Hybridization in human evolution: insights from other organisms

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Abstract

During the late Pleistocene, isolated lineages of hominins exchanged genes thus influencing genomic variation in humans in both the past and present. However, the dynamics of this genetic exchange and associated phenotypic consequences through time remain poorly understood. Gene exchange across divergent lineages can result in myriad outcomes arising from these dynamics and the environmental conditions under which it occurs. Here we draw from our collective research across various organisms, illustrating some of the ways in which gene exchange can structure genomic/phenotypic diversity within/among species. We present a range of examples relevant to questions about the evolution of hominins. These examples are not meant to be exhaustive, but rather illustrative of the diverse evolutionary causes/consequences of hybridization, highlighting potential drivers of human evolution in the context of hybridization including: influences on adaptive evolution, climate change, developmental systems, sex-differences in behavior, Haldane's rule and the large X-effect, and transgressive phenotypic variation.

1 A shifting paradigm: Introgressive hybridization and human evolution

Traditionally, the evolution of hominins – humans and our closest relatives since we collectively diverged from our common ancestor with chimpanzees/bonobos – has been represented in two distinct ways. One depicts evolutionary relationships among purported hominin species as a tree describing ancestor-descendant relationships, with evolutionary relatedness depicted by branches that split as one travels upward from the trunk to the leaves, ending in extinction for all those branches not leading to our leaf. Within this set of phylogenetic models lies "out of Africa with replacement" accounts of recent human evolution.[1] The out of Africa with replacement models propose that the entirety of the recent non-African components of individuals' ancestry (before world empires and colonialism) traces its origins back to Africa sometime between 50 to 100 thousand years ago (ka). As such, non-African human variation in the recent past is a subset of variation that was present in humans in Middle Pleistocene Africa. Under this view, the recent (pre-colonial) genetic variation was initially established by founder effects associated with modern human populations moving out of Africa, and then influenced by recurring gene flow within and among the various regions of the world over tens of millennia. It posits further that these early modern populations did not interbreed with resident groups of archaic humans such as Neanderthals, and that differentiation between them was generated by mutation, drift and natural selection acting in more or less independently evolving lineages.

In contrast, multiregional continuity evolutionary models emphasize sustained gene flow, as opposed to replacement and extinction. In the case of recent human evolution, this includes sustained gene flow across the entirety of the human inhabited world at all points throughout the Pleistocene and into the present day.[2] The neutral component of the

1 multiregional model came to be identified as isolation by distance.[3-5] Under isolation by

2 distance, the local reduction of genomic variation by random genetic drift is counteracted by

3 the addition of new variation to local groups via gene flow. Left unperturbed by major

4 evolutionary events such as range expansions and local replacement of populations, this

5 balance between gene flow and random genetic drift leads to an equilibrium between within

6 group and among group genetic variation. In this treatment, adaptation to regional

7 conditions by natural selection leads to more pronounced differences among groups. A key

8 distinguishing factor between the multiregional continuity model of recent human evolution

9 and the out of Africa with replacement model is that the former postulates that *Homo sapiens*

10 populations outside of Africa became established far earlier (~1 million years ago (Ma) or

11 more) than the latter model (~100ka or less).

12   These two models have occupied the extreme ends of a continuum of possible

13 accounts of recent human evolution. Other models of recent human evolution combined

14 features of both renditions and allowed for a combination of long periods of isolation

15 interrupted by bouts of gene flow between groups.[6,7] These models were often subsumed

16 under the general multiregional view in the 1990s and 2000s,[8] although sometimes Bräuer's

17 model (Afro European *sapiens* hypothesis) was lumped together with out of Africa.[9]

18   A striking realization in the last decade is that neither of the scenarios at the extreme

19 poles of this continuum is in fact supported by new genetic and genomic evidence.[10-15] Clear

20 evidence for reticulation among diverged lineages/populations (Neanderthals, Denisovans,

21 *H. sapiens*) falsifies the predictions of branching phylogenetic models without reticulation,

22 while evidence for periods of substantial isolation among these same groups is inconsistent

23 with the multiregional continuity model. Further studies of the phenotypic consequences of

24 hybridization across taxa[16-22] have shown that admixture of different lineages may have

1   provided genetic variation that was then favored by natural selection to drive evolutionary

2   innovation in our hominin ancestors, and perhaps contributed to bursts of exceptional

3   phenotypic diversification, not only in our recent past (e.g., emergence of *Homo sapiens*[23]), but

4   also deeper in time.

5   This shifting narrative is perhaps unsurprising when considered in a broader context.

6   For some time we have known that hybridization, resulting in gene flow and subsequent

7   introgression, together with natural selection and drift, plays an important role in speciation

8   and the evolution of diversity in animal taxa.[24-27] Recent research validates the work of earlier

9   evolutionary biologists (e.g., Anderson [28]; Anderson & Stebbins[29]), who emphasized the

10 significance of introgressive hybridization, and the phenotypic variation it can produce, to

11 adaptive evolution and biodiversification (e.g., 'divergence-with-gene-flow'[30]). Evolutionary

12 biologists are now moving past the question of whether lineages can diverge while

13 undergoing gene exchange with other lineages, towards investigating how such exchange

14 affects the interacting groups of organisms (Figure 1).[31] Hybridization can also play a role in

15 extinction.[32] There are many examples of morphologically distinct species whose

16 representation in the fossil record seems to wane or cease over time. In such cases, some

17 genetic characteristics of a lineage may continue even when anatomical morphs disappear, as

18 is arguably the case in recent human evolution.

19   Here we draw from studies of key organisms, chosen for their potential as models

20 for considering processes relevant to human evolution. We use these examples to argue four

21 points germane to understanding the relevance and potential influence of hybridization and

22 introgression in human evolution.

23

1. The human genome shows ample signs of introgression via hybridization, which is also not unusual in other organisms, including amphibians, birds, and myriad terrestrial mammals, including primates.

2. As informative as the human genome has been, it is insufficient to answer questions about the entire span of human evolution. Phenotypic approaches are needed, as are genomic data from other extant and extinct groups for comparison and context.

3. Developing phenotypic approaches to hybridization requires a better understanding of the relationships of genes, development, and phenotype for which experimental and comparative approaches are necessary.

4. Introgressive hybridization is especially relevant to the evolution of humans and other organisms because it provides an important source of genetic variation on which natural selection may act.

Demonstrating the accuracy of these points establishes both the occurrence and theoretical importance of hybridization and introgression. Our goal is not merely to highlight means for identifying hybridization in human evolution, but to provide examples that will point the way towards an exciting new set of approaches and questions, encouraging exploration of a wide range of models for understanding the potential dynamics of genetic exchange in shaping the evolutionary trajectories of our ancestors.

2 The human genome shows extensive evidence of introgression that is comparable to what is known in many other organisms

2.1 Introgression in human evolution

New genetic and genomic evidence for introgression in human evolution establish that hybridization and introgression contributed to shaping genomic variation.[10-15] If there is

1   a history of repeated hybridization and introgression, then the "species tree" itself may

2   become reticulate. These new results show that networks or braided streams,[23] as opposed to

3   trees, are a more useful way of depicting species and population relationships as inferred

4   from molecular genetic data,[33] thus invalidating division of our fossil ancestors into strictly

5   discrete units or species (at least biologically, although such division may be heuristically

6   useful). Splitting and subsequent contact and mixture of lineages is a part of human

7   evolution that cannot be ignored.

8   Recent human evolutionary genomic and genetic studies (reviewed by Smith and

9   colleagues[34]) point to a complex picture of lineage divergence and re-merging. Most of the

10   genetic studies providing evidence for introgression have focused on the contact between

11   lineages in Eurasia in the Late Pleistocene. These lineages diverged recently, over the course

12   of the past one million years or so, and repeated signatures of past hybridization events have

13   been demonstrated among them (Figure 2). The most recent estimates indicate that ancient

14   *Homo sapiens* and Neanderthals diverged from each other 520-630ka while the divergence of

15   Neanderthals and Denisovans has been dated to 390-440ka.[13] The current genetic evidence

16   for gene exchange includes movement from these ancient *H. sapiens* into Neanderthals ca.

17   100ka, and from Neanderthals into ancient *H. sapiens* ca. 50ka.[35] Gene flow between ancient

18   *H. sapiens* and Denisovans has also been demonstrated, as represented in the genomes of

19   recent Asians and Australasians/Melanesians[14,15,36], which harbor Denisovan ancestry.

20   Recently, the genome of a first generation descendent of a Neanderthal mother and a

21   Denisovan father living ca. 90ka was reported.[37] That study, along with previous analyses,

22   also demonstrates ongoing gene flow from Neanderthals into Denisovans.[14,37] There is also

23   possible evidence that the Denisovans may have acquired genes from an ancient hominin

24   that diverged from the ancestor of humans more than a million years ago.[14] Other studies

1 provide evidence for gene flow between ancient and recent lineages within Africa and for a

2 recent influx of Neanderthal genes by way of Eurasian back migration into at least East

3 Africa within the last 4,000 years.[38,39]

4   More than simply establishing that gene flow took place, genomic studies also

5 contribute insight into the dynamics of genetic exchange across populations during times of

6 hybridization and introgression, and their effects on people living today. For example,

7 current evidence indicates a 1.8-2.6% genomic contribution from Neanderthals to living

8 Eurasians,[13] and 3-6% from Denisovans to living Melanesians.[14] It is estimated that ~20% of

9 the Neanderthal genome is represented in the combined genomes of living human

10 populations, although only 2% is typically found in any particular non-African person.[40]

11

12 2.2 Hybridization in non-primate mammals

13   A look toward large bodied terrestrial mammals shows that humans are not an

14 outlier when it comes to hybridization (see also Table 1). Hybridization and introgression are

15 common in many groups, including between distantly-related species, and these systems can

16 provide referential models for human hybridization. Large canids, for example, can disperse

17 over long distances, and hence individuals can encounter both divergent conspecific

18 populations and related species as well as variation in habitat. Ancient *H. sapiens* similarly

19 dispersed throughout the six inhabited continents, coming into contact with other hominin

20 taxa across a broad spectrum of ecological settings in Eurasia and Africa. Like hominin

21 ancestors, many wolf-like canids have only recently diverged, and hence have not evolved

22 strong reproductive isolating mechanisms, resulting in a high prevalence of hybridization.

23 Examples include admixture between the gray wolf (*Canis lupus*) and coyote (*C. latrans*), that

24 have only diverged in the last ~50ka[41]; the domestic dog (*C. familaris*) and the gray wolf,

1   which diverged about 25ka[42] (see review in Freedman and Wayne[43]; Thalmann et al.[44]); as

2   well as between gray wolves and even more divergent species, such as the golden wolf (*C.*

3   *anthus*) and golden jackals (*C. aureus*; Freedman and Wayne[43]; Koepfli et al.[45]). In fact, the

4   amount of gray wolf introgression into these two taxa is strikingly similar to that seen

5   between Neanderthals and *H. sapiens*.

6   Similarly, a number of recent studies suggest that admixture between bear species is

7   widespread.[46] There is evidence for gene introgression from extinct cave bears (*Ursus spelaeus*

8   complex) into living brown bears (*Ursus arctos*), as well as some gene flow from brown bears

9   into cave bears.[47] Although cave bears have been extinct for 25,000 years, modern brown

10   bears still have between 0.9% and 2.4% of cave bear DNA remaining in their genomes. This

11   is comparable to what is seen with Neanderthals and *H. sapiens*. Significant admixture has

12   been well-established between polar bears (*Ursus maritimus*) and brown bears,[48-51] which form

13   the sister clade to cave bears. These species diverged some 479–343ka.[50] However, brown

14   bears from several populations carry mitochondrial DNA (mtDNA) haplotypes that are

15   more closely related to polar bear haplotypes than to other brown bear haplotypes.[49,52] The

16   very recent common ancestry of the mitochondria carried by these bears, as recent as 37–

17   10ka in some cases, suggests a history of admixture between these species.[49] The extant

18   brown bears that have the closest mitochondrial relationship with polar bears live on

19   Admiralty, Baranof and Chichagof (ABC) Islands in southeast Alaska.[49,52] Likewise, ABC

20   Islands brown bears show evidence of polar bear ancestry in their nuclear genomes, which

21   include at least 6-9% genetic material of polar bear origin.[48] MtDNA evidence suggests that

22   another, now extinct, admixed population of brown bears lived in Ireland around the time of

23   the Last Glacial Maximum.[49] The distribution of polar bear ancestry within the ABC Islands

1   brown bears' genomes is best explained by a maternal polar bear origin of the population

2   with substantial male brown bear immigration.[48]

3   This evidence suggests that in the past the ABC Islands populations had a much

4   higher frequency of polar bear derived alleles than it does today.[48] This alternative,

5   population conversion, or "nuclear swamping", model of admixture envisions a much

6   greater impact on the genetic diversity of populations experiencing admixture than the

7   classic model of low frequency admixture. Preliminary analyses of the Irish brown bears'

8   nuclear genomes suggest that a similar phenomenon may have taken place in those

9   populations.[53] For closely related species that rarely come into contact because of their

10   different ecological requirements, disruptive climatic events may temporarily create the

11   opportunity for admixture that substantially exceeds the amount observed in more stable

12   conditions. Again, this scenario is relevant to hominin evolution, and especially Late

13   Pleistocene Europe, where climatic fluctuations would have affected ranges of ancient

14   hominins, and potentially both the prevalence and intensity of contact.

15

16   2.3 Hybridization and introgression in non-human primates

17   Among non-human primates (NHPs), mammals often used as models for human

18   ancestors due to their close phylogenetic relatedness, hybridization has been most

19   extensively studied in baboons. The six recognized baboon species have parapatric ranges

20   with contact between neighboring species. Since natural hybridization has been recorded

21   between the most morphologically distinct (chacmas, *Papio ursinus* vs. Kinda baboons, *P.*

22   *kindae*), the most behaviorally different (hamadryas, *P. hamadryas* vs. olive, *P. anubis*) and two

23   of the most phylogenetically distant (olive vs. yellow, *P. cynocephalus*) species, it is likely that

24   hybridization occurs at all the geographic regions where baboon ranges are in contact.[54] The

best-known examples of ongoing hybridization in baboons are from hybrid-zones between

hamadryas and olive baboons in Awash National Park, Ethiopia,[55,56] and between olive and

yellow baboons in Kenya.[57,58] The earliest studies were confined to morphological and

behavioral traits, and showed, at least in the case of the hamadryas-olive hybrids, that

species-characteristic behaviors (such as the male hamadryas' herding, a behavior that is not

expressed by olive baboons) most likely have a genetic basis. Hybrid males show an outer

appearance (e.g., coat color and pattern) and behavior that is intermediate between the two

parental species.[56,59-61]

       Baboon hybrid zones are a manifestation of a long-standing evolutionary process.

Results of whole genome analyses of all six *Papio* species reveal a history of population

differentiation and genetic divergence among lineages that includes multiple episodes of gene

flow (admixture or introgression) among distinct lineages (phylogenetic species) and the

presence of ghost lineages.[62] Like the genus *Homo*, baboons are the products of a radiation

that began in non-forest, tropical Africa around two million years ago. Along with the rest of

the fauna of tropical Africa (e.g., Dolotovskaya et al.[63]; Grubb[64]; Kingdon[65]), they have been

subject to climatic fluctuations and geological events that caused repeated fragmentation and

reconnection of populations, producing successive intervals of genetic divergence due to

geographical isolation and secondary contact with admixture. The ecological and habitat

parallels make them a prime analog for hominin evolution.[21,23,66] They are especially relevant

for early African savanna-adapted hominins with possibly similar patterns of range

expansion and contraction, population isolation, secondary contact and admixture.

       Recent genetic work has revealed a complex history of natural gene flow among

baboon species lineages, and even between *Papio* and another, closely-related but distinct

genus, *Rungwecebus* (the kipunji). It suggests that we entertain the possibility of similar

1 episodes in human history, with gene flow not only among Pleistocene species of *Homo*, but

2 also, at an earlier time, between emerging *Homo* populations and other hominins, such as

3 *Paranthropus*, that were morphologically and adaptively distinct. Phylogeographic analyses

4 (mostly mitochondrial-based) show that in baboons the distribution of mitochondrial

5 haplogroups is not reciprocally monophyletic among phenotypic lineages, and geographic

6 co-occurrence with phenotypic characters that define species is weak. For example,

7 northern chacma baboons carry mitochondrial haplotypes that are closely related to those of

8 southern yellow baboons, northern yellow baboons carry mitochondrial haplotypes related

9 to those of hamadryas baboons, and ancient mitochondrial lineages exist within western

10 olive baboons, most likely derived from baboon populations that no longer exist.[67,68] These

11 incongruences between mitochondrial haplogroup and external phenotypes (and the species

12 they define) suggest past episodes of gene flow among diverging baboon lineages.[69-71]

13 Mitochondrial-nuclear discordance might result from "mitochondrial capture" or "nuclear

14 swamping".[70,72,73] These examples are relevant to hominin evolution; for example, genetic

15 affinities between mitochondrial and autosomal DNA are discordant, with closer

16 mitochondrial DNA relationships between Neandertals and modern humans, and closer

17 autosomal relationships between Neandertals and Denisovans.[15]

18   South American *Callithrix* marmosets (Figure 3) also demonstrate extensive

19 hybridization between subspecies and species, in variable environments and with different

20 levels of reproductive isolation, therefore making them an additional comparative primate

21 model for considering hominin hybridization. Speciation of current *Callithrix* marmosets

22 began approximately 3.7Ma, with the most recent divergence event taking place less than

23 1Ma between *C. jacchus* and *C. penicillata*.[74,75] Experimental interspecific crosses revealed

24 different levels of reproductive isolation between different species pairs, as captive *C. jacchus*

1   x *C. penicillata* hybridized with relative ease, but physical anomalies such as blindness were

2   common when other species pairs were crossed.[76-78] The genus originated in the humid

3   Atlantic Forest biome of southeast Brazil and migrated north to also occur in Brazil's

4   savannah- and desert-like semi-arid biomes,[79] with the six *Callithrix* species settling into

5   allopatric distributions[80] and hybridizing naturally at distribution borders under secondary

6   contact.[81] Genetic and phenotypic accounts of natural *Callithrix* hybridization exist between

7   four different *Callithrix* species pairings occurring along river barriers and in areas of

8   ecological transition.[81-84] Relationships among *Callithrix* genomes are better represented by

9   reticulating species trees as opposed to bifurcating ones, with divergence occurring under a

10 scenario of speciation with gene flow.[81] Thus, marmoset speciation also serves as a

11 referential model of the splitting, subsequent contact and admixture of closely related

12 lineages, a dynamic that was also important for recent human evolution.

13   Anthropogenic hybridization as a result of the illegal pet trade introduced *Callithrix*

14 species from northern and central Brazil, particularly *C. jacchus* and *C. penicillata*, into other

15 regions of the country and created artificial secondary contact with other exotic and native

16 *Callithrix* populations (e.g., Malukiewicz et al.[81]; Malukiewicz et al.[82]; Mendes[83]; Passamani et

17 al.[84]). Although illegal and undesirable from a conservation biology perspective, the artificial

18 introduction of marmoset into the ranges of existing species may provide unique insights

19 into the effects of demographic differences in the hybridization process of ancient hominins,

20 especially those that involved long-range (and possibly rapid) movements of hominin groups

21 into occupied territories, including the geographic radiation of Neanderthals into Asia (and

22 probably North Africa) and the movement of ancient *H. sapiens* both within and out of

23 Africa. Moreover, anthropogenic *Callithrix* hybridization may also be particularly useful for

24 considering shifts in demographic and genomic composition of admixed populations whose

1   parental taxa are closely related but display different degrees of relatedness (as in

2   Neanderthals, Denisovans, and *H. sapiens*). For example, hybridization between more

3   divergent species (e.g., *C. aurita* x *C. jacchus*; *C. aurita* x *C. penicillata*) often results in mixed

4   social groups where individuals possess both hybrid and parental phenotypes.[85,86] In both

5   cases, male *C. aurita* hybrids (with ancestry from *C. penicillata* or *C. jacchus*) tend to possess the

6   Y chromosome of the former[85,87] and mtDNA of the latter,[85] suggesting that some hybrid

7   allele combinations may be less favorable. In contrast, hybrid swarms, or highly variable

8   populations, whose genomes consist of products of subsequent segregation and

9   recombination, backcrossing, and crossing between the hybrids, are common among more

10   closely related *Callithrix* species (*C. jacchus, C. penicillata, C. geoffroyi,* and *C. kuhlii*) hybridizing

11   under artificial secondary contact.[81] Overall, anthropogenic movement of *C. jacchus* and *C.*

12   *penicillata* is driving them to dominate modern *Callithrix* hybridization - and in some cases

13   possibly causing genetic swamping of (if not only introgression into) other marmoset

14   populations. Further study of this process could provide some insight into the dynamics of

15   hominin dispersal(s) out of Africa.

16   Natural hybridization has also been genetically confirmed among more divergent

17   primate species pairs. In particular, the study of a hybrid zone between two howler monkey

18   species (*Alouatta pigra* x *A. palliata*)[88,89] has provided interesting parallels to the observed

19   outcomes of hybridization between Neanderthals and *H. sapiens*. Despite the much deeper

20   divergence (~3Ma)[90] between the parental howler monkey species than between *H. sapiens*

21   and now-extinct congeners, in both cases there is evidence of reduced or null introgression

22   of sex chromosomes. In particular, studies that mapped Neanderthal[91] and Denisovan[92]

23   ancestry in modern human genomes found reduced ancestry of these species' alleles on the

24   *H. sapiens* X chromosome. This pattern has been observed among other organisms that

1   hybridize and is referred to as the "large X-effect",[93] for which the prevailing hypothesis is

2   that the X chromosome is enriched for genes associated with reproductive barriers (e.g.,

3   hybrid sterility or inviability)[94] and therefore does not introgress during hybridization.

4   Analyses of introgression of autosomal (microsatellite) and X chromosome markers in the

5   howler monkey hybrid zone show that the X chromosome has reduced introgression when

6   compared to the autosomes.[95] Thus, despite differences in divergence, studying the

7   mechanisms that are responsible for this pattern in howler monkeys may allow us to

8   contribute to the understanding of possible scenarios that led to the observed reduction of

9   Neanderthal and Denisovan ancestry on the X chromosome in the genome of our own

10   lineage.[91]

11   With regards to the Y chromosome, analyses of 91 admixed males in the howler

12   monkey hybrid zone showed a pattern consistent with a lack of introgression of *SRY* gene

13   variants that are diagnostic for each species.[95] This pattern contrasts with the observed bi-

14   directional introgression of mtDNA haplotypes (exclusively transmitted by the mother).

15   Together these patterns are consistent with Haldane's rule, where hybrids of the

16   heterogametic sex (XY males in this case) are often inviable or infertile.[96] If males from the

17   first (F1) generation were fertile, we would expect that Y chromosome variants would be

18   passed through backcrossing to later generation hybrids in a similar fashion as the mtDNA.

19   Similarly, Mendez et al.[97] analyzed and compared Neanderthal Y chromosome sequence data

20   to those of humans and chimpanzees and found no evidence of Neanderthal Y chromosome

21   haplotypes in modern humans. The authors speculate that this may be a consequence of

22   hybrid incompatibilities. However, the ancient nature of this admixture coupled with the

23   extinction of Neanderthals makes it difficult to directly test this hypothesis. Thus, the

24   current study of the patterns of introgression in the howler monkey hybrid zone may add to

1   our understanding of the general mechanisms that led to the lack of Y chromosome

2   introgression, a topic that is also of great interest in the study of speciation genetics.

3   Comparative analyses of the evolutionary mechanisms leading to these patterns of restricted

4   introgression in sex chromosomes among model and non-model species in natural and

5   laboratory conditions will shed light on the evolutionary mechanisms that produced similar

6   patterns during the ancient hybridization among *Homo* species.

7   Although the patterns on sex chromosome introgression in the howler monkey

8   hybrid zone are similar in some respects to what is known for ancestral populations of

9   anatomically modern humans, Neanderthals, and Denisovans, the deeper divergence

10   between hybridizing howler monkey species make this system a better analogue for general

11   patterns of admixture between more divergent hominin lineages (e.g., *Paranthropus* and

12   *Homo*), comparable to what is seen between *Papio* and *Rungwecebus* (above), and may suggest

13   that admixture between more divergent hominin taxa that overlapped in time and space

14   could have been possible. Thus, this hybrid system also provides us with a living model to

15   understand the types of processes and mechanisms that may have played a role in the

16   hybridization events at different stages during our evolutionary past.

17   To sum, although we have chosen to focus here only on a select group of organisms,

18   they illustrate how hybridization and introgression are important for shaping mammal

19   genomes, comparable to what has been observed across myriad organisms living today (e.g.,

20   Arnold and Kunte[31]), including primates,[98,99] but also other organisms more distantly related

21   to us. The influence of hybridization on the genetic and phenotypic variation observed in the

22   present day suggests that the magnitude of gene exchange, the loci most affected, and

23   whether parental species persist after hybridization, are influenced by levels of divergence

24   between hybridizing taxa, as well as by climate, biogeography, and demography. These

1 results also suggest an important role for stochastic factors. This is important to keep in

2 mind when interpreting the results of hybridization between different hominin lineages.

3 Comparative models in the form of other hybridizing organisms illustrating the importance

4 of climate (bears), dispersal (canids), population dynamics and behavior (baboons; howler

5 monkeys), intrinsic hybrid fitness (howler monkeys), and more particular ecological

6 circumstances (*Callithrix*) will be vital for building a better understanding of the role of

7 hybridization among hominin taxa.

8 3 Genetic data are limited in their ability to interpret the fossil record, necessitating a

9 phenotypic approach

10

11 We cannot understand the details of evolutionary process from genetic material

12 alone. There is growing evidence that DNA can only be recovered from a small fraction of

13 human fossils, even among those from the most recent period of inter-species contact in the

14 Late Pleistocene. Furthermore, genomic studies to detect gene exchange among taxa such as

15 early *Homo*, *Australopithecus* and *Paranthropus* are currently impossible due to the advanced

16 degradation of DNA in all remains of these more ancient lineages. Genomic studies also

17 cannot tell us much about the phenotypes of our archaic ancestors because of the limits in

18 our understanding of how genotypes might influence phenotypes. Features with a simple

19 genetic basis or those with detailed and generalizable genotype-phenotype maps (e.g.,

20 pigmentation[100]) may allow reconstruction of fossil phenotypes, but complex characteristics

21 and/or characteristics with the potential for complex interactive bases (e.g., skeletal

22 morphology[101]) are not likely candidates.

1   The kinds of perturbations that hybridization imposes on morphology, however, can

2   serve as a guide to identifying admixture in the fossil record using phenotypes alone, a

3   necessary precursor to understanding the dynamics of past gene exchange. This possibility

4   exists because morphological variation within species and among closely related species

5   arises from the channeling of genetic and environmental influences into phenotypic variation

6   through conserved common developmental pathways.[102] The kinds of perturbations that

7   stem from epistatic interactions in hybrids might lead to characteristic phenotypic changes

8   even if the underlying genotypes are different.

9   Most of the morphological studies purporting to identify fossil hominin hybrids are

10   uninformed by genetic and comparative perspectives on the morphological effects of

11   hybridization (but see Ackermann[18]). In these cases, evidence for admixture is largely based

12   on the presence of mixed (mosaic) or intermediate morphology, rather than the application

13   of theory bound analyses, resulting in the identification of several candidate hybrid hominin

14   fossils. These include Lagar Velho 1,[103] Mladeč 5 and 6,[104] Cioclovina 1,[105] Peştera cu Oase

15   2,[106] Vindija,[107] Klasies River Mouth,[108] Jebel Iroud and Mugharet el 'Aliya in North

16   Africa,[108,109] Lingjing (Xuchang crania) in China,[110] Middle Pleistocene hominins[111,112] and

17   possibly others.[113,114] However, none of these specimens have been widely accepted as

18   hybrids, and hybrid status has specifically been disputed for several of them (e.g., Grine et

19   al.[115]; Harvati et al. [116]; Stringer[117]; Tattersall and Schwartz[118]).

20   Ackermann (2010)[18] used a systematic and theoretically informed approach based on

21   comparative mammalian data to identify fossil hybrids, and concluded that the fossils Skhul

22   IV and V and Peştera cu Oase 2, and other specimens from Qafzeh, Krapina and Amud,

23   possibly showed many of the characteristic signs of hybridization identified in genetic and

24   comparative studies of mammals[18] (see section below: Comparative and experimental

1   approaches to studying the phenotypic effects of hybridization). The Peştera cu Oase 1

2   individual, which, like associated Peştera cu Oase 2, shows admixture based on

3   morphology,[106,119] was confirmed to be a hybrid using ancient DNA (ca. 4-6 generations

4   prior).[10] At a population level, the recent evidence for admixture at 100ka[35] supports

5   proposals that specimens like Skhul are admixed, while genetic evidence of Neanderthal

6   influence in North Africa[120] support earlier morphology-based suggestions.[108,109] This

7   consilience between morphological and genomic approaches at the individual and

8   population levels suggests that a general biologically informed perspective on hybridization

9   may yield further insights into the dynamics of gene exchange in the fossil record.

10   The limited genomic reach into the past poses important challenges for identifying

11   hybridization in the fossil record and understanding its evolutionary consequences. A unified

12   comparative and experimental approach will afford a clearer picture of the ways in which

13   hybridization drives perturbations of development that may allow for a general set of

14   diagnostics for identifying hybrid individuals and populations in the fossil record. Moreover,

15   from a comparative perspective, we would like a better sense of the variational (phenotypic,

16   but also genetic) and evolutionary consequences of hybridization in the wild. A more

17   thorough understanding of the phenotypic consequences of hybridization, particularly in the

18   skeleton, is a pressing concern for the study of human evolution.

19   4 Comparative and experimental approaches to studying the phenotypic effects of

20   hybridization

21   4.1 Baboons as phenotypic models for hybridization

22   Currently our best comparative basis for identifying the morphological effects of

23   hybridization on the skeleton in primates comes from research on hybrids of *Papio*

1 *cynocephalus* (the yellow baboon) and *P. anubis* (the olive baboon), one of the hybridizing

2 moieties described above. Studies of captive, known-pedigree, purebred yellow and olive

3 baboons and their hybrids have shown that these hybrids exhibit high frequencies of skeletal

4 and dental traits that are rare in parents, including small and/or supernumerary canine teeth,

5 rotated molars, and sutural anomalies.[20,21] These traits suggest that hybridization results in a

6 breakdown in the coordination of early development, reflected in visible perturbations in

7 dental and sutural formation.[17,18] In addition to these rare non-metric features, baboon

8 hybrids also show a greater degree of overall size variation (Figure 4),[20,21] including in the

9 interior of the nasal cavity.[121] On average, baboon hybrid crania tend to be large, with many

10 individuals at or outside the range of the largest parent species.

11   Transgressive phenotypes are particularly marked in the craniofacial skeleton and

12 dentition.[20,21] This is a stroke of good fortune as arguments over taxonomy and phylogeny in

13 the hominin fossil record mostly revolve around dental and craniofacial characteristics. Both

14 atypical traits and extreme size are transgressive relative to the parents. Moreover, close

15 examination of specific aspects of the cranium that exhibit heterosis and dysgenesis in

16 hybrids suggest that the overall form of hybrid baboon crania differs from that of the

17 parents.[20,21] Based on overall covariation of metric features, comparisons of parents and first

18 generation (F_1) hybrids indicate that the hybrids exhibit lower overall trait covariation than

19 either parent (Ritzman & Ackermann, unpublished data). While these differences are small,

20 the fact that they occur with increased phenotypic variance suggests a decrease in integration

21 in hybrids.[102,122]

22   Results from baboons are consistent with what we know about the skeletal anatomy

23 of hybrids in other mammalian lineages. Features such as the presence of supernumerary

24 teeth, rotated teeth, and sutural anomalies in the neurocranium and face, appear in

1   ungulates,[16] rodents,[123] and primates,[17,19-21] although they manifest somewhat differently in

2   each taxon. Moreover, specific patterns in supernumerary teeth (i.e., the presence of

3   mandibular v. maxillary supernumerary teeth and/or unilateral v. bilateral expression of

4   supernumerary teeth) have also been observed to differ between hybrids and parents.[20,123]

5   The consistency of these findings across taxa strongly suggests that the presence of such

6   non-metric traits in relatively high frequencies is a general indicator of hybridization.

7   Moreover, second generation hybrids and back-crossed individuals show that these traits

8   persist in later generation hybrids[21] (see also Ackermann and Bishop[19]).

9   Although less well-studied, signatures of hybridization in the size and shape of the

10   skull have also been identified. As discussed above for baboons, the most noteworthy

11   signature of hybridization is large cranial size, with hybrids either (and statistically

12   significantly): (1) exceeding the midpoint value of the means of the parental taxa (e.g.,

13   Cheverud et al.[124]), or more strictly (2) exceeding the means of both parents. Using these

14   definitions, extreme cranial size in hybrids has been identified in mice[125-127] and in

15   primates.[20,124] Heterotic phenotypes are also evident beyond the F_1 generation. Taken

16   together, these results suggest that, in addition to the presence of rare non-metric traits (as

17   above), large cranial size may be a more general feature of mammalian hybrids. Further

18   research needs to be done into the ways in which hybridization causes the genomic

19   interactions that underlie these changes in conserved developmental pathways. Finally, the

20   effects of hybridization on the postcranial skeleton are largely unstudied, except insofar as

21   many previous studies in mice and primates have found that hybrids generally exhibit longer

22   limbs and increased body size relative to parents.[18,20,21,125,127-133] Furthermore, the apparent

23   effect of hybridization on overall morphology may be diminished after multiple generations

1   of backcrossing, making backcrossed individuals physically undistinguishable from the

2   parental species with whom they share most of their genome.[130]

3

4   4.2 Mice as phenotypic models for hybridization

5   Outside of primates, mice stand out as a powerful mammalian model for

6   investigating the effects of hybridization on phenotypic variation because they can be bred in

7   controlled conditions and have short generation times, making it feasible to perform large,

8   multigenerational experiments with replication. This makes them excellent model organisms

9   for understanding the morphology of mammalian hybrids, including hominins. There is also

10   a broad literature regarding hybridization and introgression among sub-species of *Mus*

11   *musculus*,[134-137] as well as some research focusing on hybridization among more divergent

12   species of the genus *Mus*.[138-140] In addition to comparative analysis of wild and captive

13   organisms, an ongoing experimental research project aims to determine whether hybrids

14   show any relationships between variation in coat color and variation in cranio-

15   mandibular/skeletal traits, as a result of shared developmental processes being affected by

16   hybridization.[22,141,142] Breeding experiments have produced multi-generation mouse

17   recombinants of three closely related subspecies of *M. musculus*, as well as two species (*M.*

18   *musculus* and *M. spretus*), with various degrees of introgression.

19   Morphometric analyses of variation in cranio-mandibular size and shape have been

20   performed among the subspecies, first generation (F_1), second generation (F_2) and first

21   generation backcrossed (B_1) hybrids.[22,141] Important patterns are emerging that might shed

22   light on human evolution. In particular, the results indicate that hybrids are typically as large

23   or larger than the parent taxon, with mean shape generally intermediate to the parents but

24   more closely resembling the smaller parent.[22,141] Features such as molar length are relatively

1 large in hybrids, while later generation (F_2, B_2) hybrids more variable that F_1s, and

2 backcrosses more closely approximating the shape of the parental groups they are

3 backcrossing into. When combined with unusual non-metric traits,[20,21] these features can be

4 considered suggestive of mixed ancestry in the fossil record (see also Ackermann[18]). For the

5 mice, this pattern appears to hold across very different scenarios of hybridization, e.g., 1)

6 between species that hybridize in nature but gene-flow and fertility rates of hybrids are low;

7 2) between species that hybridize in nature and the hybrids are successful; and 3) between

8 species that do not hybridize in nature (due to geographic separation), but where hybrids can

9 be produced under laboratory conditions.[22] This suggests that these results are fairly robust

10 and can be applied to a wide range of contact scenarios in different sets of lineages.

11   Analyses of coat color variation, focused on comparisons of dorsal-ventral (DV)

12 patterning in F_1 animals and parental strains,[142] indicate that hybrids have highly variable coat

13 morphologies.[143,144] Given that the DV pattern is established during prenatal development,[145]

14 observed differences in the ventral coat morphology of the F_1 mouse hybrids relative to the

15 parents, as well as new combinations of dorsal and ventral coat colors, could be the result of

16 two differently co-adapted genomes and developmental patterns coming together.

17 Interestingly, the development of DV patterning can be tied to the development of the

18 skeleton, with mutations in the *Tbx15* gene affecting both DV patterning and skeletal

19 morphology.[146] This has interesting potential implications for human evolution. We know

20 some of the major changes in human evolution are soft tissue changes, such as changes in

21 hair and sweat gland structure, function and distribution,[147,148] and that genes related to

22 skin/hair phenotypes have introgressed from other ancient lineages into our own lineage and

23 remain in people today (e.g.,Vernot and Akey[40]; Sankararaman et al.[91]). A variant of the

24 *TBX15* gene which is derived from a hominin closely related to the Denisovans is found at

1   high frequencies in some modern human populations.[149] The results from the mice suggest

2   that some of the skeletal changes/differences we observe in hominins could result from

3   introgression of gene variants that were retained due to the adaptive value of other

4   phenotypes. Further understanding of the links between these systems has the potential to

5   provide information into the underlying target of selection and could allow us to extrapolate

6   from the fossil skeletal phenotype to such soft-tissue features.

7   Some suggested hominin hybrid samples express patterns similar to what the mouse

8   and baboon studies indicate for hybrids (although it is not possible to know what generation

9   - F_1, F_2, B_1 etc.- the fossil samples represent). For example, the Vindija Neanderthals (Figure

10   5) have an intermediate facial anatomy compared to most Neanderthals and early modern

11   humans; facial size is more like modern humans but morphological features of the mandible

12   and supraorbital torus are more like the Neanderthals.[107,150] At Klasies River Mouth, there is

13   evidence of extensive intra-sample variation with indications of a very large face (for one

14   individual) and mandibles that exhibit a mosaic of both modern and archaic features.[108]

15   These and other individuals/samples are generally more like the smaller hominin on the

16   landscape (*H. sapiens*) in terms of morphology, if not gracility (e.g., Cioclovina 1, Mladeč 5

17   and 6, Oase 1 and 2, Jebel Irhoud and Lagar Velho1). Atypical traits are also present in

18   hominins,[151] including a number of anomalies of the maxilla and dentition in Upper

19   Palaeolithic samples. Strikingly, Abri Pataud 1 has two supernumerary teeth adjacent to the

20   right upper second molar, while the isolated tooth Dolní Věstonice 33 has been suggested to

21   be a distomolar.[151] Although these patterns are commensurate with hybridization, clearly

22   more work is necessary to identify conclusively the prevalence, demographics, and lingering

23   morphological effects of hybridization in past humans (but see[152-154] for recent attempts at

24   the latter).

1   5 The interplay between hybridization and adaptation

2

3   The burgeoning literature on the phenotypic and adaptive consequences of

4   hybridization in the wild provides several further insights relevant to problems we encounter

5   in understanding human evolution. Hybridization and introgression can facilitate adaptation

6   in several distinct ways. By introducing alleles into a new population that have already been a

7   part of the evolution of an adaptation to a local condition in a different population, a new

8   population borrows fitness-enhancing variants. Hybridized populations will, in most cases,

9   have higher heterozygosity than either parent population. This can lead to an increase in the

10   genetic variance underlying individual differences in a phenotypic characteristic and a

11   concomitant increase in its propensity to respond to directional selection. Likewise,

12   interactions arising from novel combinations of alleles at loci (dominance) and genotypes

13   across loci (epistasis) can cause increases in the genetic variance of phenotypic characteristics

14   out of proportion to any increase in genomic variation. The generation of new variation can

15   thereby aid in the adaptation of a population to novel conditions.

16   Adaptive radiations are canonical examples of divergence through natural selection

17   resulting in species with diverse phenotypes associated with ecological variation in their

18   habitats.[155] For instance, recent (post-australopithecine) hominins and Darwin's finches both

19   diversified over the last 1-2Ma, and both diversifications were influenced by glacial cycles of

20   changing climate. Continental habitats and Galápagos Islands fluctuated in size and

21   connectivity along with the availability of conspecific mates, with periods of isolation. A

22   feature common to both systems was the exchange of genes between previously isolated

23   populations. In some cases, the genes were adaptive, for example genes affecting beak size in

24   finches, and genes affecting properties of the immune system in hominins.[91,156]

1   A long-term study of one adaptive radiation, Darwin's finches (Subfamily:

2   Geospizinae) in the Galápagos archipelago, provides an example of how hybridization and

3   its consequences can facilitate adaptation to new environments and the origins of new

4   species. Two features make this group suitable for intensive study. Most of the islands are in,

5   or close to, the natural state, and no finch species has become extinct through human

6   activity.[157] An uninterrupted 40-year study of finches on the small (0.34 ha) island of Daphne

7   Major has demonstrated instances of evolution by natural selection and identified the

8   circumstances under which it occurs.[158] However, it has also revealed the unsuspected

9   prevalence of introgressive hybridization.[159]

10   A central concern in the study of hybridization in the human fossil record is the

11   degree to which hominin hybrids might have been viable and capable of reproduction.[91,160,161]

12   Darwin's finches add some perspective to this issue. Hybridization in the finches was

13   observed in the first year of the long-term breeding study on the island.[158] A few breeding

14   pairs of *Geospiza fortis*, the medium ground finch, bred successfully with *G. fuliginosa*, the

15   small ground finch, and with *G. scandens*, the cactus finch. Offspring fledged from nests of

16   both types of heterospecific pairs, thus demonstrating the lack of strong genetic barriers to

17   reproduction in the early stages of offspring development. Unanswered, however, was the

18   question of whether the hybrids were fertile. Another seven years elapsed before there was

19   an (affirmative) answer: when ecological conditions were favorable for their survival in dry

20   seasons they bred successfully in the following wet seasons. They did not, however, breed

21   with each other but backcrossed to one or other of the parental species according to the

22   song of their fathers that they learned when in the nest and during the period of parental

23   dependence as fledglings. The comparisons demonstrated that hybrids and backcrosses

24   survived as well as, and perhaps better than, contemporary non-hybrids in each of the three

1   cohorts. Moreover, they were as successful in obtaining mates and raising offspring as were

2   *G. fortis* and *G. scandens* (*G. fuliginosa* does not have an independent breeding population on

3   the island). Thus, in terms of survival and reproduction they were as fit as their respective

4   parental species.[159] Additionally, the importance of song in this scenario highlights the degree

5   to which the dynamics of hybridization and introgression are behaviorally/culturally

6   mediated, a particularly relevant and relatively unexplored aspect in hominin contact

7   scenarios.

8   Hybridization has the potential to lead to the formation of a new species through

9   introgression of genes from one species to another, and hybrids then evolve along a new

10   trajectory in a different environment.[158] Again Darwin's finches on Daphne provide an

11   example. An immigrant *G. conirostris* arrived in 1981, bred with *G. fortis* and initiated a new

12   lineage. After two generations a severe drought in 2003-04 caused heavy mortality among all

13   finches leaving two survivors. They were a brother and a sister, and they bred with each

14   other. Their offspring and grand-offspring also bred only with other members of the lineage

15   and not with *G. fortis* or *G. scandens*. Their beaks were larger than the beaks of either species,

16   and the males sang a unique song and, coupled with apparent reproductive isolation, the

17   lineage behaves as a new species.[158,162] This example differs from the standard allopatric

18   model of speciation by incorporating introgressive hybridization as an important factor in

19   the development of reproductive isolation on a small island. It also once again highlights the

20   importance of altered behavior as a phenotypic outcome of hybridization, and something on

21   which selection can act, a phenomenon also seen in primates. For example, in the case of

22   hybridization between olive and hamadryas baboons, behavior can be strongly affected by

23   hybridization. Hybrid males between these two species show intermediate forms of mating

24   behavior. Whereas olive baboon males form temporary consortships with estrous females,

1   hamadryas baboon males monopolize females irrespective of their reproductive status.

2   Hybrid males show less monopolization tendencies than hamadryas males and also show a

3   weak form of the hamadryas typical herding behavior.[56,59,163] The possibility that

4   hybridization-induced behavioral novelty might have played a role in human evolution has

5   not been well-explored (but see Ackermann et al[23]).

6   Another example of hybrid speciation from even more phylogenetically diverged

7   organisms are African clawed frogs of the genus *Xenopus*. About 30 allo-tetraploid, allo-

8   octoploid, and allo-dodecaploid species exist in this genus, and each was formed by

9   speciation of hybrid individuals (the progeny of two diploids, two tetraploids, and tetraploid

10   and octoploid species, respectively).[164] Potential adaptive consequences of these hybrid

11   speciation events include increased resistance to parasites[165,166] and increased tolerance to an

12   acidic embryonic environment.[167] Allopolyploid *Xenopus* provide an interesting perspective

13   into early genomic evolution of ancient polyploid ancestors of hominins;[168] also similar to

14   hominins, some hybrid *Xenopus* are not polyploid (e.g., Furman et al.[169]). Moreover, hominins

15   are themselves descended from ancient ancestors that underwent two rounds of

16   polyplopidization before jawed vertebrates diversified over 500 million years ago.[170] Some of

17   the duplicated genes that arose from these ancient events persist today, and small scale gene

18   duplication contributes to copy number variation between closely related primate species.[171]

19   Gene copy number variation thus may contribute to adaptation and reproductive isolation in

20   modern primates, including humans. Whether the ancient (>500 million years old) whole

21   genome duplication events occurred via spontaneous genome duplication within a species

22   (autopolyploidization) or in association with hybridization among species

23   (allopolyploidization)[172] may never be known, though the later possibility has several

24   intriguing implications. Similar to the benefits associated with hybridization without genome

1   duplication, allopolyploidization brings together (a) beneficial alleles that evolved

2   independently in two diverged parental species, (b) deleterious alleles from each parental

3   species, and perhaps most significantly, (c) genetic variants that function well in each

4   parental species but that are incompatible when combined.

5   Returning to our previous example of gray wolves, the transfer of an allelic variant

6   that causes black coat color in most dogs to North American gray wolves provides another

7   insight into the adaptive consequences of hybridization.[173] In North America, black wolves

8   are common in many populations and are nearly as frequent as gray (wild type) wolves.

9   Genetic analysis has demonstrated that the genetic variant, called the K locus, originated in

10   domestic dogs, and was likely transferred to wolves from pre-Columbian dogs of Native

11   Americans.[173] This dominant mutation causing black coat color enhances the fitness of

12   heterozygote black individuals, but decreases the fitness of homozygous black wolves[174,175]

13   suggesting coat color alone is not the primary object of selection. Black wolves may have

14   higher survivorship during viral disease epidemics, such as distemper and mange, given that

15   the K locus is a beta-defensin gene that responds to viral infections.[173] Moreover, selection

16   has favored disassortative mating, where individuals have a preference for mates of a

17   different color.[176] One possible model for the persistence of the black gene is that in areas

18   where canine disease is common and persists in carnivore reservoirs such as domestic dogs

19   or other wild carnivore species, the coat color polymorphism is maintained. In other areas

20   where this is not the case, such as the High Arctic, the disease burden is lower, and observed

21   black wolves are rare. Such adaptive introgression can occur from wolves into dogs as well.

22   Hypoxia adaptation in high altitude Tibetan wolves and dogs involves selection at the

23   *EPAS1* gene, for which some alleles may have been transferred to dogs from wolves as the

1   former have recently arrived in the Tibetan Plateau. Living Tibetans also obtained new allelic

2   variation for the same gene via ancient admixture between *H. sapiens* and Denisovans.[36,177,178]

3   In the wild, coyotes and wolves hybridize, most commonly in the Great Lakes area

4   of the US and Canada.[179-182] A genome-wide analysis showed that all genomic segments did

5   not introgress equivalently, as some fragments had a more extensive distribution and were

6   more frequent than predicted by the effects of background levels of admixture alone.[41] The

7   regions that were differentially introgressed from gray wolves into coyotes, and from coyotes

8   into gray wolves, contained genes that affected morphology and physiology, which are gene

9   categories that might be expected to have important functions in hybrids, as body size and

10   morphology are essential components of successful prey capture. Moreover, the prey size in

11   the Great Lakes is smaller than elsewhere consisting of deer rather than larger prey such as

12   elk or moose. In this situation, an intermediate sized canid (between coyote and gray wolf)

13   may have higher fitness than the parental forms. Interestingly, this intermediate morphology

14   was detected in preliminary studies of the morphology of the Eastern coyote or "coywolf,"[179]

15   and an ongoing study suggests they have atypical cranio-dental traits (L. Schroeder,

16   unpublished data). As with Darwin's finches, should the nature of available food change, a

17   different sized canid may be selected. In fact, body size has changed in coyote-sized canids in

18   North America throughout the Pleistocene,[183] and some of these body size changes may

19   reflect admixture between coyote and wolf-sized canids as observed today. Moreover, many

20   of the North American wolf species (including *Canis lupus*, *Canis rufus* and *Canis lupus lycaon*)

21   are hybrids themselves, with these populations displaying between 30% and 50% coyote

22   ancestry.[41]

23   The canid example is useful for understanding the dynamics and potential adaptive

24   consequences of introgression in hominins. Like canids, hominins dispersed widely resulting

1 in gene introgression between lineages that diverged recently in some cases and more deeply

2 in others. Introgressed DNA linked to phenotypic characteristics in living people has been

3 subject to the effects of natural selection after introgression. Jolly (2001) and Garrigan &

4 Kingan (2007) hypothesized that introgression from now-extinct species of *Homo* may have

5 provided *H. sapiens* with locally adapted allelic variation;[66,184] this hypothesis is now well

6 substantiated.[36,40,91,154,185-187] The persistence of ancient gene variants in extant human

7 populations, especially those associated with skin and hair characteristics (including

8 pigmentation, toughness of the skin (perhaps tied to better cold adaptation), and other

9 factors related to keratin (e.g., Vernot and Akey[40]; Sankararaman et al.[91]; Dannemann and

10 Kelso[185])), immunity (specifically the human leucocyte antigen (HLA) class 1 genes),[156,188]

11 and high-altitude adaptations,[36,186] is in striking parallel to what we see in canids. Genes

12 affecting morphology and physiology have also diverged in hominin ancestral groups and

13 could have been affected by hybridization.

14   Returning to the *EPAS1* example, strong selection at the *EPAS1* locus in Tibetan

15 populations living at extreme elevation led to changes in oxygen metabolism, which allowed

16 individuals in this group to better function and reproduce in hypoxic environment.[36,186] The

17 allele subject to the resulting selective sweep is derived from *EPAS1* alleles introgressed

18 from the Denisovan lineage.[36] Hackinger *et al.* (2016) showed a similar effect of *EPAS1* was

19 present in other high elevation parts of the Himalayan region.[186] The Denisovan 'Core

20 haplotype' in human populations living above 2,000 meters in elevation was enriched.

21 Introgressed Denisovan alleles were absent in human samples from lowland populations.[186]

22 Variants apparently conferring adaptive advantages for cold adaptation,[189] immune

23 responses,[188] and sundry other functions[185,190] introgressed from ancient hominins are also

24 evident in the genome today.

Adaptation to combinations of local and novel conditions is not the entire story, however. Genetic drift and neutral mutations drive human genome evolution to the extent that expectations of neutrality form the null hypothesis of tests for natural selection in the genome.[191] Additionally, some of the genomic evidence for hybridization observed in living humans suggests that there may have been purifying selection against variants formerly in Neanderthal populations,[192-194] although recent research suggests that negative selection against Neandertal ancestry did not play as strong a role in recent human evolution as previously suggested.[195]

Taken together, these different pieces of evidence point to the ways in which hybridization and introgression form an indispensable part of the understanding of the role of natural selection and adaptation in recent human evolution. They provide a path to produce novel genotypic combinations that would not readily arise through mutation alone. Some of these novel genotypic combinations influence fitness, sometimes for ill, but often to adaptive ends.

6 Conclusion: the (exciting!) way forward

The question of what makes humans different from other species has captured the imagination of both scientists and non-scientists. At a certain level, we know the answer: our DNA is different from that of other species, and this allows us to abstract, create, and destroy like no other. So how did our species acquire its unique genome? Genetic and fossil evidence demonstrate that the ancestors of humans split into distinct branches as they spread and diversified, adapting to local conditions. Archaic human "cousins," often

1   recognized as species separate from *Homo sapiens*, were similar to us in many ways – they

2   wore clothes, buried their dead, and made art (e.g., Klein[160]; Hoffmann et al.[196]; Rodríguez-

3   Vidal et al.[197]). Before they became extinct, they exchanged genetic material with humans by

4   hybridizing on multiple occasions (e.g., Green et al.[12]; Kuhlwilm et al.[35]; Vernot and Akey[40];

5   Sankararaman[92]; Vernot et al.[198]). Which bits of our DNA did we get from these archaic

6   "cousins", and what are the biological consequences? We are just starting to learn this. We

7   know, for example, that several disease-related genes were affected, not all people got the

8   same bits of DNA, and not all parts of our genomes received the same amount of DNA

9   from these extinct species. The question now is why and how this happened.

10   Beyond documenting the quantity and results of gene exchange, this exciting avenue

11   of research also challenges much of the existing framework for considering hominin

12   diversity. Yes, it is causing us to rethink the details of modern human origins and accept that

13   neither a strict replacement scenario nor a multiregional gene flow model can explain recent

14   human evolution. But more profoundly, it is expanding the model of divergence through

15   reproductive isolation and adaptation, to one that recognizes gene exchange as a key player

16   in the speciation process. We now know that gene exchange has played a central role in

17   providing new diversity, injecting new variation from one population into another, and

18   thereby facilitating the rapid (adaptive) diversification of lineages in well studied and

19   evolutionarily relevant taxa. We have detailed much of this evidence in the preceding

20   sections of this paper and argue that human evolution provides yet another example of this

21   critical evolutionary process.

22   The interspecific exchange of gene variants also complicates our concepts of species.

23   This is a real challenge for palaeoanthropologists, for whom finding and categorizing new

24   fossils – or even new species – is sometimes a primary (and exciting) goal. How do we

1   recognize and appreciate diversity when it has been shaped by gene exchange? How do we

2   rethink and visualize our phylogenies as a reticulating network rather than a branching bush?

3   How do we continue to improve our models of population dynamics through time to reflect

4   this? Part of that will involve a much better grasp of within-taxon variation and the effects

5   interacting evolutionary forces have on complex developmental systems and on the

6   phenotype. Paleoanthropologists can benefit from considering other organisms and

7   disciplines, where there has been a growing acceptance that boundaries of species are

8   imprecise and more porous than previously believed, and that the dynamics of gene

9   exchange complicate relationships. These issues provide conceptual and practical challenges

10   for our field, but they also provide opportunities for fresh exploration into the dynamics of

11   human evolution. More broadly, gene flow between related species is one of several ways

12   the generation of variation produces macroevolutionary implications.[199]

13   The research presented here provides some exciting material for commencing such

14   exploration. These organismal models can help us consider new explanations, and develop

15   new explanatory hypotheses, for the patterns we observe in the fossil record. For example,

16   the majority of closely related hybridizing taxa discussed here have been shown to have a

17   greater frequency of hybridization and amount of introgression than originally thought, as

18   well as differential contribution of sexes in hybridization, a model which is likely to fit the

19   Middle Pleistocene hominin situation. It is also quite plausible that – like in finches – the

20   combined effects of introgression and natural selection were important for hominin gene

21   exchange, but that cultural mechanisms like language were critical factors in the dynamics of

22   this exchange. Climate fluctuations are also likely to have played a crucial role in these

23   dynamics, bringing taxa together that are normally allopatric (as seen in bears), but also

24   moving the geographic boundaries between taxa and shifting which taxa are favored over

1   time. Wide geographic dispersion (e.g., wolf-like canids) is also a characteristic of later

2   hominins and the differentiation of skeletal phenotypes and skin/hair characteristics surely

3   played a role in the emergent morphology of their hybrids (as suggested in canids, baboons

4   and mice). All of these applications (and more; see Table 1) provide a rich opportuntiy for

5   better understanding how, when and why human complexity emerged.

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9

Glossary

Adaptive introgression When the incorporation of new genetic variants through introgression leads to an increase of the fitness of the recipient gene pool.

Backcross The breeding of a hybrid with a member of one of the parental species.

Cohort A group of individuals born in the same year (or reproductive cycle).

Dysgenesis Hybrid dysfunction, including sterility or lowered function. For analyses of morphology, dysgenesis can refer to measured features that are smaller or reduced in the hybrids relative to parents and/or to the mid-parental value.

Enriched gene/haplotype Increased presence or expression of a gene/haplotype in a sample.

Epistasis/Epistatic interactions Interactions between alleles at different loci, where the effects of an allele at one locus is modified by alleles at other loci in an interacting complex.

Gene Flow The transfer of genetic variants (or alleles) from one population to another.

Genome duplication Production of cells/organisms with additional copies of entire genome; resulting cells and organisms are polyploid.

Ghost lineages Lineages that are now phenotypically extinct but whose presence can be detected by their genomic contribution to extant lineages.

Heterosis Hybrid vigor that can result from heterozygote advantage or recombinant hybrid vigor. For analyses of morphology, heterosis is often used to describe measured features which are larger in hybrids relative to parents and/or to the mid-parental value.

Heterospecific Other species, in contrast to same species (conspecific)

Heterozygosity The probability that two alleles at a locus drawn from a population will differ. High heterozygosity indicates large amounts of genetic variation.

Haldane's Rule In the case where hybrids between taxa produce only one sex that is inviable or sterile, that sex is more likely to be the heterogametic sex, e.g., in mammals males with XY chromosomes (as opposed to the homogametic, e.g., in mammals females with XX chromosomes).

Hybrid Offspring of a cross between genetically/phylogenetically divergent taxa (verb: hybridize).

Hybridization Interbreeding between individuals from genetically differentiated lineages (typically at or above the rank of subspecies).

Hybrid speciation A form of speciation where hybridization between two distinct species leads to the formation of a new (third) species.

Hybrid vigor Increased fitness in the hybrid relative to the parents, often due to increased heterozygosity.

Introgression Incorporation of gene variants (i.e., alleles) from one lineage into the gene pool of another.

Large X-effect The disproportionately large involvement of the X chromosome in the reproductive isolation of closely related species and the process of speciation.

Mitochondrial capture Complete mitochondrial introgression, e.g., the replacement of the original mitochondrial genome of a population/taxon with that of another as a result of female movement/invasion and interbreeding.

Nuclear swamping Replacement of the nuclear genome in one population by the nuclear genome of another by repeated unilateral introgression, while leaving the mitochondrial genome in place, e.g., as a result of the repeat movement/invasion of males.

Parapatric Spatial relationship between populations/taxa whose ranges do not significantly overlap but are immediately adjacent.

Phylogeographic Relationship between the structure of gene genealogies and geography.

Reticulation/Reticulate evolution The fusing of previously separated branches on an evolutionary tree, through repeated hybridization events, or other forms of horizontal gene transfer.

Selective sweep A reduction or elimination of allelic variation due to strong positive selection on and subsequent fixation of (an)other allele(s).

Transgressive phenotypes When traits in hybrids are outside of the range of the parents.

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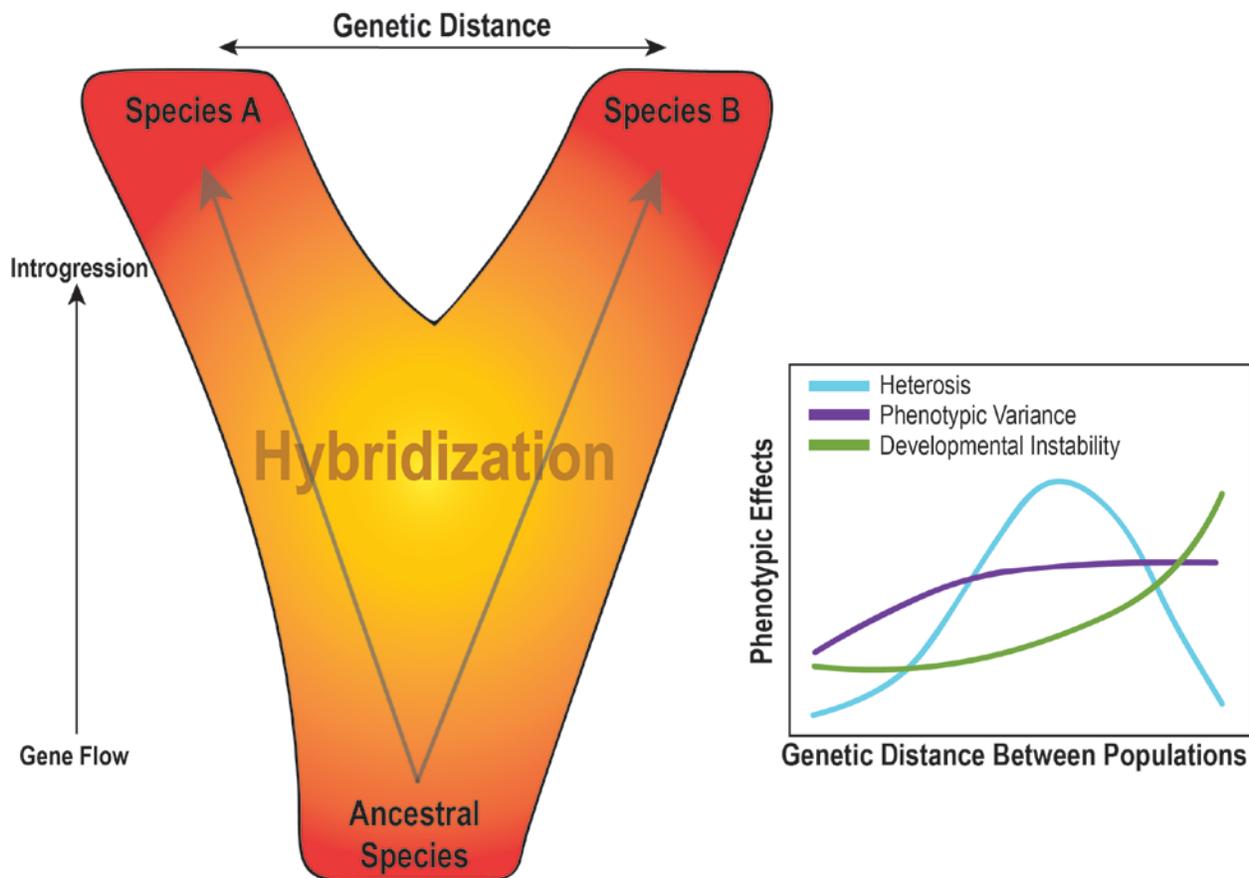
Figure 1: Illustration of the gradation from gene flow to introgression along a continuum of speciation, resulting in a reticulated pattern of speciation at the population level. Genetic distance refers to distance between the hybridizing parents (increasing as you move through time). Changing phenotypic effects with increasing genetic distance are shown to the right. Phenotypic variance refers to within population variance of the hybrid population. The shapes of the effect curves are qualitative and so not to any scale; though based on available evidence to date, they remain working hypotheses.
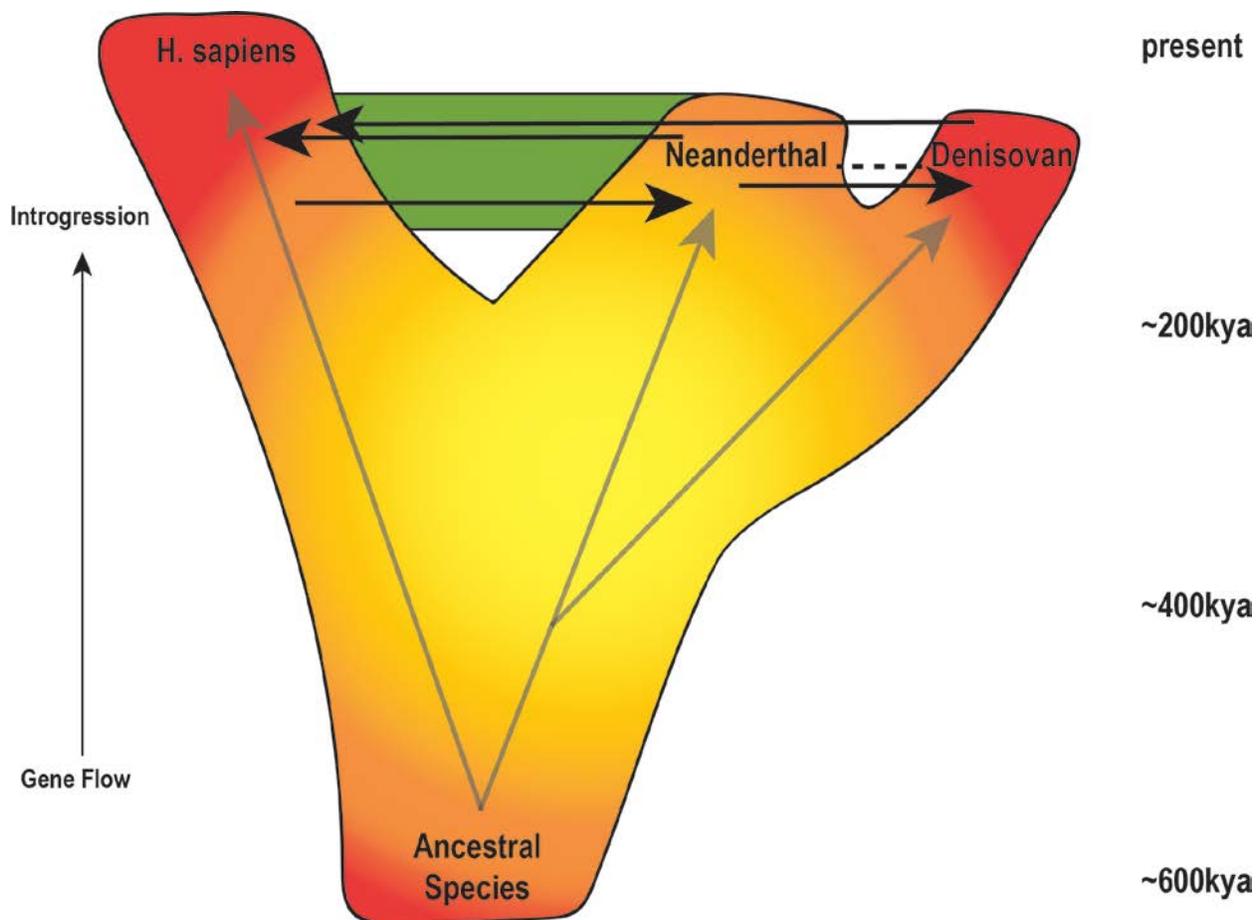
Figure 2: Hypothesized directions and magnitudes of introgression in hominin evolution. Genetic evidence for known introgression indicated by black arrows between lineages. The green region indicates the time period of purported fossil (phenotypic) evidence for introgression between Neanderthals and H. sapiens (fossil/phenotypic evidence for introgression between Denisovans and other taxa is currently unknown, due to our limited understanding of the morphology of Denisovans). Genetic evidence of a first generation hybrid (Denisova 11)[37] between Neanderthals and Denisovans is shown with a dotted line, though the introgressive effect of this on future lineages is currently unknown. Presumably, evidence (both genotypic and fossil/phenotypic) for gene flow earlier in the separation of lineages would be more difficult to detect, as would phenotypic/genotypic differences among the hybridizing taxa. This is consistent with the hominin fossil record of the Middle Pleistocene.

Figure 3: A comparison of facial variation among two *Callithrix* species and their hybrid. Left: anthropogenic *Callthrix penicillata* x *C. geoffroyi* hybrid from Viçosa, MG, Brazil. Top right: *C. geoffroyi.* Bottom right: *C. penicillata.*
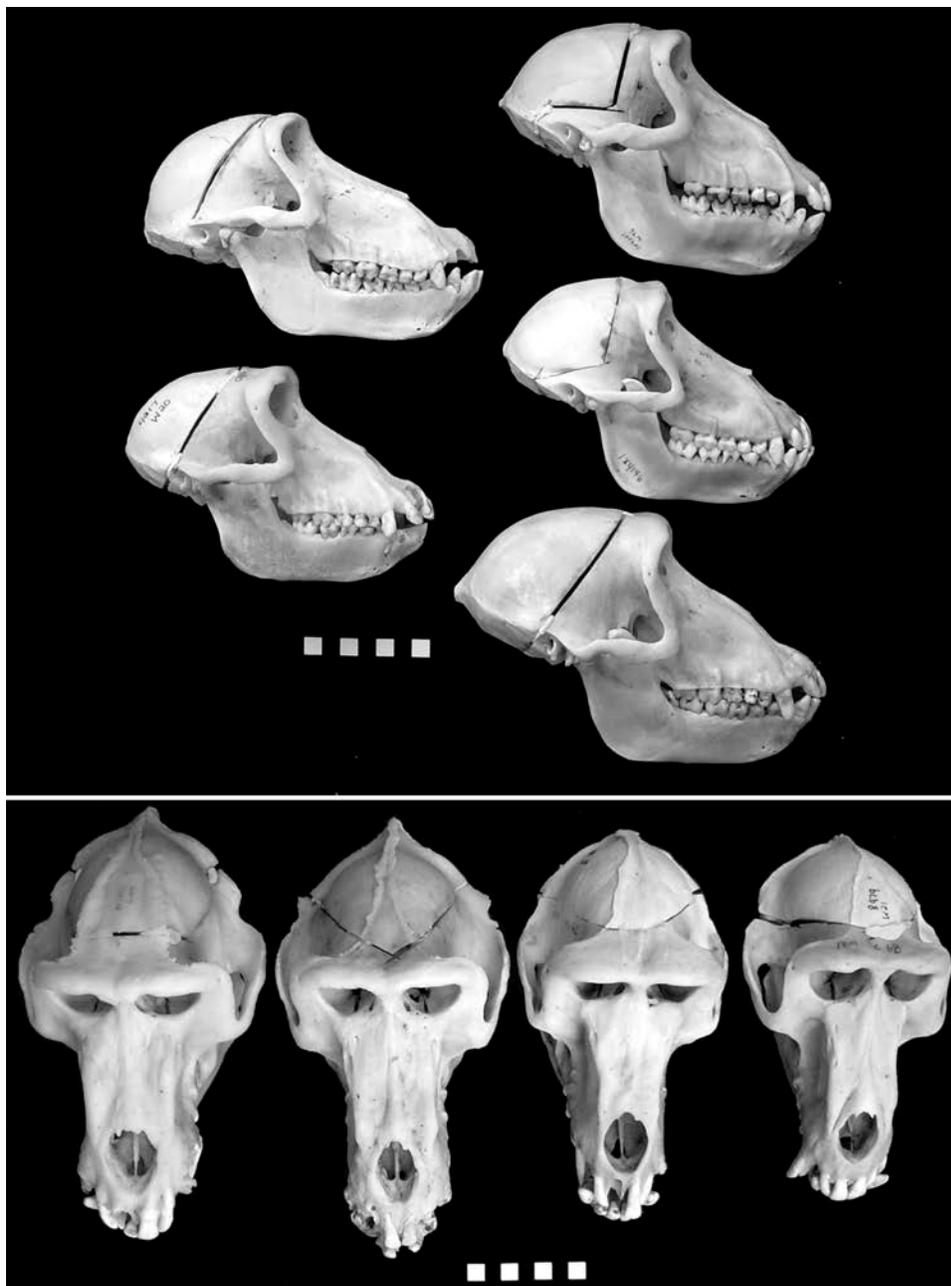
Figure 4: Hybrid and purebred baboon crania, illustrating the wide variation and relatively large size of hybrids relative to their parent taxa. Top: Female baboons, with parent taxa on left (*Papio anubis*, top, *P. cynocephalus*, bottom), and three F1 hybrids on right. Bottom: Male baboons, from left to right, F1 hybrid, F1 hybrid, *P. cynocephalus*, and *P. anubis*. Images reprinted from Journal of Human Evolution, Vol 51, RR Ackermann, J Rogers and JM Cheverud, Identifying the morphological signatures of hybridization in primate and human evolution, Pages 632-645, Copyright (2006), with permission from Elsevier.

Figure 5: Intermediate features of the Vindija Neandertals. Details and data are available in Smith, et al.[107] Clockwise from top left: (1) Vindija 259 left adult maxilla. Reconstructed nasal breadth falls almost three standard deviations (s.d.) below the Neandertal mean. (2) Vindija mandible 206 (lingual view). An incipient *incurvatio mandibulae* and *mentum osseum* are visible on the external mandibular symphysis. (3) Vindija mandible 231, oriented to the alveolar plane. The almost vertical symphysis reflects reduction of facial prognathism. The symphyseal angles of Vi 206 and Vi 231 fall more than three s.d. below the Neandertal mean. (4) Vindija 231 mandible. The symphysis exhibits a weak outline of the mental trigone, a modern human feature.

Table 1: Factors relating to hybridization in non-hominin organisms included in this discussion and their importance to understanding hybridization's role in hominin evolution

	Greater Frequency of Introgression Than Expected	Evidence for Introgression of Positively Selected Genes (Adaptation)	Hybrids Exhibiting Increased Variation or Heterosis	Hybridization and its Relationship to Climate and Environment	Differential Contribution of Sexes in Hybridization – Including Haldane's Rule and Large X Effect	Direct Association Between Genetic and Morphological Traits Relating to Hybridization	Specific Applications to Hybridization in Hominin Evolution
Galapagos finches	X	X	X	X		X	demonstration of combined effects of introgression and natural selection, evidence for long-term introgression in closely related species, evidence of critical role of climate, ecology and "cultural mechanisms" in successful hybridization
Clawed frogs	X	speculated	speculated	speculated		X	traits that appear identical in phenotype may actually have different patterns of genetic control; allopolyploidization may be a good model for understanding ancient polyplodization in jawed vertebrates
Mice	X		X		X		demonstrate greater variability in hybrids and backcrossed samples than in parental groups, show that relatively high amounts of hybridization ($\geq$ 30% in mice) are necessary to accurately detect hybridization in a sample

Wolf-like canids		X	X			X	impact of wide geographic dispersions, examples of relatively recent divergence in many lineages and impact of this on establishment of reproductive barriers, role of skin/hair characteristics
Recent and ancient bears				X	X		impact of climate, especially bringing species/populations together that normally are fully allopatric
Marmosets	X		X	X			nature of hybrid zones critical in determining outcomes of hybridization
Howler monkeys				X	X		both Haldane's rule and large X effects can be critical factors in primate hybridization
Baboons	X		X	X	X		closely-related, relatively young species that commonly hybridize at species borders; hybrids can exhibit heterosis and high frequencies of skeletal anomalies. Extensive, ancient "swamping" hybridization by male introgression is attested by patterns of mitochondrial variation among populations