectively. This is therefore comparable to the minimum and maximum values of F_{st} values in population genetics.

Some ethnographic records were available for the cranial collections, but in most cases the languages spoken by the individuals could not be uniquely identified. ASJP contains meta-data for each doculect, such as geographic location and expert classifications. We chose a group of candidate doculects from the ASJP database for each population, using a combination of three heuristics. First, subpopulation information consisting of ethnic affiliation was used to narrow down the space of candidate languages. For instance, the South India population is specified as Tamil; hence Tamil is the only candidate doculect for it. Second, if the population was from islands (e.g. Japan, Melanesia, New Caledonia), only doculects from these islands were considered. Third, whenever no more specific information was available, the candidate doculects were those ASJP doculects whose geographic coordinates (according to the ASJP meta-data) are situated within a distance of at most 500 km from the population in question. In all, linguistic distance (*L*) between population pairs was calculated as the arithmetic mean of all linguistic distances between candidate doculects assigned to each population. Similarly, distances between two language families (*F*) were computed as the arithmetic mean of all linguistic distances between sampled doculets. We followed the classification of languages into families according to the World Atlas of Language Structure (WALS) (Dryer and Haspelmath 2013). This classification is fairly inclusive, assuming several large families such as Altaic or Australian.

Geographic data. We computed direct geodesic distances (*G*) between populations, as well as land-based *G* following previous studies (e.g. Ramachandran et al. 2005; Atkinson 2011). In the latter, paths between locations on different continents were constrained to pass through key waypoints, namely Cairo (31 E, 30 N) linking Africa and Asia and Phnom Penh (105 E, 11.5 N) linking Asia and Australia. This approach considers oceans as barriers and, more broadly, represents a parsimonious model of human dispersal routes between continents. Calculations were made in the geopy Python package, which assumes a spherical terrestrial shape and a radius of ~6,373 km.

Correlation tests. Statistical significance of the association between any two matrices is evaluated against a null distribution by the Mantel test (Mantel 1967). Simple Mantel tests were used to assess the correlation between linguistic (*L* or *F*) and cranial phenotype (P_{st}) distances, as well as between these and geography (*G*). We used partial Mantel tests (Smouse et al. 1986) to evaluate the association of *L* and P_{st} when controlling for *G*. We applied a Bonferroni correction in order to account for multiple P_{st} comparisons (α=0.17), i.e. the different cranial segments. Correlations between distance matrices were computed as Spearman's rank correlation coefficients, as the dependencies between linguistic distances and both cranial phenotype and geographical distances are non-linear. In order to assess the whether the P_{st} values of a given cranial segment was statistically correlated more with *L* than the P_{st} values of another cranial segment, we applied the Dow-Cheverud test (Dow and Cheverud 1985). In all cases, two tailed *p*-values were determined with 10,000 permutations. We cross-checked Mantel results using the XLSTAT v2014.4.02 commercial software and the ecodist R package (Goslee and Urban 2007), reporting here those derived from the former.

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PUBLICATIONS

2014 **Reyes-Centeno H**, Ghirotto S, Détroit F, Grimaud-Hervé D, Barbujani G, and Harvati K. Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. *Proceedings of the National Academy of Sciences USA* 111(20):7248-7253.

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Conference Reports

2015 **Reyes-Centeno H**, Mentzer SM, and Kandel AW. Fourth annual meeting of the European Society for the study of Human Evolution. *Evolutionary Anthropology: Issues, News, and Reviews* 24(1):1-2.

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