Genetic and climatic factors in the dispersal of Anatomically Modern Humans Out of Africa

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Genetic and climatic factors in the dispersal of Anatomically Modern Humans Out of Africa

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Summary

The evolutionarily recent dispersal of Anatomically Modern Humans (AMH) out of Africa and across Eurasia provides an opportunity to study rapid genetic adaptation to multiple new environments. Genomic analyses of modern human populations have detected limited signals of strong selection such as hard sweeps[1], but genetic admixture between populations[2,3] is capable of obscuring these patterns and is well known in recent human history, such as during the Bronze Age[4]. Here we show that ancient human genomic datasets contain multiple genetic signatures of strong selection including 57 hard sweeps, many with strong associations with cold adaptation. Similar genetic signatures of adaptation are also observed in adaptively-introgressed archaic hominin loci, as well as modern Arctic human groups. Consistent targets include the regulation of fat storage, skin physiology, cilia function and neural development; with multiple associations to modern western diseases. The spatiotemporal patterns of the hard sweeps allow reconstruction of early AMH population dispersals, and reveal a prolonged period of genetic adaptation (~80-50,000 years) following their initial out of Africa movement, before a rapid spread across Eurasia reaching as far as Australia.

When Anatomically Modern Human populations moved Out of Africa (OoA) they encountered a range of environments that were markedly different from their African past. Despite this, modern human populations show few classical genetic signatures of strong selection such as hard sweeps, where new or rare beneficial alleles have been driven to high-frequency by selection. This has led to the suggestion that most recent human genetic adaptation may have instead involved alternate modes of selection that leave less pronounced signatures in genomes[5,6] (*e.g.* 'soft' sweeps and polygenic selection; Supplementary Information 1).

To examine whether recent population admixture may have obscured signatures of past genetic adaptation we constructed a dataset containing genomic information and curated metadata from 1,162 ancient western Eurasian genome datasets including both low-coverage genomes and high-density Single Nucleotide Polymorphism (SNP) scans[7], which are concentrated mostly in western Eurasia between the early Holocene (~12ka) and Bronze Age[8] (Fig. 1, Extended Data Figs. 1, 2, Extended Data Table 1). We were able to group 18 distinct ancient populations based on their archaeological and genetic relationships. The genomic sequences within each population were aligned and scanned for evidence of distorted allele frequency patterns characteristic of hard selective sweeps (*e.g.* anomalously low diversity) using *SweepFinder2*[9], which uses a dynamic sliding window approach to control for demographic history and population structure (Supplementary Information 1). For comparison, we also analysed five modern human populations (three from European ancestry: Utah residents with Northern and Western European ancestry (CEU); Finnish in Finland (FIN); Toscani in Italy (TSI); one Asian: Han Chinese in Beijing (CHB); and one African: Yoruba in Ibadan, Nigeria (YRI); ref. [10]).

Ancient human genomes reveal a hidden history of hard sweeps

In direct contrast to studies of modern human genomes[11], we were able to identify 57 hard sweeps (Extended Data Fig. 3, Extended Data Table 2) in the ancient populations with high-confidence (study-wide false positive rate <11%; ref. [7]), all of which were limited to Eurasian populations and absent in the YRI African population. While some of the 56 detected hard sweeps were very common, none were present in all of the ancient Eurasian populations, and they were almost entirely absent amongst other contemporary African populations. This suggests that the sweeps most likely arose after the separation of the founding AMH OoA population from African groups, but were probably not fixed prior to the subsequent dispersal of this population across Eurasia. The SNP frequency differences between ancient Eurasians and the Yoruba population were used to determine a set of divergent marker alleles that characterize each sweep haplotype. These allowed the ascertainment of 56 sweep haplotypes in ancient and modern human samples, after discarding one (*LINC01153)* with too few marker SNPs to make accurate measurements (Supplementary Information 2).

The spatiotemporal distribution of the 56 hard sweeps provides a novel genetic marker for early AMH population movements out of Africa and across Eurasia, analogous to the ~2% Neandertal genomic content observed globally in modern non-African populations[12,13]. The

Neandertal admixture signal[14] has been used to trace the dispersal of the ancestors of modern populations across Eurasia and Island Southeast Asia (ISEA) as far as Australia and to date this movement to 60-50ka[12], and potentially as late as ~53-50ka (Supplementary Information 2). This timing is concordant with a sudden proliferation of early archaeological dates reliably associated with AMH presence across Asia and Australia around 50ka[15,16], and molecular clock dating of mitochondrial, Y chromosome, and autosomal DNA which all indicates the last common genetic ancestors of global non-African populations existed around 45-55ka[17,18]. Together, this suggests a major dispersal of AMH across Eurasia around 50-55ka and indicates that any earlier AMH movements OoA did not measurably contribute to subsequent human groups[12].

The Eurasian dispersal appears to have occurred a considerable period (~50,000 years) after the estimated ~100ka genetic separation of the OoA population from other African populations[12]. This timing is consistent with widespread evidence of early AMH groups from around 125ka throughout the Arabian Peninsula, from the Levant to the Gulf of Oman[19]. We refer to this apparent prolonged delay as the Arabian Standstill (Supplementary Information 2), and during this period previous genetic studies have suggested the OoA population split into the now extinct Basal Eurasians, and the Main Eurasians which subsequently admixed with Neandertals and dispersed globally[12] (Fig. 1).

Genetic selection in Paleolithic Eurasia

To examine potential genetic selection during these events we reconstructed the spatiotemporal pattern of the hard sweep haplotypes using moderate- to high-coverage genomic sequences of Late Pleistocene western Eurasian individuals up to ~45ka in age, as well as indigenous Oceanic groups, such as Aboriginal Australians, whose genetic ancestry stems from the initial Main Eurasian dispersal and who have remained largely isolated since (Supplementary Information 2). We used the oldest point at which the sweep haplotype was observed or inferred within the genetically reconstructed Eurasian dispersal process[13] as evidence that the selection pressure was likely to have been present at that time point, even if the locus was potentially not yet fixed in all individuals. The sweeps appear to persist through the complex series of population admixture events in late Pleistocene Europe[20], suggesting the selective pressure remained ongoing (Fig. 2). In Europe, the highest sweep frequencies occurred prior to the onset of the Holocene before decreasing markedly, most notably during the Bronze Age (from 5ka) which is a known period of extensive population admixture[4].

Around half of the hard sweeps (31/56) appear to have reached relatively high-frequencies during the Arabian Standstill phase as they are distributed very broadly across Eurasia in the descendant ancient and modern populations, including distant Oceanic populations in very different selective environments (Fig. 1, Extended Data Tables 2, 3). This large number of sweeps suggests the ancestral OoA population had experienced selection over an extended period of isolation, and model-based and linear regression analyses suggest this originated around 80ka (Extended Data Fig. 4). A marked period of AMH population movements occurred within the Arabian Peninsula around this time, associated with a brief moist climatic phase 80ka[19].

The genomic data records the subsequent appearance of several additional groups of hard sweeps as Main Eurasian populations pushed into the colder northern latitudes of Eurasia around 53-51ka (Fig. 1; Supplementary Information 2). Genomes from the first (Initial Upper Paleolithic) European and Asian AMH populations (~45-40ka; ref. [21]) contain the earliest observations of eight sweeps, while early West Eurasian individuals dated between 38-18ka record a further ten sweeps (Fig. 1, Extended Data Table 3). The sweeps in western Eurasian specimens appear to group into four distinct time bins, which correlate with early European archaeological cultures (Fig. 1). After the Initial Upper Paleolithic, nine further sweeps were detected in two specimens (Kostenki14, 38ka, and GoyetQ116-1, 35ka) associated with the Aurignacian Culture (~43-35ka), often referred to as the first pan-European technocomplex[22]. Further single sweeps appear in individuals associated with the subsequent Gravettian Culture (35-25ka; represented by the Sunghir 1-4, 35-33ka, and Věstonice16, 31ka, individuals; refs. [22,23]), and towards the end of the Last Glacial Maximum in the Magdalenian cultures as represented by the El Mirón specimen (19ka). The pattern of shared sweep signals are consistent with previously recognized genetic replacements between the IUP, Aurignacian, and Gravettian populations (Extended Data Table 4; Supplementary Information 2), which also occur close in time to two major geomagnetic events (the Laschamps and Mono Lake excursions, respectively) suggested to have caused rapid environmental shifts[24]. Individuals from late-glacial/Epigravettian cultures (*e.g.* Villabruna and the Azilian Bichon, both ~14ka) contain a further six sweeps which appear to have originated earlier in populations to the east, largely outside the sampling area, but spread geographically westward into view of this study around this time.

It is notable that 14 of the hard sweeps (~25%) overlap with known regions of introgressed archaic hominin DNA that have previously been identified as putative targets of selection (Extended Data Figs. 5, 6), raising the possibility that some of the 56 sweeps may have been driven by adaptively-introgressed (AI) hominin variants. This is consistent with suggestions that Neandertal genetic adaptation to colder northern environments may have provided beneficial alleles to the early Eurasian populations, and known AI variants associated with immune [25], dietary, and climate adaptation[26] (Supplementary Information 3). However, most of these putative AI loci lie on the periphery of our sweep regions, and introgressed hominin regions were actually underrepresented near the peak sweep signal (Fig. 3, Extended Data Fig. 6). This suggests that the beneficial sweep variants were most likely AMH-derived, removing introgressed hominin loci lying near to the beneficial variant while bringing linked introgressed loci to higher frequencies through genetic hitchhiking, producing false positive signals of adaptive introgression in previous studies.

Sustained adaptation to cold Eurasian environments

We applied *iSAFE* a recently developed method for localizing the adaptive locus[27] to the 56 sweep regions observed in ancient Eurasians, and in 32 we were able to identify single driver genes as the putative target for selective pressure, permitting functional analyses (Extended Data Tables 4, 5; Supplementary Information 3). Surprisingly, the 32 ancient Eurasian driver genes revealed a pattern of gene classes and biological functions strongly reminiscent of loci previously identified as being under population-specific selection in multiple present-day

Arctic human populations (Supplementary Information 3). Both the ancient Eurasian driver genes and a set of 49 high-confidence selected (*i.e.* candidate) genes from modern Arctic human populations grouped with marked concordance around three functional categories: neurological (31% and 33%, respectively); developmental (both 31%); and metabolic (28% and 16%) (Tables 1, Extended Data 5). Furthermore, a similar level of functional concordance was also observed with a set of 54 adaptively-introgressed Neandertal and Denisovan candidate loci identified in modern OoA populations (neurological 35%, developmental 33% and metabolic 22%).

A closer examination of the functions across the 32 ancient Eurasian driver genes, the 49 candidate selected genes in modern Arctic human populations[28], and the 54 archaic hominin AI loci revealed a number of layers of concordant biological connectivity, including multiple biological processes known to be involved in human cold adaptation[29] (Supplementary Information 3). For instance, three ancient Eurasian driver genes play roles in fat metabolism (Fig. 4), a key metabolic nexus for mammalian cold adaptation[30]. Namely, *PPARD,* a metabolically-sensitive transcription factor that regulates fatty acid oxidation for the generation of ATP or heat and is involved in adipogenesis, and *SMCO* and *TMCC1* which have been linked to variation in body fat. Within archaic hominin AI loci, *PPARG* (a PPAR-family nuclear receptor like *PPARD*) and *WDFY* are required for formation of white and brown adipocytes, which provide fuel storage as triglycerides or heat generation from oxidative phosphorylation, respectively. Similarly, *FADS1*, *2* and *3* within the selected genes in modern Arctic groups also regulate fatty acid synthesis. Remarkably, most of these selected genes are also directly linked in regulatory networks (Fig. 4). *PPARD* is a transcription factor that regulates the expression of *PPARG*, which in turn is also a transcription factor that regulates the expression of *FADS1* and *FADS2*, as well as the archaic hominin AI metabolism gene *AGL*[26,31].

A third of the Eurasian single gene sweeps were associated with development (Supplementary Information 3). *DNAH6* and *FBN1* are associated with body pattern and body size (Extended Data Table 5), and cold temperature has been identified as a major selective pressure for increased body size in humans[32]. There was also an unexpected enrichment of genes involved in both the developmental formation and function of cilia within the ancient Eurasian driver genes. This was mirrored within the putatively adaptive genes in both modern Arctic populations and archaic hominin AI loci, and a similar pattern previously identified in Arctic mammalian populations[26,30] (Fig. 4; Supplementary Information 3). Cilia are evolutionarily-conserved hair-like cell structures that can function as cellular environmental sensors or provide locomotion, but are also important for lung and airway health in cold and dry environments.

Genes associated with neuronal functions comprised 31% (10/32 genes) of the Eurasian driver genes, 33% of selected loci in cold-adapted modern humans, and 35% of AI genes from archaic hominins (Supplementary Information 3). The dominance of signals for neurology-associated genes was not necessarily expected, but neural tissues play a central role in coordinating environmental information into physiological and behavioural responses necessary to navigate new environments[33]. Human cognitive performance is also impaired in

cold conditions[34], and, intriguingly, eight of the ten selected Eurasian driver genes associated with neuronal function are associated with severe retardation and developmental delay phenotypes in humans (Tables 1, Extended Data Table 5). Collectively, the neuronal selected genes highlight fundamental neurological processes of vesicle trafficking, growth of neurites and cerebral cortex formation, suggesting that there has been selection on the maintenance of environmental perception and cognitive functions in cold environments (Extended Data Table 5). In this regard, the driver gene *MPP6* is required for nerve myelination, which changes in response to environmental cues throughout life and may represent a plastic neural response to environmental challenges (Supplementary Information 3).

Human genetic adaptation through time

Based on the temporal patterns, the genetic signals appear to reflect a consistent selective pressure for cold adaptation, which had started by the middle of the Arabian Standstill period and continued through the colonization of Eurasia and into the Last Glacial Maximum (20ka). While the marked cold conditions characterizing much of late Pleistocene Eurasia are well known, the Arabian Standstill was also characterized by a pronounced and sustained cooling phase from 80ka, associated with the termination of Marine Isotope Stage 5, during which the mean annual temperatures in the Arabian Peninsula are estimated to have decreased ~4˚C (likely greater during the boreal winter)[35]. The limited ability of AS populations to migrate in response to this major climatic change is likely to have exacerbated selective pressure, consistent with the ~80ka estimated age for the earliest sweeps[26] (Supplementary Information 2). Further major environmental challenges potentially included the Mt. Toba supervolcanic eruption at 74ka, which heavily impacted the Indian Ocean and Arabian Peninsula area[36]. The impacts of Mt. Toba on low latitude sites has been suggested to have been severe, with a pronounced cooling period of centuries to millennia, associated with extreme aridity and vegetation change[36].

The large amount of genomic information now available from ancient and modern AMH specimens, along with extensive databases of human functional and disease genetics, provides a unique opportunity to use the global spread of AMH as a model system to study the tempo and mode of evolutionary selection from a genomic perspective. Our analyses have revealed the prevalence of hard sweeps in recent human history, many of which appear to have been subsequently eroded by recent population admixture, with only around half previously identified as potential soft, partial, or hard sweeps in modern population data[7].

The hard sweeps provide an unexpected view of evolution, with the majority of gene targets concentrated around evolutionarily-conserved intracellular machinery (Table 1, Extended Data Table 5), dominated by enzymes, components of intracellular protein signaling complexes, and transcription regulators as opposed to cell surface receptors and ligands, which might seem more obviously associated with sensing and responding to new environments. We also find that neurological processes appear to be under-appreciated candidates for selection in adaptive responses. The latter observation most likely relates to the critical role the nervous system and brain play in regulating homeostasis of peripheral physiology in response to environmental cues including body temperature, circadian clock

responses, pregnancy, as well as the cardiovascular, metabolic and immune systems[26,37–39] (Supplementary Information 3). Thus, recalibration of neurological processes towards new physiological optima may represent a critical mechanism for rapid adaptation to changed environmental conditions (*e.g.* cold). In contrast, the absence of genes involved in the immune system stands out, especially as these appear to have been repeat targets for Arctic human populations and archaic hominin AI loci after the initial Neandertal admixture ~53ka[40,41]. The latter raises the question of whether immune selection may have been promoted by hominin admixture itself.

The large number and broad function of the selected loci detected in ancient Eurasians raises the possibility that the speed of AMH movement Out of Africa and across Eurasia may have been limited by the need for genetic adaptation to new environments (*e.g.* during the AS), as much as the existing occupation of areas by archaic hominin groups. For example, the Eurasian dispersal moved very rapidly eastwards through Asia and down as far as southern Australia following a familiar savannah ecozone[15,42] despite the presence of multiple Denisovan and other ISEA hominin groups along this route (where admixture occurred), as well as significant marine barriers through ISEA[15,42]. The contrasting delay before AMH groups start to spread northwestwards throughout Europe from 47ka has often been explained by the presence of Neandertal populations in the area[43], but here we show this delay was potentially associated with a distinct phase of genetic adaptation to cold northern environments, first seen in our dataset as the set of sweeps in the Initial Upper Paleolithic individuals.

This study also highlights the importance of evolutionary history for understanding modern disease. Haploinsufficiency in over half of the Eurasian driver genes causes Mendelian disease phenotypes while 25% are associated with premature lethality (Table 1, Supplementary Information 3), and their medical relevance is further indicated by the lack of loss-of-function mutations in human lineages[26,44] (Extended Data Fig. 7, Extended Data Table 5). Importantly, a number of the loci involve genes or functions associated with major modern diseases including: the ciliopathies (*e.g. DNAH6*; *RCBTB2*), a recently recognized severe disease class that includes sensory, immunological, reproductive as well as developmental abnormalities[45] (Extended Data Table 5); metabolic syndrome, including obesity and diabetes (*e.g. PPARD*); and neurodegenerative diseases including dementia and autism (*TAF15*; *AMBRA1*), all of which represent increasing or significant medical maladies in present-day populations[46,47]. Our study highlights how understanding the evolutionary history and specific environmental pressures shaping modern population genetic structure can aid our understanding of the genetic basis of disease.

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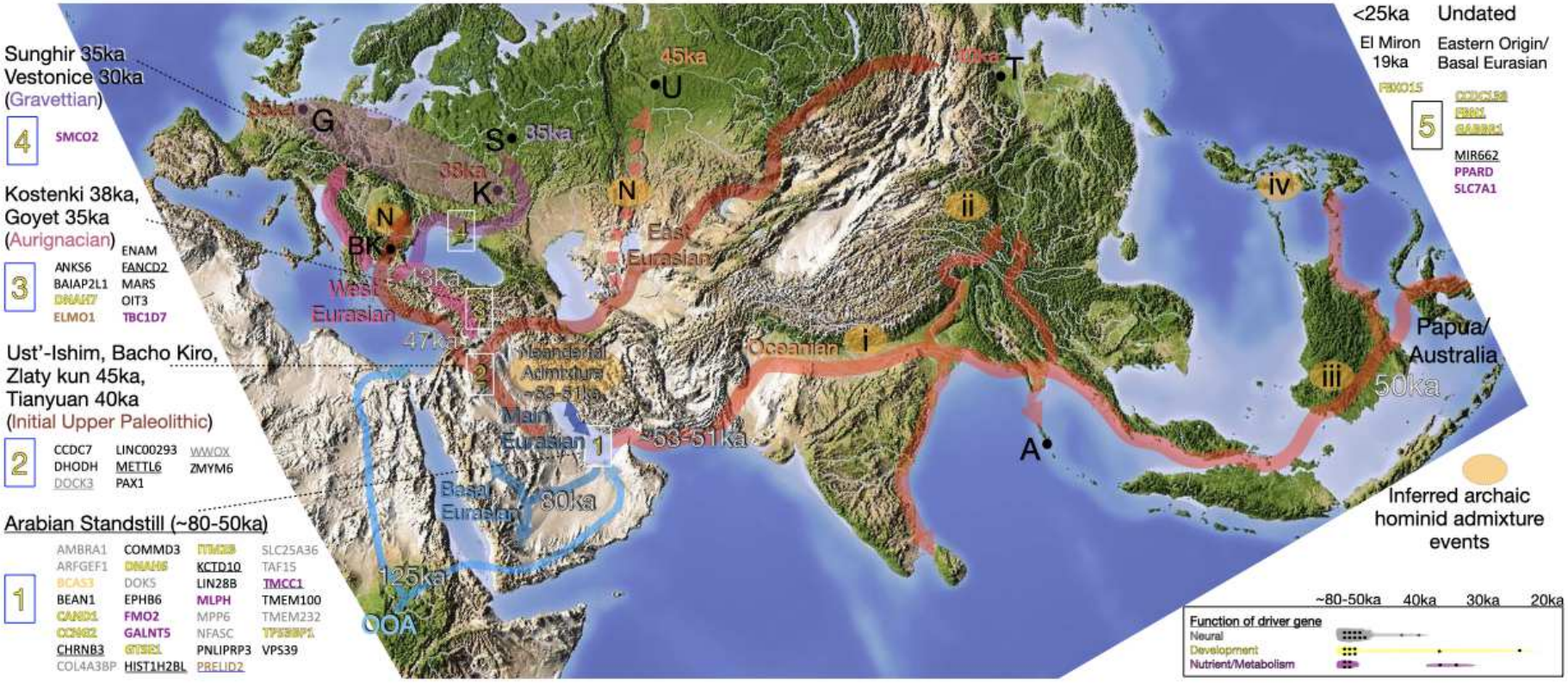
Supplementary Information

Extended Data Figures 1-12

Extended Data Tables 1-8

Data Files 1 to 56

References (*50-203*)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Ust'-Ishim, Bacho Kiro,
Zlaty kun 45ka,
Tianyuan 40ka
(Initial Upper Paleolithic)
2
CCDC7
DHODH
DOCK3
LINC00293
METTL6
PAX1
WWOX
ZMYM6
Arabian Standstill (~80-50ka)
1
AMBRA1
ARFGEF1
BCAS3
BEAN1
CAND1
CCNG2
CHRNB3
COL4A3BP
COMMD3
DNAH5
DOK5
EPHB6
FMO2
GALNT5
GTSE1
HIST1H2BL
ITM2B
KCTD10
LIN28B
MLPH
MPP6
NFASC
PNLIPRP3
PRELID2
SLC25A36
TAF15
TMCC1
TMEM100
TMEM232
TPST2IP1
VPS39
45ka
35ka
38ka
48ka
47ka
Neanderial Admixture ~53-51ka
Main Eurasian
Basal Eurasian
80ka
125ka
OOA
53-51ka
East Eurasian
West Eurasian
Oceanian
50ka
Papua/ Australia
i
ii
iii
iv
A
G
S
K
N
BK
U
T
<25ka
El Miron
19ka
Undated
Eastern Origin/
Basal Eurasian
PRKO15
5
MIR662
PPARD
SLC7A1
Inferred archaic hominid admixture events
~80-50ka
40ka
30ka
20ka
Function of driver gene
Neural
Development
Nutrient/Metabolism

Figure 1. Dispersal of Anatomically Modern Humans Out of Africa. Simplified reconstruction of the movement Out of Africa (125-80ka) into Arabia, and subsequent rapid expansion across Eurasia 60-50ka (or potentially 53-51ka[26,44]; see Supplementary Information 2), based on the spatiotemporal distribution of the 56 hard sweeps and archaeological data. Initial AMH movement into the Arabian Peninsula (~125ka) was followed by an extended period of genetic isolation starting around ~100ka, termed here the Arabian Standstill, during which Basal and Main Eurasians split and hard sweeps accumulate from ~80-70ka. Shortly after a major phase of Neandertal gene flow (dark blue arrow) ~53-50ka, the Main Eurasian lineage rapidly dispersed across Eurasia as far as Australia by 50ka. Discrete spatiotemporal groupings of the 56 hard sweeps are shown (boxes 1-4), with an undated group (box 5) appearing to originate outside the sampling range. Early European movements are simplified into 3 time bins (boxes 2-4) for clarity, with an oval representing the Aurignacian. Areas of inferred admixture with archaic hominins are indicated (i-iv; Denisovans: N; Neandertals). Key ancient specimens/sites: U=Ust'-Ishim, T=Tianyuan, K=Kostenki, S=Sunghir, G=Goyet, A=Andaman Islands. The function of identified driver genes is indicated by colour (key, along with an approximate timescale. brown = reproduction, orange = cardiovascular). Underlining indicates sweeps identified as overlapping with adaptively-introgressed archaic hominin loci.

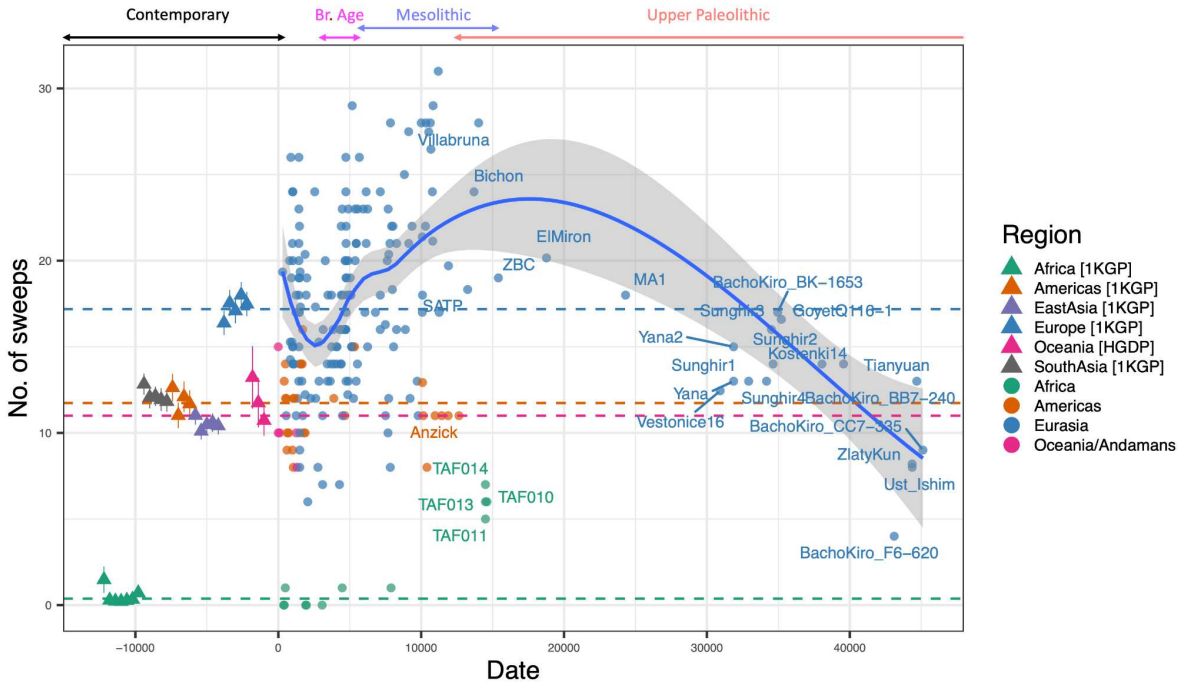

Figure 2. The accumulation of sweep haplotypes through time. Presence of each of the 56 sweep haplotypes in ancient samples (circles) and modern populations (triangles; averages and standard deviations shown; data obtained from the 1000 Genomes Project [1KGP] and Human Genome Diversity Panel [HGDP]). By fitting a local regression (LOESS) of sweep count (y-axis) as a function of sample age (x-axis; samples >10ka are individually labelled) in ancient West Eurasians, we observe that the number of sweeps steadily increases throughout the Upper Paleolithic (~50ka to ~12ka), before plateauing in the early Mesolithic (~15ka) and undergoing a sharp decline that was most pronounced in the Bronze Age (~5ka to ~2.5ka), coincident with high population admixture in Europe. Sweep numbers increase again in European populations across the past few thousand years, potentially as a result of the underlying sweep pressure persisting until recent times. Mean sweep counts for ancient samples (dashed lines; with Moroccan Iberomaurusian samples [*i.e.* TAF10-14] omitted) are consistent with their modern counterparts, suggesting that modern Oceanians should provide reasonable proxies for estimating ancestral sweep presence at the time of population separation from Main Eurasian lineages.

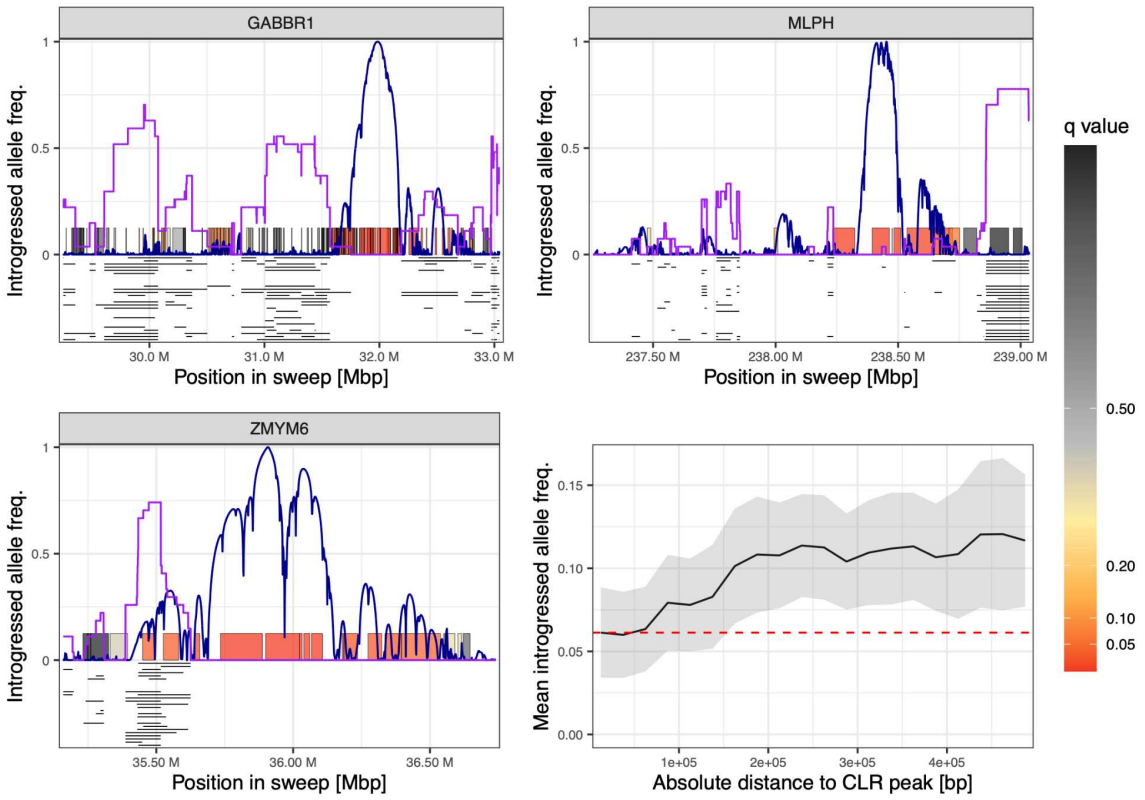

Figure 3. Introgressed archaic hominin loci in the vicinity of ancient hard sweeps. To determine the distribution of introgressed hominin loci around each sweep, we used *admixfrog* software [48] to directly infer these loci in ancient genomes prior to the Holocene admixture events. The inferred loci are shown for each of the 27 Anatolian EF individuals (black lines) for three sweeps (labelled panels), with the resulting allele frequencies at each position being shown as a purple line. For comparison, we also show the *SweepFinder2* CLR scores (blue lines), with the maximum score indicating the most likely location of the underlying causal allele. Each gene in the region is shown as a coloured rectangle, with the colour indicating the genescore used to identify sweeps (see key). Notably, introgressed loci tend to occur at negligible frequencies beneath the peak CLR score and at higher frequencies when moving further away from the peak. This pattern that was more generally borne out across all sweeps (bottom right panel; black line = mean frequency in 25kb bins either side of peak, grey shading = 2 standard errors, red dashed line = mean frequency near peak) – with introgressed loci being significantly more common >150kb from the peak than at the peak – consistent with introgressed loci hitchhiking on a beneficial AMH-derived variant.

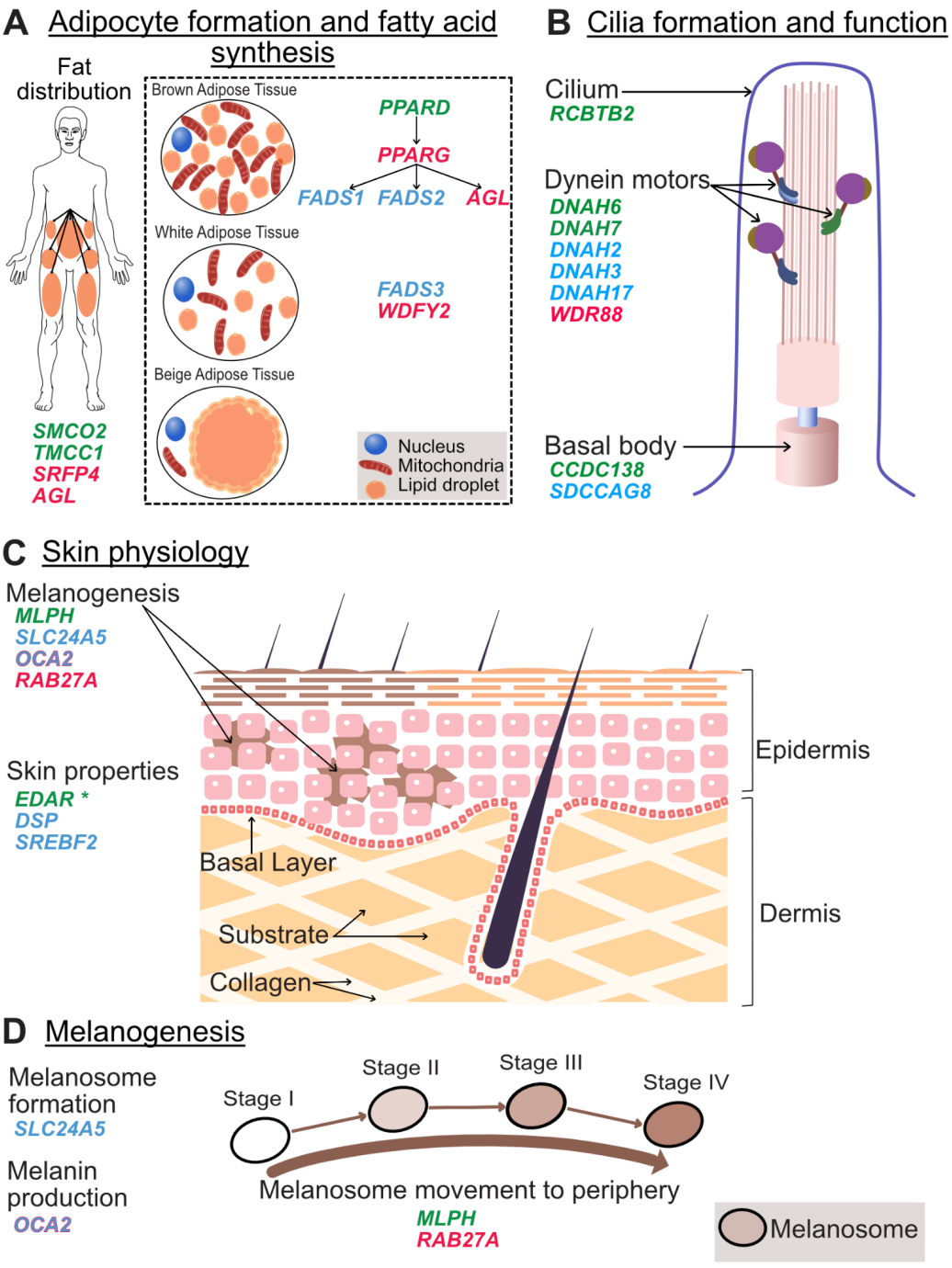

Figure 4. Convergent signals of selection in ancient Eurasian (Green), archaic hominin (Red), modern cold-adapted human groups (Blue); both ancient Eurasian and cold-adapted humans (Green*); both archaic hominin and cold-adapted humans (Purple) in genes that: (A), regulate metabolism through adipogenesis, as well as fat synthesis and fat distribution. Arrows indicate gene regulatory networks; (B) genes involved in cilia function, particularly formation of the basal body complex and dynein motor complexes; and (C) genes that control skin physiology including the 'woolly' phenotype, wound healing, and skin formation; as well as (D) pigmentation through the formation of melanosomes, melanin synthesis within melanosomes and melanosome transport to the cell periphery. See S5 for detailed gene characteristics and functions.

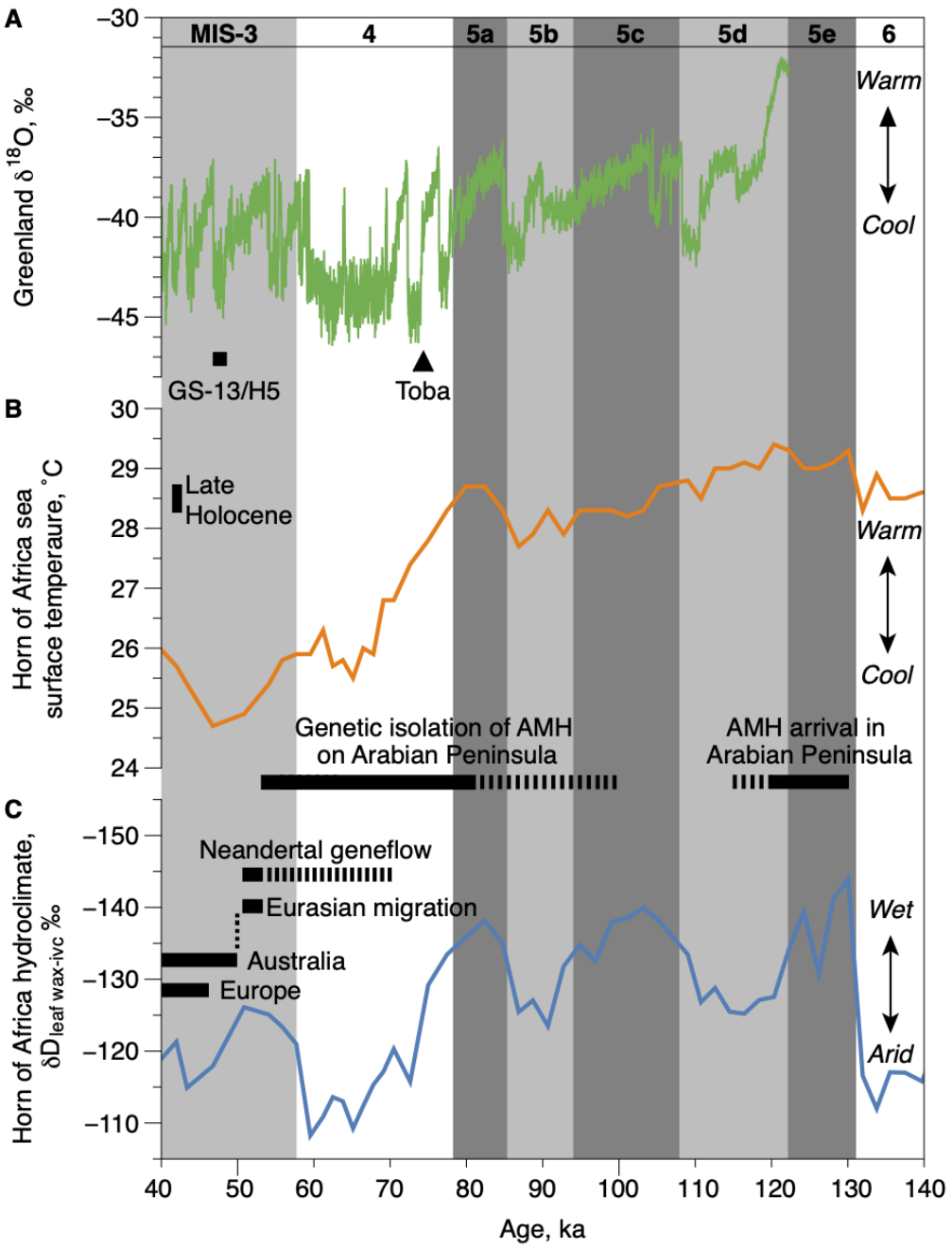

Figure 5. Environmental reconstruction for the Arabian Standstill. AMH groups on the Arabian Peninsula experienced severe cold conditions with the onset of Marine Isotope Stage 4 (~79ka), potentially further exacerbated by the Toba Eruption (~74ka). (A) NGRIP $\delta^{18}O$ record reported on the GICC05 timescale Before Present (CE 1950) [49]; Greenland Stadial 13 (GS-13) and Heinrich 5 (H5), and Mt. Toba eruption [36] are shown. (B) Mean annual sea surface temperatures (SSTs) from the Gulf of Aden marine core MD90-963 [35]. Late Holocene (last 2.5ka) temperature range shown for comparison. (C) Hydroclimate changes in northeast Africa reconstructed from stable hydrogen isotopic composition of leaf waxes corrected for ice volume contributions from MD90-963 [35]. Horizontal bars define age ranges for key AMH events across the Arabian Peninsula and Eurasia, including potential for earlier Neandertal gene flow (dashed line) during Arabian Standstill [26,44].

Table 1. (A) Biological role of genes identified as under strong selection in Ancient Eurasians, cold-adapted modern human groups and archaic hominin introgressed loci. Frequency [%] is calculated from the total number of genes annotated for each respective data set (Extended Data Table 5). (B) Key biological impacts and functions of genes identified as under strong selection in Ancient Eurasians. Frequency [%] is calculated from the total number of genes annotated for each respective data set (Extended Data Table 5). Lethal phenotype defined by spontaneous embryonic lethality or premature lethality post-partum in humans or animals. Constrained genes identified by LOUEF score ≤0.5. Major physiology impact defined as a loss-of-function mutation in human subjects and or from gene targeting studies in animal models which cause at least one of; premature lethality; physical malformations; or, developmental delay. Gene functions defined as Membrane Proteins (receptors, ion pumps, transporters, tethered proteins), Extracellular Proteins (secreted or otherwise released), or Intracellular Proteins (defined as either Enzymes; Transcription Regulators, Signalling molecules etc). Signalling molecules were able to be further classified.

A. Biological impact of selected driver or candidate gene	**Ancient Eurasians** (n = 32)	**Archaic hominin Introgressed** (n = 54)	**Cold adapted human groups** (n = 49)
Neurology	31%	35%	33%
Development	31%	33%	31%
Metabolism	28%	22%	16%
Reproduction	6%	2%	0%
Angiogenesis	3%	0%	0%
Immune	0%	7%	20%

B. Ancient Eurasian Driver Genes	
Lethal Phenotype	**25%**
Constrained Gene	**50%**
Major Physiological Impact	**59%**
Membrane Proteins	**9%**
Extracellular Proteins	**3%**
Intracellular Proteins	**88%**
- Enzyme	22%
- Transcription Regulator	9%
- Molecular Motors	6%
- Other	13%
- Signalling	38%
- Adapters	16%
- Molecular Complex	9%
- Guanidine Exchange Factor	9%
- Kinase	3%

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tobler2021NatureSI.pdf
- EDTable1.SamplesMetadata.xlsx
- EDTable2.57outliersweeps.xlsx
- EDTable3.Sweepfreqsanddates20210711.xlsx
- EDTable4.iSAFEsummary.xlsx
- EDTable5.Functionsummary19.07.21.xlsx
- EDTable6.Ancsampledetails14.July.2021.xlsx
- EDTable7.IntCal2May20.xlsx
- EDTable8.DivergeneGorrillaanalysis.xlsx