Supplementary Information for

The role of ancient genetic selection and climatic factors in the dispersal of anatomically modern humans out of Africa

Raymond Tobler*,‡, Yassine Souilmi*,‡, Christian D. Huber* , Nigel Bean, Chris S.M. Turney, Shane T. Grey,†,‡, Alan Cooper,†,‡

* These authors contributed equally to this work

† These authors contributed equally to this work

 \ddagger Corresponding authors: R.T.: [ray.tobler@anu.edu.au;](mailto:ray.tobler@anu.edu.au) Y.S.: yassine.souilmi@adelaide.edu.au; S.T.G.: [s.grey@garvan.org.au;](mailto:s.grey@garvan.org.au) A.C.: alanjcooper42@gmail.com

This document includes:

Supplemental Materials 1-4

Supplemental Figures S1-S13

Supplemental Tables S1-S10

Links to additional Datasets:

Datasets S1-S56:<https://doi.org/10.25909/22359865>

Dataset S57:<https://doi.org/10.25909/22359874>

Table of Contents

Supplemental Materials 1. Data processing and sweep detection pipeline

Information on genomic population genomic sequence processing and selection scans are outlined in ref. [\(1\),](https://paperpile.com/c/UfkLXS/fbXtc) which examines the masking effects of Holocene admixture on the 57 historical hard sweep signals. Key aspects are summarized in this section for convenience.

1.1 Population designation

The assignment of individuals to 18 distinct populations was governed by minimizing temporal and spatial variability among samples previously defined in the ancient DNA literature as sharing genetic affinities, while also preserving the archaeological context and retaining enough individuals to ensure that our analyses were sufficiently powerful to detect selection. The population assignments in this study produce reasonably distinct genetic clusters in principal component analysis (PCA) space (Fig. S1) that align with previously reported PCA results [\(2–4\).](https://paperpile.com/c/UfkLXS/UdaTS+uplme+zNJEb) We use a population nomenclature that follows the guidelines recently proposed for ancient DNA research [\(5\).](https://paperpile.com/c/UfkLXS/6DuKi)

1.2 Selection terminology and evidence of selection in human history

The classical definition of a hard sweep is based on the fixation of a new beneficial allele and linked neutral variants [\(6\).](https://paperpile.com/c/UfkLXS/cQaKJ) In contrast, soft sweeps capture scenarios where either the beneficial allele is present prior to the onset of selection, such that the allele is present on multiple haplotypes that can potentially be picked up by selection, or where the mutation rate is sufficiently high at the beneficial locus that no single version of the allele is likely to become fixed. In the current study, a 'hard sweep' refers to a locus that has produced a specific distortion of the site frequency spectrum that is detectable by SweepFinder2 (see [section 1.4\)](#page-4-0). This pattern is the characteristic genetic signal produced by a classical hard sweep, but such signals can also be created in cases where selection has driven an initially rare haplotype to high frequencies [\(7\).](https://paperpile.com/c/UfkLXS/UlgdI) Formal evaluation of this issue is provided in ref. [\(1\).](https://paperpile.com/c/UfkLXS/fbXtc)

Another form of selection, known as polygenic selection, involves simultaneous changes across multiple genomic loci that all contribute to the beneficial trait. This mode of selection tends to result in numerous subtle allele frequency shifts that are subsequently unlikely to produce distinctive sweep signals at individual beneficial loci [\(8, 9\)](https://paperpile.com/c/UfkLXS/wEWpQ+vwMBK) and be detected in our analyses.

1.3 Data collection and processing

To produce a robust dataset and avoid potential bioinformatic batch effects, the raw sequence read data for 1,162 ancient genomic datasets (Table S1) was retrieved from the Short Read Archive [\(SRP029640,](https://www.ncbi.nlm.nih.gov/sra/?term=SRP029640) [SRP057056\)](https://www.ncbi.nlm.nih.gov/sra/?term=SRP057056) or the European Nucleotide Archive [\(ERP003900,](https://www.ebi.ac.uk/ena/data/view/ERP003900) [PRJEB6622,](https://www.ebi.ac.uk/ena/browser/view/PRJEB6622) [PRJEB6272,](https://www.ebi.ac.uk/ena/browser/view/PRJEB6272)

[PRJNA230689,](https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA230689) [PRJEB7618,](https://www.ebi.ac.uk/ena/browser/view/PRJEB7618) [PRJEB609,](https://www.ebi.ac.uk/ena/browser/view/PRJEB609) [PRJEB9021,](https://www.ebi.ac.uk/ena/browser/view/PRJEB9021) [PRJEB8987,](https://www.ebi.ac.uk/ena/browser/view/PRJEB8987) [PRJEB9783,](https://www.ebi.ac.uk/ena/browser/view/PRJEB9783) [PRJEB11364,](https://www.ebi.ac.uk/ena/data/view/PRJEB11364) [PRJEB11450,](https://www.ebi.ac.uk/ena/data/view/PRJEB11450) [PRJEB1418,](https://www.ebi.ac.uk/ena/browser/view/PRJEB1418) [PRJEB13123,](https://www.ebi.ac.uk/ena/data/view/PRJEB13123) [PRJEB11848,](https://www.ebi.ac.uk/ena/data/view/PRJEB11848) [PRJEB14455,](https://www.ebi.ac.uk/ena/data/view/PRJEB14455) [PRJEB22629,](https://www.ebi.ac.uk/ena/data/view/PRJEB22629) [PRJEB12155,](https://www.ebi.ac.uk/ena/data/view/PRJEB12155) [PRJEB22652,](https://www.ebi.ac.uk/ena/data/view/PRJEB22652) [PRJEB23635,](https://www.ebi.ac.uk/ena/data/view/PRJEB23635) [PRJEB24794,](https://www.ebi.ac.uk/ena/data/view/PRJEB24794) [PRJEB29603\)](https://www.ebi.ac.uk/ena/data/view/PRJEB29603) and processed through a standardized pipeline. To minimize the risk of modern contamination, the forward and reverse reads of the pairedend reads were merged (collapsed) using fastp [\(10\),](https://paperpile.com/c/UfkLXS/s9Hkq) and only merged reads were retained (modern data is more likely to comprise large DNA fragments that do not collapse). All collapsed reads were filtered for potential residual adaptor sequences and chimeras using Poly-X with fastp [\(10\).](https://paperpile.com/c/UfkLXS/s9Hkq) The retained filtered set of sequence reads were aligned to the human reference genome (h37d) using the Burrows-Wheeler Aligner v0.7.15 [\(11\).](https://paperpile.com/c/UfkLXS/35QS5) All mapped reads were sorted using SAMtools v1.3 [\(12\)](https://paperpile.com/c/UfkLXS/3iD4C) and then realigned around insertions and deletions and potential PCR duplicate reads marked and removed using the Genome Analysis ToolKit (GATK) v3.5 [\(13\).](https://paperpile.com/c/UfkLXS/3S8Li)

Prior to variant calling, all remaining aligned reads were screened and base-calls recalibrated for aDNA postmortem damage using mapDamage2 [\(14\).](https://paperpile.com/c/UfkLXS/FvOrc) To further limit the impact of postmortem damage on variant calling [\(15\),](https://paperpile.com/c/UfkLXS/1UpR1) bamUtil [\(16\)w](https://paperpile.com/c/UfkLXS/HINEx)as used to trim 3 base-pairs from each of the 5' and 3' ends of each mapped read. From the resulting set of reads, pseudohaploid variants were called at the set of 1240k capture SNPs [\(3\)](https://paperpile.com/c/UfkLXS/uplme) across the 22 autosomes, using a combination of SAMtools mpileup [\(17\)](https://paperpile.com/c/UfkLXS/5HsUt) and sequenceTools [\(https://github.com/stschiff/sequenceTools\)](https://github.com/stschiff/sequenceTools). The 1240k capture was developed to minimize ascertainment in non-African populations and was used to generate data for most samples used in the study, whereby concentrating on the 1240k variants ensured a common and robust set of variants for the subsequent analyses. Pseudohaploidization of read data is a standard strategy in aDNA analyses, whereby a single read is randomly sampled at each prespecified SNP position [\(3\)](https://paperpile.com/c/UfkLXS/uplme) in order to mitigate potential biases introduced by differences in coverage or post-mortem damage between samples [\(2\).](https://paperpile.com/c/UfkLXS/UdaTS) The pseudohaploid variant calls were converted from EIGENSOFT format [\(18, 19\)](https://paperpile.com/c/UfkLXS/viNdO+VeGSI) to binary Plink format using EIGENSOFT. Plink v1.9 [\(20, 21\)](https://paperpile.com/c/UfkLXS/Dnxs7+3J8lJ) was used to assign samples to the predefined populations (Table S2) and convert the variants to reference polarized VCF files, with correct polarization being checked using BCFtools [\(17\).](https://paperpile.com/c/UfkLXS/5HsUt) Finally, a custom Python script was used to generate the site frequency spectrum (SFS) input files for SweepFinder2 analysis [\(https://gist.github.com/yassineS/fe2712ad52d76460b927e3f391ea51f6\)](https://gist.github.com/yassineS/fe2712ad52d76460b927e3f391ea51f6).

1.4 Sweep scans

We computed the SweepFinder2 CLR (composite likelihood ratio) statistic [\(22, 23\)](https://paperpile.com/c/UfkLXS/xxu9W+tQHiA) across the genome in successive 1kb intervals for all 18 ancient, along with five modern human populations from the 1,000 Genomes Project (i.e. Utah residents with Northern and Western European ancestry (CEU); Finnish in Finland (FIN); Toscani in Italy (TSI); Han Chinese in Beijing (CHB); Yoruba in Ibadan, Nigeria (YRI); ref. [\(24\)\)](https://paperpile.com/c/UfkLXS/0VsCz). Allele frequency data and SweepFinder2 results for individual ancient populations can be accessed at [https://doi.org/10.25909/6324956ee6ba6.](https://doi.org/10.25909/6324956ee6ba6)

The CLR statistic evaluates evidence for hard sweeps in dynamically sized windows, by comparing the distribution of allele frequencies expected under a mathematical model of a hard sweep with the expectation under neutral evolution (larger CLR scores indicate more evidence for selection). The

expected site frequency spectrum (SFS) under the hard selective sweep model is computed conditional on the neutral SFS, assuming a certain selection coefficient and recombination rate. The neutral SFS is based on the background SFS calculated from the whole genome, assuming that the influence of sweeps on the SFS on a genome-wide scale is negligible.

SweepFinder2 is robust to genome-wide effects such as ascertainment bias and demography [\(25\)](https://paperpile.com/c/UfkLXS/FQvA4) by allowing these processes to affect the expected SFS under neutrality (i.e. the background SFS). Further, unlike many other selection methods, the assumptions on the input data for SweepFinder2 are suitable for the low coverage and ascertained nature of ancient DNA datasets. Since it is only based on the spatial (genomic) pattern of allele frequencies but not on haplotype homozygosity or population differentiation, it is possible to detect selection without reference to a second population, calling genotypes, or phasing haplotypes. The reliance on an empirically estimated null model (i.e. the background SFS) and the model-based alternative hypothesis makes it both more powerful and more robust compared to alternate test statistics that are based on deviations of the SFS from expectations under the standard neutral model (e.g. Tajima's *D*, Fay and Wu's *H*).

While SweepFinder2 also has an option to detect sweeps based on local genomic reductions in diversity, we did not calculate this diversity-based metric since accurate and unbiased estimation of diversity requires full genome data, whereas our dataset consists of a set of ascertained SNPs.

1.5 Outlier gene detection

Human gene annotations were obtained from ENSEMBL database [\(26\)](https://paperpile.com/c/UfkLXS/UlrjD) (genome reference version GRCh37), which was accessed using the R bioMart package [\(27, 28\)](https://paperpile.com/c/UfkLXS/LFrsy+uuXJ5) (version 2.36.1). Of the 24,554 annotated 'genes' on the bioMart database, we removed any that were not annotated in the NCBI database [\(ftp.ncbi.nih.gov/gene/DATA/GENE_INFO/Mammalia/Homo_sapiens.gene_info.gz\)](http://ftp.ncbi.nih.gov/gene/DATA/GENE_INFO/Mammalia/Homo_sapiens.gene_info.gz) and also excluded those that lacked specific protein and RNA based annotations (in the bioMart transcript biotype field). This resulted in a list of 19,603 genes, from which we removed 26 that did not contain any polymorphic sites in our datasets (all such genes being situated in the most terminal areas of chromosomes), leaving 19,577 genes that were used in the subsequent analyses. For each population, all SweepFinder2 CLR scores were *log*10 transformed and assigned to each of 19,577 genes by binning the transformed scores within the genomic boundaries of each gene. The gene boundaries were extended by 50kb on either side to also capture *cis-*regulatory regions. Because this typically resulted in several scores per gene, we took the maximum score to represent the evidence for a sweep involving that gene. Each gene score was corrected for gene-length using a non-parametric standardization algorithm [\(29, 30\),](https://paperpile.com/c/UfkLXS/tpaRA+q333K) resulting in the gene scores having an approximately standard normal distribution. Finally, *p* values were calculated for all genes and a *q* value correction [\(27\)](https://paperpile.com/c/UfkLXS/LFrsy) applied for each population. The *q* value is a Bayesian posterior estimate of the *p* value that accounts for the expected inflation of false positives due to multiple testing [\(27\),](https://paperpile.com/c/UfkLXS/LFrsy) whereby a *q* value of 0.01 implies a false discovery rate of 1% per population.

1.6 Candidate sweep classification

Sweeps were identified by determining a set of outlier genes across all populations (above), which were classified into sweep regions according to 1) the distance between the mid-point of neighboring pairs of outlier genes (i.e. inter-gene distance) and 2) overlapping sweep regions between populations. Step 1 was performed independently for each population, whereby all outlier genes with midpoints that were less than a specific distance apart from the midpoint of a neighboring outlier gene were collapsed into a single category. After generating the collapsed categories for each population, step 2 was applied to ensure that the sweep categories sharing at least one gene across different populations were considered as a single historical sweep.

We ran our sweep quantification pipeline at three *q* value thresholds (i.e. $q \le 0.01, 0.05$ or 0.10, which imply false discovery rates of 1%, 5% and 10% per population, respectively) and the three different inter-gene distances (midpoint distances less than 250kb, 500kb or 1Mb). As expected, changing the *q* value had a large impact on the number of sweeps (ranging from ~ 50 for $q \le 0.01$ to ~ 500 for $q \le 0.1$), whereas changing the inter-gene midpoint distance had comparatively little impact overall, particularly at more stringent *q* value cutoffs (see ref. [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc). Based on these results, we decided to use the most stringent *q* value cutoff and the most liberal inter-gene distance to define a robust set of candidate sweeps for all further analysis. However, because this stringent cutoff might lead to the removal of potentially causal genes in a sweep (which could have values slightly above 0.01), we first defined our sweeps based on the more permissive $q \leq 0.1$ threshold, and then removed all sweeps that did not have at least one gene with $q < 0.01$.

To further improve sweep determination, we removed populations with small sample sizes from the sweep determination process, as previous results of modern genomes suggest that SweepFinder2 has poor power to detect sweeps when less than 10 haploid genome copies are being analyzed [\(31\).](https://paperpile.com/c/UfkLXS/TEYxV) Specifically, we removed populations with an effective sample size, *n*eff, less than 10, as these populations had poor power and exhibited notable distorted gene score distributions in both empirical data and under neutral simulations of population history (see ref. [\(1\)](https://paperpile.com/c/UfkLXS/fbXtc) for a full description of the simulation framework and statistical properties of the analytical pipeline). The *n*eff metric captures the composite effect of sample size, ploidy and data missingness in a paleogenomic context, and is defined as $n_{\text{eff}} = k \times n \times (1 - M)$, i.e. the product of the ploidy of each sample (*k*) with the sample size (*n*) and the average proportion of non-missing sites (*M*) (also see ref. [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc).

Finally, to ensure that the sweeps being defined were all relevant to western Eurasian history, the two modern populations from East Asia (CHB) and Africa (YRI) were also excluded from the sweep classification process. This strategy resulted in a total of 57 candidate sweeps that were used in subsequent analyses. Plots showing the distribution of SweepFinder2 CLR scores and the transformed gene scores within each candidate sweep are provided as Datasets S1-S56 [\(https://doi.org/10.25909/22359865\)](https://doi.org/10.25909/22359865).

1.7 Impact of SNP missingness on sweep detection

We examined if SNP missingness (i.e. the proportion of samples that lack a pseudohaploid allele call at a given SNP) was impacting sweep detection in the ancient populations by regressing gene scores against the average level of SNP missingness observed in each gene (extending gene boundaries by 50kb to make gene definitions compatible with our analytical pipeline). This regression analysis was performed separately for each ancient population used in the sweep detection assay (i.e. populations with $n_{\text{eff}} \geq 10$; see [section 1.6](#page-6-0) and ref. [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc).

For all ancient populations, gene scores tended to decrease gradually as the mean SNP missingness increased (Fig. S2). These results likely reflect a loss of power to detect selection in regions with reduced genetic information and suggest that SNP missingness is unlikely to have inflated the number of false positives in our study.

1.8 Comparison with SweepFinder2 scans in modern African populations

The 57 sweep signals observed in ancient Eurasian populations were absent in modern Yorubans from West Africa (i.e. YRI), consistent with the underlying selection pressure most likely arising after the separation of African and non-African human lineages. To explore the origin of the sweeps in more detail, we examined if any of our 57 sweep regions overlapped with positively selected regions identified in a recent study of high coverage genomes from multiple African populations [\(32\).](https://paperpile.com/c/UfkLXS/qiJub) We compared our 57 sweeps to the 492 reported candidate loci identified in six different African populations, finding nine unique African candidate loci that overlap four of our sweeps (namely, *DOCK3*, *GABBR1*, *PNLIPRP3*, *MIR662*). To test if the four selected regions found in our study and also ref. [\(32\)](https://paperpile.com/c/UfkLXS/qiJub) were consistent with random expectations, we used the R package regioneR [\(33\)](https://paperpile.com/c/UfkLXS/6yy9l) to randomly sample 57 genomic windows from across the genome that matched the sizes of our sweeps, then counted the number of sweeps that overlapped at least one of the 492 candidate regions from ref. [\(32\).](https://paperpile.com/c/UfkLXS/qiJub) We obtained an empirical *p val*ue by repeating this sampling process 10,000 times and calculating the proportion of random samples that had an equal or larger number of sweeps overlapping African candidate regions than we observe (i.e. four unique sweeps).

We also repeated this process to account for the possibility that both our hard sweep signals and the reported outlier windows were more likely to be detected regions with low recombination rates (which may have more power in genome-wide selection scans), by sampling from a modified genome that had been rescaled according to the local recombination rate. Specifically, we used the sex-averaged recombination rates measured across 10kb genomic intervals [\(34\)](https://paperpile.com/c/UfkLXS/8fPLj) to rescale the length of each interval (l_i) according to $l_i = 1/(1+r_i)$, where r_i is the recombination rate for the *i*th genomic interval. We also rescaled each sweep window through linear interpolation to the recombination-rescaled genome and used regioneR [\(33\)](https://paperpile.com/c/UfkLXS/6yy9l) to randomly sample 10,000 sets of 57 genomic windows matching these lengths from the rescaled genome. The sampled windows were then converted back to a standard physical length by interpolating to the original (unscaled) genome, and the overlap with outlier regions tested in the standard way.

Both the standard permutation test and the recombination rate adjusted test returned non-significant results (Standard test: expected number of overlapping sweeps \sim 2.92, $p = 0.33$; Recombination rate adjusted test: expected number of overlapping sweeps \sim 3.32, p = 0.3986), consistent with the number of overlaps between the two studies matching chance expectations. Thus, our results are consistent with the 57 sweeps observed in this study arising after the separation of ancestors of modern Eurasians from African lineages.

Supplemental Materials 2. Inferring selection onset and sweep dynamics

2.1 Determining marker alleles for sweep haplotypes

Our analyses suggest that the underlying selection pressure driving the 57 sweeps most likely arose following the separation of the ancestors of non-African populations with ancestral African AMH lineages (see [section 1.8\)](#page-7-1). The deep antiquity of this separation $(\sim 100$ ka; [\(35\)\)](https://paperpile.com/c/UfkLXS/8Lch1) should mean that SNPs linked to the 57 sweep haplotypes have become highly diverged when contrasting Eurasian populations with contemporary African populations. Accordingly, we sought to identify a set of up to 30 marker SNPs in each sweep that were highly divergent in all pairwise comparisons between modern Yorubans (i.e. *YRI*) and the tested Eurasian populations.

To calculate population divergence, we used Hudson's F_{st} estimator (specifically, equation 10 from ref. [\(36\)\)](https://paperpile.com/c/UfkLXS/75UoE) to calculate pairwise F_{st} in each Yoruban-Eurasian pair across all \sim 1M SNPs in the genome. For each pairwise test, we excluded SNPs that did not have at least 10 copies in each population (this condition was always satisfied for the Yoruban population, so was dependent on the number of samples and SNP missingness in the relevant Eurasian population). For each sweep, we then averaged the *F*st values after omitting values from Eurasian populations that did not show evidence for the sweep signal (i.e. populations that had no gene with $q < 0.2$ across the specific sweep region). In addition to estimating the mean *F*st for SNPs within sweep regions, we also computed this statistic for all SNPs occurring in regions of the genome lying outside of the 57 sweep regions. These SNPs provide a conservative 'neutral' background (conservative because it will also include SNPs from regions impacted by positive selection that are not detected by our selection scan), which we used to calculate thresholds to identify the most strongly differentiated SNPs in each sweep region. Accordingly, we excluded all SNPs in sweep regions with mean F_{st} values below the 80th percentile of 'neutral' mean *F*_{st} values (the threshold mean *F*_{st} value ranged from ~0.2 to 0.27 across all sweeps and tended to increase as an inverse function of the number of Eurasian populations used to compute the mean). The remaining SNPs were ranked according to the mean *F*st and up to 30 with the lowest ranks (i.e. highest mean *F*st) were chosen as marker SNPs.

After identifying the set of marker SNPs for each sweep region, for each marker SNP we determined the putative allele linked to the sweep haplotype as the most common (major) allele across the same subset of European populations that were used to calculate the mean *F*st. To ensure that the major allele was robust to our choice of frequency estimator, we calculated the mean SNP frequency in two ways – either by 1) calculating the average across the raw population frequencies or 2) weighting the population frequencies by the by number of samples in each population – and only kept SNPs that produced the same major allele with both estimators. Applying this procedure to each sweep resulted in a unique set of up to 30 marker alleles. The position of the marker SNPs in the sweep is shown in Datasets S1-S56 [\(https://doi.org/10.25909/22359865\)](https://doi.org/10.25909/22359865). To ensure that sweep haplotype estimation was robust to SNP missingness, only samples with at least 50% of marker SNPs in a particular sweep were evaluated. Note that one sweep (*LINC01153*) was excluded from further marker-based analyses as it

only had 3 SNPs that passed all marker filtering criteria, whereas all other sweeps had ≥ 6 marker SNPs and the majority $(46/57; -81\%)$ had 30 or more marker SNPs.

2.2 Sweep haplotype detection methods and datasets

Sweep haplotypes were defined as present in the genome of a particular ancient sample if a certain minimum proportion of marker alleles were observed at all called pseudohaploid sites within a sweep region. Specifically, to determine sweep presence, we tested different combinations of the number of marker SNPs and the minimum proportion of marker alleles observed – i.e. either 90% or 95% of the top 10, 20, or 30 ranked marker alleles – creating six categories overall. For each sample, we determined sweep presence based on the aggregate signal across all six categories, requiring the sweep to be present in at least three of the six categories. We chose this intermediate value as it provides a reasonable balance of the false positive and false negative rate (see [section 2.5](#page-15-0) for details). For samples where diploid calls were available (i.e. all modern samples and high coverage ancient samples such as Ust'-Ishim), we randomly selected a single allele at all SNPs to mimic pseudohaploidy prior to making haplotype calls. The statistical consequences of the pseudohaploidization process on our sweep haplotype inferences are discussed in [section 2.5.](#page-15-0)

Sweep haplotype presence was quantified in ancient and modern genomic data to perform three complementary sets of analyses: (1) model-based inference of sweep haplotype dynamics in Eurasian history [\(section 2.3\)](#page-12-0) (2) regression and population genetic models to estimate the approximate onset of the underlying selection pressures [\(section 2.4\)](#page-13-0), and (3) a heuristic approach to reconstruct migratory movements subsequent to AMH dispersal into Eurasia [\(section 2.8\)](#page-23-0).

For all three analyses, we created a set of 39 ancient Eurasian samples, which comprised recently published samples from the Eurasian Upper Paleolithic – namely, Zlaty kun [\(37\)](https://paperpile.com/c/UfkLXS/PDeTe) in Czechia and six specimens from Bacho Kiro [\(38\)](https://paperpile.com/c/UfkLXS/H5LT2) in Bulgaria – and 32 high quality ancient samples curated in the Allen Ancient DNA Resource (AADR; version 42.4), a collection of ancient, archaic, and modern human genomes curated by the Reich Laboratory in Harvard University [\(https://reich.hms.harvard.edu/allen](https://reich.hms.harvard.edu/allen-ancient-dna-resource-aadr-downloadable-genotypes-present-day-and-ancient-dna-data)[ancient-dna-resource-aadr-downloadable-genotypes-present-day-and-ancient-dna-data\)](https://reich.hms.harvard.edu/allen-ancient-dna-resource-aadr-downloadable-genotypes-present-day-and-ancient-dna-data). These AADR samples were all at least 10,000 years old and had a valid pseudohaploid call for more than 600k of the \sim 1.1M capture probe SNPs. Alignment (i.e. BAM; [\(12\)\)](https://paperpile.com/c/UfkLXS/3iD4C) files for the Zlaty kun and six Bacho Kiro specimens were downloaded from links provided in each paper and pseudohaploidized according to the protocols outlined in [section 1.3](#page-3-3) of the Methods. Two of the Bacho Kiro samples (BachoKiro_AA7- 738 and BachoKiro_CC7-2289) had too few sites for robust haplotype detection and were removed from all subsequent analyses.

In addition to the 32 ancient samples, for the haplotype dynamics model [\(section 2.3\)](#page-12-0) we included an additional 424 Holocene-era (<10ka) European individuals from the AADR with reasonable SNP coverage ($\geq 600k$ SNPs), focusing on samples from three distinct geographical regions with reasonable temporal coverage over the Holocene period (sample numbers indicated in square brackets, see Table S3 for the full sample list):

- 1) The British Isles: Great Britain [110], Ireland [7]
- 2) Central Europe: Germany [50], Czech Republic [52], Hungary [75], Poland [43]
- 3) the Iberian Peninsula: Portugal [15], Spain [72].

The broad temporal coverage within each of these three regions allowed us to discriminate the impacts of Holocene admixture events within geographically bounded regions and to ascertain whether any spatiotemporal variation in the sweep haplotype frequencies conformed with reported shifts in genetic ancestry observed across Europe [\(4, 39\).](https://paperpile.com/c/UfkLXS/zNJEb+2DG9v)

For the heuristic analysis of AMH migratory movements [\(section 2.8\)](#page-23-0) we complemented the 32 Paleolithic Eurasian samples with 50 samples from the European Holocene (i.e. < 10,000 years old) that had at least 1 million SNPs with valid pseudohaploid calls. High quality genomes were prioritized for this analysis as initial evidence for sweep haplotype presence was important for inferring possible migratory routes, and higher sample availability and better DNA preservation for the Holocene period permitted more stringent selection criteria for samples from this period (see Table S2). To provide a broad representation of human populations outside of continental Eurasia, we also included historic and ancient samples from Africa (12 samples), the Americas (26 samples), and Oceania and the Andamans (5 samples; collectively referred to as the `Oceanic` group) that had at least 600k marker SNPs present, along with all 2,504 samples from phase 3 of the 1,000 Genomes Project [\(24\)](https://paperpile.com/c/UfkLXS/0VsCz) (all available in the AADR v42.4). Finally, to provide additional representation for the ancient migrations that brought modern humans into Island Southeast Asia and Sahul, we also included 28 Papuan samples from the recent Human Genome Diversity Panel (HGDP; [\(40\)\)](https://paperpile.com/c/UfkLXS/3b8FY). Improved estimates of sample age were obtained for several ancient Eurasian samples (Table S10) using the recent IntCal20 calibration curve [\(41\).](https://paperpile.com/c/UfkLXS/bWLVT)

For the onset time analyses [\(section 2.4\)](#page-13-0) we reused a subset of 22 ancient and modern genomes that we had used in our heuristic analysis of AMH movements (Fig. S11). This set includes Western Hunter Gatherers (WHG) and moderate- to high-coverage specimens from the early period of the Upper Paleolithic, along with several Oceanic samples that our haplotype dynamics analyses (Figs. 1, S3, S4) suggest should provide a reasonable proxy for sweep presence around the separation time of these lineages from the Main Eurasian branch $(\sim 54-51$ ka; see [section 2.6\)](#page-16-0).

Finally, we noticed a strong male bias in the available genomic sequences older than the Holocene that are of sufficient coverage for analysis (20 of 23 samples [87%]; Table S2, Fig. S13). Male sex biases have been detected in Pleistocene megafaunal remains and have been related to behavioral and ranging differences between male and female individuals, particularly young males, and resulting changes in the probabilities of preservation and discovery in the environment [\(42\).](https://paperpile.com/c/UfkLXS/paPSU) However, the vast majority of the 23 pre-Holocene AMH samples were found in human occupation sites (caves, rock shelters, camps) and range widely in geographic location (from western Europe to Beijing) and temporal age (across 35,000 years). This broad range helps provide a reasonable survey despite the small sample size. The high frequency of male specimens with genomic data raises the possibility that there has been a sexbias in burials, at least for sites likely to be sampled for ancient DNA. In contrast, there are nine available hominin genomic datasets that pass our quality filtering criteria for sufficient genomic coverage (one Denisovan, one hybrid Denisovan-Neandertal, seven Neandertal), and of these only one

Neandertal specimen is known to be male, although more are know[n \(43\).](https://paperpile.com/c/UfkLXS/rSoi4) While potentially important from an anthropological perspective, it is not obvious that there are any reasons that a pronounced male bias in the older part of our AMH dataset should noticeably influence our analyses or conclusions.

2.3 Estimating sweep haplotype dynamics

To infer the collective sweep dynamics, we enumerated the number of sweeps present in each sample and regressed this against the reported sample age, using local (LOESS) regression to allow for nonlinear changes in sweep haplotype frequencies (using the loess function from the base R programming language [\(44\)\)](https://paperpile.com/c/UfkLXS/7jxaw). Instances of sweeps missing at least 50% of the total marker SNPs for a particular sample were not evaluated, such that we used the proportion of total sweeps (i.e. the number of sweeps present in a sample relative to all evaluated sweeps) as the explanatory variable to account for missing sweep information in some samples. Separate LOESS regressions were performed for each of the three Holocene groups combined with 32 Paleolithic Eurasian samples, and also using three different values for the span parameter (i.e. 0.35, 0.5, 0.65, which determines the proportion of neighboring samples used to fit the local regression). These span values were based on the range of optimal spans obtained across all three geographically bounded regions and also the three haplotype detection criteria used in this study (see [section 2.2\)](#page-10-0), which were estimated using generalized cross validation (loess.as function from the fANOVA R package v. 0.6-1 [\(45\)\)](https://paperpile.com/c/UfkLXS/NVuRl).

The LOESS regression trends reveal that the hard sweeps accumulate steadily across the Eurasian Upper Paleolithic before undergoing a marked decrease in all three regional European groups from the late Glacial/early Holocene (Figs. 1, S3). While the lack of British Isle samples dated prior to 6ka preclude obtaining more nuanced patterns of events during the early Holocene period, several trends are evident among the Iberian and Central European samples that corroborate previous work showing admixture to be an effective means of masking historical hard sweep signals [\(1\).](https://paperpile.com/c/UfkLXS/fbXtc) First, the sweep haplotype counts exhibit two broadly synchronous periods of marked decline around 8ka and 4.5ka in both Iberian and Central European populations, which coincide with the documented introduction of Anatolian and Steepe related ancestry into these regions, respectively [\(2, 39, 46\).](https://paperpile.com/c/UfkLXS/UdaTS+2DG9v+4wtl4) Second, the sweep haplotype counts rebound strongly in between these two admixture events, a period coincident with the re-emergence of local hunter gatherer ancestry reported across much of Europe [\(2, 4, 39, 46–48\).](https://paperpile.com/c/UfkLXS/UdaTS+2DG9v+4wtl4+Uree8+PG7W8+zNJEb) Finally, the sweep counts appear to have undergone a further decline within the past thousand years in Iberian populations before recovering again in contemporary populations from this region (Figs. 2, S4). This trend aligns with previous reports of an influx of North African, sub-Saharan African, and Levantine related ancestries during the Moorish conquest of Iberia from ~700 CE and the subsequent resurgence in local European ancestry following the expulsion of Moor-related descendant communities over the ensuing centuries [\(39\).](https://paperpile.com/c/UfkLXS/2DG9v)

Importantly, all observed relationships between sweep presence and sample age were almost identical after accounting for the SNP missingness among the samples (i.e. redoing the LOESS analysis using residuals from a linear regression of sweep presence against SNP presence for all 456 samples; Fig. S4), indicating missing data was not a confounding factor in our analyses. Overall, our results closely

corroborate the temporal patterns of sweep signal degradation documented in ref. [\(1\)](https://paperpile.com/c/UfkLXS/fbXtc) and confirm that previously reported admixture events [\(2, 39\)](https://paperpile.com/c/UfkLXS/UdaTS+2DG9v) most likely caused the dilution of historic hard sweeps signals in European Holocene populations.

2.4. Estimating the onset of selection and genetic isolation of OoA migrants

Our LOESS analyses of the aggregate sweep patterns [\(section 2.3\)](#page-12-0) suggest that sweep presence increased at a relatively linear rate in the ancestors of modern Europeans throughout the Upper Paleolithic period. To investigate this pattern further, we used the *lm* function in R v3.6.3 [\(49\)](https://paperpile.com/c/UfkLXS/Sp8IW) to regress the total number of sweeps as a linear function of sample date. Notably, the linear function provided an excellent fit to the 22 ancient and modern samples (see [section 2.2](#page-10-0) for sample list), with an adjusted- R^2 of 0.7048 (Fig. S11A). Under the assumption that sweeps have aggregated in an approximately linear fashion since humans first left Africa, we explored the age when this linear model would indicate the date estimate for zero sweeps (i.e. the predicted x-intercept in the regression model), as this provides a rough estimate for the initial isolation of the OoA population. To account for the uncertainty in the specimen age, for each specimen we sampled ages from a Gaussian distribution that was parameterized by the reported mean and standard deviation estimates (Table S10). For each set of sampled ages, we used the bootstrap *boot* package v1.3-24 in R [\(44\)](https://paperpile.com/c/UfkLXS/7jxaw) to resample the residuals and refit a linear model, to determine 1,000 samples for the x-intercept. We aggregated the x-intercept samples from each of the 1,000 sets of sampled dates and then determined the mean x-intercept to be 83,141 yBP and the associated empirical 95% confidence interval to be between 72,369 and 97,284 yBP.

Since the linear regression model assumes that hard sweeps will accumulate linearly through time – an assumption that may be unrealistic given the complexities of Western Eurasian evolutionary history – we also performed a more extensive analysis that explicitly models key aspects of Eurasian demography and evolutionary history, drawing the relevant parameters from recent population genetic studies of Eurasian history. Specifically, we simulated a demographic scenario where novel beneficial mutations arise at random in a single panmictic population over the last 200,000 years, with the mutation frequency depending on the current effective population size (i.e. beneficial mutations are more[less] likely to occur as *N*^e gets larger[smaller]). The population size dynamics are based on *N*^e estimates leading up to Early European Farmers (EEF) from ref. [\(50\),](https://paperpile.com/c/UfkLXS/r6N7y) which included ancient Eurasian samples in their inference procedure. For simplicity, we ignore other historical events in our model, such as the separation of Main Eurasian and Basal Eurasian lineages and also the Neandertal admixture event. Using the coalescent simulator msms [\(51\),](https://paperpile.com/c/UfkLXS/EoGqe) we simulated 5,000 selected allele frequency trajectories under this evolutionary model. For each selected locus, we also simulated linked neutral genetic variation data across a 5Mb region for the hypothetical EEF population from ~8ka (i.e. LBK branch in ref. [\(50\)\)](https://paperpile.com/c/UfkLXS/r6N7y) and ran these sequences through SweepFinder2 to filter out selected loci that did not leave a significant sweep signal in this population. To ensure that the simulated data match the statistical properties of the ancient data used in the present study, we replicated the empirical SNP ascertainment scheme by conditioning on SNP presence in a simulated African population and also generated the same number of simulated 5Mb sequences as observed for the Neolithic Anatolian

population in the present study. Similarly, selection coefficients were sampled from an exponential distribution with a mean selection coefficient of $s = 1\%$, which leads to selection coefficients that broadly match those estimated from our sweeps (s ranging between \sim 1 to \sim 11%; see ref. [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc). More details of our simulation approach, including command line parameters and estimation of selection coefficients, are available in ref. [\(1\).](https://paperpile.com/c/UfkLXS/fbXtc)

To infer the earliest time for the onset of selection that best fits the data under our evolutionary model, we removed all simulated loci with a significant SFS signal that started prior to time point *x*, and then averaged the frequency trajectories of remaining loci to estimate the aggregate probability of observing a sweep haplotype across time. This is equivalent to estimating the proportion of all sweeps that are observable at each time point, conditional on the sweep arising after time point *x* and being detected by SweepFinder2 in the EEF population 8,000 years ago. Additionally, to incorporate the statistical properties introduced by missing data and sample pseudohaploidization (see [section 2.5\)](#page-15-0) in our estimation, we modeled the probability of detecting a particular sweep haplotype in an individual as *px* $= (1-f_x)^2$ x 0.061 + 2 $f_x(1-f_x)$ x 0.256 + f_x^2 , where f_x is the frequency of the sweep at time point *x*. In other words, we are estimating the expected weighted frequency of the beneficial haplotype at a given time, where the genotype frequencies (assuming Hardy-Weinberg equilibrium) are weighted by the estimated probability of detecting a sweep haplotype given that genotype (see [section 2.5\)](#page-15-0). The subsequent estimates of p_x are then averaged over all selected loci to obtain the probability for detecting a sweep haplotype at time *x*.

To compare the simulated results to our empirical estimates, we used maximum likelihood (ML) to measure the fit of key ancient and modern samples to the predicted p_x value, varying the earliest onset of selection over successive 1,000-year intervals between 25ka to 150ka. Because our simulations were based on a single panmictic population, we only estimated the ML function for ancient Eurasian specimens >30ky old, as more recent specimens are likely to be affected by the substantial structuring observed in West Eurasian populations that arose during the Last Glacial Maximum ~30-15ka [\(52\),](https://paperpile.com/c/UfkLXS/54xGg) and consequently are only expected to contain a subset of all sweeps that occurred along the ancestral lineage that leads to the EEF population. Using the same samples that were used for the linear regression analysis reported above (other than samples dated within the past 30ka), we inferred the probable onset of selection to be 79ka, with a 95% confidence interval spanning between 74 and 91ka (Fig. S11B). Thus, the linear regression and model-based approach arrive at very similar point estimates, ca. 80ka, and concordant confidence intervals (97-72ka and 91-74ka, respectively) for the earliest starting time of selection for the hard sweeps we have detected.

Notably, samples from the Mesolithic (which were not included in the model) have >30% fewer sweeps than expected assuming sweeps aggregate at the constant rate across time. This may result from our model conditioning on the presence of sweep signatures in a hypothetical single panmictic Mainland Eurasian population during the Neolithic, whereas the sampled individuals come from structured Mesolithic West Eurasian populations. Each population is expected to accumulate local sweeps, increasing the number of sweeps overall but depressing the proportion of observed sweep haplotypes in any single subpopulation below what is expected under a panmictic model.

Taken together, the two approaches suggest that following the early initial isolation of the OoA migrants from other African populations (e.g. around \sim 100ka based on genomic data [\(35\)\)](https://paperpile.com/c/UfkLXS/8Lch1), the Main Eurasians became genetically isolated from other contemporaneous populations and started to accumulate hard sweeps from around $80ka$ (\sim 74-91ka). The resulting prolonged period of genetic isolation of \sim 20 to 30 thousand years is far more compatible with the large number of hard sweeps observed in the earliest Oceanic and Eurasian groups than the commonly used 50-60ka estimate for the OoA movement, which is largely based on the mean time of Neandertal gene flow into Main Eurasians. The estimated ~80ka origin for the period of genetic isolation and selection in the ancestral Main Eurasian group also closely coincides with archaeological evidence for the widespread dispersal of AMH populations throughout the Arabian Peninsula area (including the southern Iranian coast) during the final MIS 5 moist phase ~80ka (Fig. 5). Paleoenvironmental reconstructions indicate AMH populations would have been rapidly fragmented and isolated by the return of cold arid conditions shortly thereafter, especially during MIS 4 (\sim 71-57ka), which is consistent with the absence of archaeological evidence for AMH populations in the Arabian Peninsula during this time [\(53, 54\).](https://paperpile.com/c/UfkLXS/Zv06+5q0d) The population fragmentation caused by these movements may also have initiated the separation of the Main and Basal Eurasian populations within the Arabian Peninsula area, which genetic estimates indicate occurred around this time [\(35\).](https://paperpile.com/c/UfkLXS/8Lch1) The above events are shown in Fig. 4, as part of the Arabian Standstill model, while the relationship to the moist phases, and timing of major global drying and cooling events following the onset of MIS 4 (\sim) 71ka) are indicated in Fig. 5.

2.5 Statistical properties of the sweep haplotype detection method

An important consequence of the pseudohaploidization process for our sweep haplotype detection method is that samples that are heterozygous for a specific sweep haplotype may be more likely to be classified as non-sweep carriers, leading to underestimates of the true sweep haplotype frequency in populations where the sweep is at intermediate frequencies. To quantify the impact of pseudohaploidy on our estimation procedure, we measured the presence of each sweep using the phased 1KGP modern datasets, and again after randomly sampling a single allele at each marker SNP to mimic the pseudohaploidy of ancient samples. As expected, the frequency of the sweep haplotype was consistently underestimated for pseudohaploid samples, and underestimates were proportionate to the level of heterozygosity of the sweep haplotype in that population (underestimating the sweep frequency by as much as 20% when the true frequency is around 50%; Fig. S09).

For individual samples, pseudohaploidization will not affect sweep detection in samples that are homozygous for the sweep haplotype (i.e. sweep homozygotes), even in ancient samples where information from some of the marker SNPs may be missing. While errors in allele calling or recombination could potentially result in other alleles appearing at the marker SNPs, the potential impact of these factors will be diminished to some extent because our detection method does not require all SNPs to be present. Thus, we expect that false negatives will be rare and interpret the patchy sweep detection patterns observed across ancient samples to imply that no sweep was fixed prior to the

colonization of Eurasia ~55-50 thousand years ago, although *DOK5* and *LIN28B* appear to have been in very high frequency in the Oceanic and IUP samples.

Ancient samples that carry two non-sweep haplotypes, i.e. non-sweep homozygotes, can still be falsely called as sweep carriers. Such false positive sweeps are expected to largely depend upon the number and informativeness of missing marker SNPs and the similarity of the alleles on non-sweep and sweep haplotypes. Further, our previous results suggest that ancient samples that carry one sweep haplotype and one non-sweep haplotype (i.e. sweep heterozygotes) will tend to be called as non-sweep carriers, but this will be ameliorated to some extent by the factors that impact false positive calls (i.e. the patterns of SNP missingness and allelic similarities between sweep and non-sweep haplotypes). Accordingly, we quantified the impact of pseudohaploidization on the sweep haplotype calling rate for non-sweep homozygotes (i.e. the false positive rate; FPR) and for sweep heterozygotes in ancient samples. To estimate the FPR, for each sweep we randomly sampled 2,000 non-sweep haplotypes from the 1KGP phased samples. We then randomly paired these haplotypes to create 1,000 diploid genomes and sampled a single allele for each marker SNP to generate pseudohaploids. Finally, we set specific marker SNPs to missing, according to the SNP missingness observed in the ancient samples and modern samples that were used to infer the timing of the onset of the selection pressure for each sweep (see [section 2.2\)](#page-10-0). To measure the calling rate for sweep heterozygotes, we repeated the process outlined above after randomly replacing one of the non-sweep haplotypes with a sweep haplotype.

Applying the same test criteria used to detect sweep haplotypes – i.e. the sweep is called in at least three of the six possible tested categories (i.e. combinations of 90% or 95% of the top 10, 20, or 30 marker SNPs) – we found that the FPR was generally below 10% for all combinations of sweeps and samples (Fig. S10). As expected, the sweep detection rate is systematically elevated in sweep heterozygotes (i.e. when replacing one of the non-sweep haplotypes with a sweep haplotype), and this is strongly positively correlated with the FPR (Fig. S10). This positive correlation appears to be largely the result of non-sweep haplotypes being more like the sweep haplotype, as this increases the probability that alleles on the non-sweep haplotype will match the homologous sweep marker allele.

Taken together, our results indicate that our sweep detection method will tend to underestimate sweep presence in ancient samples. Based on the criteria used in the study (i.e. the sweep is called in at least three of the six possible tested categories), only around 26% of sweep heterozygotes will be called as sweep carriers on average (Fig. S10). Because the FPR is comparatively lower under the same criteria $(-6\%; Fig. S10)$, on balance we are more likely to miss sweep haplotypes in heterozygotes rather than to falsely call them in non-sweep homozygotes.

2.6 Recalibration of age of Neandertal admixture

Genomic data reveals that Neandertal admixture with AMH has been occurring for some time. For example, a limited early admixture event between Neandertals and an early human lineage related to modern AMH (possibly between 270-370 ka, although this is unclear) appears to have resulted in the replacement of the Neandertal Y and mitochondrial genomes by early modern human variants [\(43\).](https://paperpile.com/c/UfkLXS/rSoi4)

This admixture event may have potentially involved the late-surviving Middle Pleistocene fossil *Homo* group recently identified in the Levant [\(55\),](https://paperpile.com/c/UfkLXS/aB2Qz) or *Homo heidelbergensis* in other areas. However, modern global non-African populations contain Neandertal DNA resulting from a much more recent admixture event between Main Eurasians and Neandertals around 50-60ka, thought to have occurred in the Near East immediately prior to the dispersal of AMH across Eurasia. The timing of this admixture has been studied using the size of the Neandertal genomic fragments in the Ust'-Ishim AMH specimen from western Siberia, whose age and high-quality genomic data provide a useful calibration point close in time to the events. The Ust'-Ishim femur has been radiocarbon dated at (41,410 +/- 960 BP), calibrated via IntCal20 at 42.9-46.0ka cal BP (68% CI) [\(41\)](https://paperpile.com/c/UfkLXS/bWLVT) (Table S10). The original calibration via IntCal13 was 44-45.8 (68% CI), or 43.2-46.8ka cal BP (95% CI) [\(52, 56\).](https://paperpile.com/c/UfkLXS/54xGg+XrMro) A recombination clock suggested that 232-430 generations would be required to produce the size distribution of introgressed Neandertal fragments in the Ust'-Ishim genome, under a simple model of a single pulse of Neandertal admixture. This would give an admixture date of 50-60ka using the standard generation time of around 29 years [\(52, 56\).](https://paperpile.com/c/UfkLXS/54xGg+XrMro) This temporal range was constrained by more detailed modeling which indicated the credible range of peak Neandertal gene flow was 7,521 +/- 854y (260 +/-30 generations) earlier than Ust'-Ishim (equating to 50-54ka with the IntCal20 calibration), again under a single pulse model [\(52, 56\).](https://paperpile.com/c/UfkLXS/54xGg+XrMro) However, two distinct size classes of Neandertal fragments were identified in the Ust'-Ishim genome, such that a model of two admixture pulses was much more strongly supported [\(52, 56\).](https://paperpile.com/c/UfkLXS/54xGg+XrMro) The two-pulse model indicated the Ust'-Ishim genome Neandertal content resulted from a major early admixture event (estimated at $6,660 +/- 218y$, or $\sim 228 +/- 21$ generations before Ust'-Ishim, or 49-53ka), along with a minor secondary event that occurred considerably later $(1,258 +113y)$, or $-43 +14$ generations before Ust'-Ishim, or 44-47ka). The latter event was potentially restricted to just the Ust'-Ishim lineage and took place several millennia after the dispersal of AMH groups across Eurasia.

Recent modeling suggests that the admixture date estimates may be sensitive to inhomogeneous recombination rates and have difficulty discerning a single pulse of admixture from ongoing gene flow over potentially hundreds of generations [\(57\).](https://paperpile.com/c/UfkLXS/PRXuj) As a result, the 50-54ka estimate should be regarded as a credible range for the mean time of Neandertal gene flow rather than an absolute range, as this may have started earlier. Similarly, recent analyses using different recombination clocks have suggested a smaller number of generations between Ust'-Ishim and the main Neandertal introgression event, potentially as few as 119 generations, or \sim 3500y [\(37\).](https://paperpile.com/c/UfkLXS/PDeTe) This would suggest the credible range for the main Neandertal introgression event as recently as 46.5-49.5ka, slightly younger than current dates of confirmed AMH presence in Eurasia.

Given the uncertainty around these estimates, we adopt a conservative date estimate of \sim 50-54ka for the main Neandertal gene flow. Importantly, this window aligns closely with a prolonged period of northern hemisphere warmer temperatures recorded in ice core records between the intense cold periods of Marine Isotope Stage (MIS) 4 beforehand (71-57ka), and Heinrich 5 afterwards (49-47ka), shown in Fig. 5. As a result, this period is likely to have seen a rapid increase in size and movement of AMH populations, increasing the likelihood of interactions with neighboring Neandertal populations.

The younger bound for the timeframe of the estimated Neandertal gene flow (50ka) agrees with, and is presumably also constrained by, the AMH settlement of Australia given that Indigenous Australian and New Guinea populations appear to possess the standard Main Eurasian ~2% Neandertal signal, and show no signs of genetic input after their initial settlement of the Sahul continent (mainland Australia, Tasmania, New Guinea and related islands) [\(58–60\).](https://paperpile.com/c/UfkLXS/gX1LT+ShE0F+OrR6h) AMH settlement of Australia has been estimated by several genetic and archaeological studies at being close to 50 ka or slightly earlier, with a range of dated archaeological sites rapidly appearing across Australia between 50-47ka. In contrast, the few dates earlier than 52ka have been widely questioned [\(58–60\).](https://paperpile.com/c/UfkLXS/gX1LT+ShE0F+OrR6h) Similarly, the notable lack of clear archaeological evidence for AMH presence in southeast Asia prior to this period has been highlighted [\(61, 62\).](https://paperpile.com/c/UfkLXS/j9dX7+6FQvz)

The presence of Neandertal genomic content in Aboriginal and New Guinea populations at comparable levels to other Out of African AMH populations suggests that their ancestral lineage diverged from other Main Eurasians after the majority of Neandertal admixture had occurred. Hence, while it is possible that Neandertal admixture with the Main Eurasian lineage may have been ongoing (potentially for many thousands of years) prior to the 54-50ka estimates for the geneflow [\(57\),](https://paperpile.com/c/UfkLXS/PRXuj) it seems likely that the Main Eurasian dispersal (including Ust'-Ishim and the Oceanic group) had not occurred prior to this date. In contrast, the dates associated with AMH settlement of Australia indicates it had definitely occurred by 50ka.

The movement from the Arabian Peninsula area to Australia/New Guinea would presumably take some time as this represents an overland distance of around 18,000 km, and required major marine voyages through eastern ISEA, even with increased land exposure due to \sim 50m lower sea levels [\(62, 63\).](https://paperpile.com/c/UfkLXS/6FQvz+UAu6i) If one millennia is allowed for this movement as a relatively conservative estimate (*i.e.* an average of 18km/yr, which is lower than some suggestions for hunter-gatherer movement through new territory [\(64\)\)](https://paperpile.com/c/UfkLXS/73tFG) this would mean that the Neandertal genomic content of the Sahul populations probably constrains the main Neandertal admixture to being older than ~51ka. As a result of the above lines of evidence, we assume a date of \sim 54-51ka for the Main Eurasian dispersal as our best estimate and use this in the main text and Fig. 4. Importantly however, a more conservative ~50-54ka date (or even 50- 60ka) would not change our conclusions.

One interesting implication of an inferred dispersal of AMH populations from the Arabian Peninsula to New Guinea before 50ka is the rapid nature of the movement, which has been noted previously and has raised questions about the apparent speed of progress through ISEA given that over-the-horizon marine voyaging for hundreds to thousands of individuals was required [\(65, 66\).](https://paperpile.com/c/UfkLXS/rmxXJ+D2p4d) While archaeological evidence during the Arabian Standstill phase is limited as noted above, the potentially prolonged restriction (e.g. from >71-57ka) of main Eurasian populations to coastal sites, such as the southern end of the Euphrates river valley created by lowered sea levels in the Arabian Gulf, has been used to suggest a potential development of nascent marine technology [\(67\).](https://paperpile.com/c/UfkLXS/BF57) Alternatively, analyses of southern African deep mitochondrial branches have been used to suggest early AMH origins in paleo-wetland areas, and that nascent watercraft technology may have been developed early in our history [\(68\).](https://paperpile.com/c/UfkLXS/bIuhF) Either of these scenarios could provide a potential explanation of the apparent lack of noticeable delay for the development of marine technology during the ISEA migration, addressing debates about the extent to which purposeful voyaging and boat construction was possible during this event [\(65\).](https://paperpile.com/c/UfkLXS/rmxXJ) Interestingly, while recent reports place an initial, potentially short-lived, presence of AMH in southern Europe at

54ka [\(69\),](https://paperpile.com/c/UfkLXS/BWXxl) the successful settlement of Europe appears to have been comparatively delayed until ~47ka [\(70, 71\)](https://paperpile.com/c/UfkLXS/w3i5e+uMA3g) possibly due to the cold conditions of Greenland Stadial 13/Heinrich Event 5 (Fig. 5), and the requirement for further genetic adaptation to cold conditions, first seen as the sweeps appearing in the IUP specimens (Figs. 1, 4, Tables S2, S9). Genetic studies of the Zlaty kun specimen from Czechia have suggested that it might represent the earliest member of the OoA population in Europe [\(37\),](https://paperpile.com/c/UfkLXS/PDeTe) but unfortunately partial genomic coverage, a lack of accurate dating and phylogenetic results confound interpretation. As a result, for the moment we have conservatively regarded it as being an early part of the initial IUP invasion of Europe depicted in Figure 4, potentially around 45-47ka.

2.7 Location of Neandertal admixture event and Main Eurasian dispersal

While the geographic location of the inferred Neandertal-Main Eurasian admixture remains unclear, it is likely this took place in the Arabian Peninsula area as essentially all modern and ancient non-African individuals outside of this area appear to carry introgressed Neandertal DNA from this admixture. (Lineages descended from the extinct sister Basal Eurasian group, such as the Bedouin, are thought to have occupied the same area (Fig. 4) but have lower amounts of Neandertal DNA.) The long-term presence of adjacent AMH and Neandertal populations in the northern Arabian Peninsula area provides further support. The apparent consistency of the amount and distribution of introgressed Neandertal DNA in modern non-African human populations suggests that the initial admixing Main Eurasian population was both relatively small, and also stayed together for some time either during or after the admixture phase to allow for the homogenization of the Neandertal genetic contribution across the population prior to the subsequent dispersal across Eurasia. Indeed, some studies have estimated the starting Neandertal genomic content in the admixed AMH population may have been as high as 10% [\(72\)](https://paperpile.com/c/UfkLXS/wIcEX) prior to purifying selection removing deleterious alleles, although it has been noted that this value would be influenced by the nature and timing of the Neandertal gene flow [\(57\).](https://paperpile.com/c/UfkLXS/PRXuj) Similarly, analyses of long-term selection against the Neandertal genomic ancestry content found that most of the decline occurs quickly within the first few hundred generations [\(73\).](https://paperpile.com/c/UfkLXS/H1rVy) Interestingly, a large-scale global genomic analysis indicated that between 2-4 Neandertal individuals would be sufficient to explain the allelic diversity of Neandertal DNA observed in modern AMH populations [\(40\).](https://paperpile.com/c/UfkLXS/3b8FY) The strong implication is that the long-term effective population size of the admixing OoA AMH population must have been very small indeed (potentially a few hundreds) if as few as 2-4 Neandertal individual admixture events could produce an initial post-admixture Neandertal genomic content of 2-3%, or potentially even as high as 10% or more. This is further evidence that the ancestral Main Eurasian population existed as a small population in late MIS 4, consistent with the lack of MIS 4 archaeological records in the Arabian Peninsula area, outside of southern Iran [\(74\).](https://paperpile.com/c/UfkLXS/1MhC)

Paleoanthropological studies suggest early dispersals out of Africa (OoA) and throughout the Arabian Peninsula occurred during climatic moist phases as far back as 400ka, although it is currently unclear as to which movements might represent AMH [\(53, 54, 75\).](https://paperpile.com/c/UfkLXS/Zv06+vvOi+5q0d) By early MIS 5, around ~130ka, stone tools [\(75\)](https://paperpile.com/c/UfkLXS/vvOi) and footprints [\(76\)](https://paperpile.com/c/UfkLXS/rRne) indicate AMH presence (Figs. 4, 5) with initial sites ranging from northern Arabia, to coastal sites such as the Levant (Skhul and Qafzeh) and the Arabian Sea (Jebel Faya) [\(54,](https://paperpile.com/c/UfkLXS/Lqq1+vvOi+5q0d)

[75, 77\).](https://paperpile.com/c/UfkLXS/Lqq1+vvOi+5q0d) Recent fossil discoveries have raised the potential that populations around 140-120ka in the Levant and Negev Desert might have represented a separate, late-surviving, group of Middle Pleistocene *Homo,* which may have interacted with initial AMH populations moving OoA [\(55\).](https://paperpile.com/c/UfkLXS/aB2Qz) However, no genetic signature of this group has been detected in modern genomes, and archaeological evidence suggests that the MIS 5 Arabian Gulf populations in sites like Jebel Faya resulted from a southern dispersal from north eastern Africa across the Red Sea and southern Arabian Peninsula (Fig. 4) and do not appear to have been connected with northern groups [\(54, 77\).](https://paperpile.com/c/UfkLXS/Lqq1+5q0d) However, as noted above, a late-surviving, group of Middle Pleistocene *Homo* in the Levant area may have provided the early human-like mtDNA and Y variants that introgressed into late surviving Neandertals somewhere between 270-416ka [\(43\).](https://paperpile.com/c/UfkLXS/rSoi4) Paleoenvironmental reconstructions also suggest the Levant may have been cut off from AMH populations to the south for much of the past 130ka, or more [\(53, 75\).](https://paperpile.com/c/UfkLXS/Zv06+vvOi)

AMH occupation throughout the interior of the Arabian Peninsula and potentially the adjacent Iranian plateau was associated with short periods of relatively moist climatic conditions in MIS 5e, 5c, and 5a, around 125, 100, and 80ka (Fig. 5), when paleorivers and lakes were apparent [\(74, 78\).](https://paperpile.com/c/UfkLXS/l22d+1MhC) Lowered sea levels during glacial conditions have been proposed to have facilitated AMH movement out of Africa either across the southern margin of the Red Sea and Bab el-Mandeb Strait into the adjacent biodiverse Yemen highlands (southern route; [\(54, 76, 77, 79\)\)](https://paperpile.com/c/UfkLXS/Lqq1+dnVl+rRne+5q0d), or northwards alongside the Red Sea or Nile River Valley, and through the Sinai (northern route; [\(54, 75\)\)](https://paperpile.com/c/UfkLXS/vvOi+5q0d). It has been proposed that arid or mountainous conditions to the north, east, and west of the Arabian Peninsula area in combination with periodic cold arid conditions, limited colonization outside this area [\(53, 54, 75, 77, 78, 80\).](https://paperpile.com/c/UfkLXS/Lqq1+Hul4+l22d+Zv06+vvOi+5q0d) While archaeological evidence demonstrates AMH presence across the Arabian Peninsula during the wet climatic phases, the lack of continuity in material cultures through time has been interpreted as indicating that the intervening cold arid spells (MIS 5b, 5d) caused population contraction and local abandonment. As a result, the predominantly cold arid conditions between 100-57ka (Fig. 5) could help explain the limited signs of AMH dispersal much further than the Arabian Peninsula during this time, with archaeological data suggesting population isolation and primary occupation of coastal sites during arid phases [\(81\).](https://paperpile.com/c/UfkLXS/uWNC) Important coastal sites include the Arabian Gulf, where lowered sea levels during cold stadial periods would have largely exposed the entire Gulf region potentially creating a site allowing AMH population continuity over long periods of time [\(54, 67, 77, 81\).](https://paperpile.com/c/UfkLXS/BF57+Lqq1+uWNC+5q0d) The exposed Gulf is thought to have been a broad river valley featuring numerous subterranean water sources (submarine freshwater springs exist in the southern and southwestern areas today) and a marshy southern margin, creating a potentially important site for AMH populations in the cold arid MIS 4 conditions between \sim 71 and 57ka [\(54, 67, 77\),](https://paperpile.com/c/UfkLXS/BF57+Lqq1+5q0d) although currently the archaeological evidence for MIS 4 occupation in the area is limited to southern Iranian sites such as Boof Cave [\(74\)](https://paperpile.com/c/UfkLXS/1MhC) that borders the northern Gulf. The long-term AMH occupation of this area though different periods of human history has been described as the Arabian Gulf Oasis model [\(54, 67\),](https://paperpile.com/c/UfkLXS/BF57+5q0d) and recent genetic studies suggest that Basal Eurasian populations may have also occupied this area [\(82\).](https://paperpile.com/c/UfkLXS/zbEWX) The Arabian Gulf would have remained a potentially stable occupation area until the early Holocene rise in global sea levels to -40m (~10,000ya) which would have flooded much of the low-lying areas, potentially concealing many archaeological records of earlier occupation. The timing of this inundation is consistent with inferred dispersals of Basal Eurasian populations out of this area in the early Holocene [\(82\),](https://paperpile.com/c/UfkLXS/zbEWX) and the subsequent decrease in apparent sweep frequencies observed across central/southern Europe (Fig. 1; [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc).

Apart from potential MIS 4 southern Iranian sites [\(74\),](https://paperpile.com/c/UfkLXS/1MhC) the current lack of archaeological evidence for AMH presence in the Arabian Peninsula during MIS 4 has been interpreted as indicating a local abandonment of the area due to the cold arid conditions [\(54, 75, 81\).](https://paperpile.com/c/UfkLXS/uWNC+vvOi+5q0d) Consequently, it is important to consider that the extended phase of isolation and strong genetic selection indicated by the hard sweeps may have occurred in a location somewhere outside the Arabian Peninsula area. However, the requirement for genetic isolation from other African populations over the extended 30,000 year period suggests that it is unlikely to be a location on mainland Africa, such as in northern Africa (e.g. Egypt or Morocco). This is another relatively isolated area where archaeological evidence indicates a long AMH presence [\(54\),](https://paperpile.com/c/UfkLXS/5q0d) but also has extensive potential connection routes for AMH populations [\(83\).](https://paperpile.com/c/UfkLXS/KHwuo) Since there is little to no evidence during MIS 5-4 for long-term AMH presence outside of either Africa or the Arabian Peninsula area to act as an alternative, the genetic patterns would appear to suggest that despite the relative lack of archaeological records in the greater Arabian Peninsula area, at least a single AMH population (and potentially two – the Main and Basal Eurasians) survived from the end of MIS 5 through MIS 4 somewhere. Potential locations include poorly dated or explored sites on the Iranian plateau, where Middle Paleolithic sites such as Boof Cave on the northern coast of the Arabian Gulf contain MIS 4 archaeological dates [\(74\),](https://paperpile.com/c/UfkLXS/1MhC) although it is not certain that they are AMH in origin. Alternatively, other potential cryptic refugia in the Arabian Peninsula area include the southern Arabian coast of the Yemen highlands, and the southern areas of both the Red Sea and Arabian Gulf [\(54\).](https://paperpile.com/c/UfkLXS/5q0d) Both latter sites include significant areas now under water, which may explain the apparent lack of archaeological records, especially if the ancestral AMH populations (e.g. Main and Basal Eurasians) remained small, or geographically constrained during the harsh conditions of MIS 4. Overall, the Arabian Gulf is a good match to the genetic, archaeological, paleoenvironmental and geographic patterns and as a result is depicted in Fig. 4 as a potential location for a long-term population refugium. However, while we have used the term Arabian Standstill to refer to this event, we acknowledge that further evidence will be required to confirm the exact locations where the ancestral OoA population(s) underwent isolation (from \sim 100ka), and subsequent strong genetic selection (from \sim 80ka).

The genetic data suggest the following model for the Arabian Standstill. The ancestral OoA population moved into the Arabian Peninsula area during either the MIS 5c moist phase ~100ka, or potentially the subsequent moist phase starting ~85ka (MIS 5a) after having separated from other African groups earlier. Previous AMH populations in the Arabian Peninsula area during MIS 5e (~125ka) had abandoned the area during the cold MIS 5d phase and did not contribute genetically to subsequent groups. The MIS 5a moist phase caused AMH population expansion and movements throughout the area but was quickly followed by the return of severe cold arid conditions during MIS 4, which caused a phase of population contraction and isolation that explains the separation of the Main and Basal Eurasian AMH populations ~80ka. The Main Eurasian population subsequently remained genetically isolated for a long period between ~80ka (the estimated origin date for the hard sweeps), through MIS 4 and until warming conditions ~54-51ka when the Main Eurasian group dispersed across Eurasia. During MIS 4 the average temperatures consistently declined, potentially creating an environmental trap around refugial areas (Fig 5) [\(53, 75\),](https://paperpile.com/c/UfkLXS/Zv06+vvOi) where small populations might leave little archaeological record. As noted above, the genetic signals indicate the AS population(s) were of small size, and the Main Eurasian population appears to have contained just two African L3 haplogroup mitochondrial sub-branch lineages, which are ancestral to the N and M haplogroups that gave rise to all mitochondrial

lineages outside of Africa. This scenario is shown in simplistic fashion in Figure 4, with the Arabian Gulf depicted as the location of the Arabian Standstill population(s). While the geographic source of the Neandertal admixture is unknown, the location depicted in Figure 4 corresponds to the Zagros Mountains of Iran, which had a concentration of Neandertal individuals geographically close to the inferred location of the Arabian Standstill population. Other potential areas include the Levant and the Caucasus regions. It is possible that the more cold-adapted Neandertal populations in these regions expanded further southwards during cold periods, and retreated northwards during warmer periods while the warm-adapted AS population potentially mirrored these movements. In this way, effective contact between the populations may have been minimized despite the close geographic proximity and availability of corridors such as the Euphrates River valley between them. The timing of peak Neandertal gene flow into the Main Eurasian population is estimated to have been around 54-51ka (see above) during an extended period of wetter climatic conditions when AMH populations may have expanded northwards into Neandertal territory (Fig. 5), although it possibly had been ongoing at lower rates over a much longer time prior to this period [\(57\).](https://paperpile.com/c/UfkLXS/PRXuj) It is notable that while northern hemisphere conditions were warming during the 54-51ka period, the temperatures in the Arabian area continued to fall (Fig. 5), potentially creating a push-pull factor encouraging AMH population movement northwards and into the rest of Eurasia.

The migration routes indicated in Figure 4 are a synthesis of current archaeological and genetic data but involve considerable amounts of inference and had to be simplified for visual clarity. This simplification includes the initial movements OoA and across the Arabian Peninsula ~130ka towards Jebel Faya in the UAE, shown as either the southern (via Yemen) or northern (via the Sinai) routes. This initial MIS 5e phase is combined visually with the subsequent movements throughout the interior during wet phases including around 80ka, which is shown as resulting in the separation of the Main and Basal Eurasian populations (Figs. 4, 5). The latter split has been shown towards the lower Arabian Gulf area due to Basal Eurasian genetic ancestry exhibiting an east to west gradient in the area [\(82\),](https://paperpile.com/c/UfkLXS/zbEWX) and high levels present today in groups such as the Bedouin. While Basal Eurasian ancestry is currently most common in northern Iran, a movement into this area is not shown in Figure 4 purely for visual simplicity. For similar reasons, the settlement of Europe is simplified and shown as three pulses (as there is no genetic evidence from the earlier temporary presence prior to Heinrich 5 [\(69\),](https://paperpile.com/c/UfkLXS/BWXxl) unless this is represented by the Zlaty kun individual [\(37, 38\)\)](https://paperpile.com/c/UfkLXS/H5LT2+PDeTe), with the Initial Upper Paleolithic (IUP) and (Proto)Aurignacian entering via the southeast near Bulgaria, and the Gravettian diverging from the Aurignacian within Europe. Tools at IUP and Proto-Aurignacian sites appear to represent dispersals from at least two cultural phases related to the Levant area (Emiran and Ahmarian), consistent with their divergent genetic backgrounds including the hard sweep signals. Based on the shared hard sweep heritage, the Gravettian is shown as diverging from the Proto-Aurignacian lineage and crossing the exposed Black Sea shelf before appearing for the first time in the Sunghir specimens, shortly after 35ka. While the earliest Gravettian sites currently appear in the mid-upper Danube and Crimea, it was not possible to depict this detail.

Similarly, the movement into eastern Eurasia has been simplified to show a likely northern IUP route resulting in the Tianyuan lineage, and separate southern routes into Southeast Asia and Oceania. The

initial phase of the southern route might be considered more likely to have followed the Arabian Gulf but has been depicted further east simply for presentation clarity.

The proposed route through lower southeastern Asia (Thailand, Vietnam, southern China) follows river courses through the savannah habitat thought to exist in the area at the time [\(63\).](https://paperpile.com/c/UfkLXS/UAu6i) Similarly, early AMH movement throughout the broader Southeast Asian area has been proposed to track savannah habitat which presumably was somewhat familiar to the African ancestral ecosystems to which these groups had originated. Inferred areas of hominid genetic introgression [\(63\)](https://paperpile.com/c/UfkLXS/UAu6i) are depicted but are likely underestimates of the true number of events. While these movements on Figure 4 are necessarily simplistic depictions of far more complex processes, they are designed to highlight key points of the model.

2.8 Using sweep haplotype presence to reconstruct Paleolithic Eurasian population history

The spatiotemporal patterns of the hard sweeps provide a view on the timing and location of selective pressures, and potentially also carry information about broadscale historical migration patterns during the Upper Paleolithic, which remain poorly understood. Because the combination of pseudohaploidy and missing SNP data will make detection of sweep haplotype presence in single ancient samples less reliable, we combined sweep calling results from multiple ancient and modern samples to create temporally consistent consensus signals. To identify the earliest group of sweeps we examined isolated populations thought to be formed from the initial Main Eurasian population movement that colonized ISEA and Sahul (i.e. the former landmass comprising modern Australia and New Guinea) by \sim 50ka (which we term the Oceanic group), shortly after the main Neandertal gene flow \sim 54-51ka (section [2.7\)](#page-19-0). We searched for the presence of sweeps within genomic data from ancient and modern individuals of the Andaman Islands (ref. [\(84\);](https://paperpile.com/c/UfkLXS/P4IOV) *n* = 1), Australia (ref. [\(85\);](https://paperpile.com/c/UfkLXS/gajBe) *n* = 2), Vanuatu (refs. [\(85, 86\);](https://paperpile.com/c/UfkLXS/gajBe+e5GdN) *n* = 4) and Papua New Guinea (ref. [\(40\);](https://paperpile.com/c/UfkLXS/3b8FY) *n* = 28; comprising individuals from the Highlands, Sepik, and Bougainville populations, using a 35% frequency of the sweep loci within any of these three groups as the cut-off for detection). While the number of individuals surveyed in several of the Oceanic groups was small, the combination of the relative genetic isolation of these groups following the initial AMH colonization, and the four distinct sampling areas across a broad geographic region, is expected to provide a reasonable estimate of the hard sweep haplotypes that were present at moderate frequencies in the initial colonizing population. (If any earlier AMH groups were present in the southeast Asia area they do not appear to have contributed genetically to modern populations, as the latter all feature the standard Main Eurasian ~2% Neandertal genome content, along with additional proportions of Denisovan genomic DNA [\(62, 63\).](https://paperpile.com/c/UfkLXS/6FQvz+UAu6i) In this regard, a number of recent studies have questioned stone tool or fragmentary fossil sites in Asia used to support the much earlier presence of AMH as opposed to earlier Homo species (e.g. *H. heidelbergensis*) or archaic hominid groups such as Denisovans [\(62, 87\).](https://paperpile.com/c/UfkLXS/BpLAc+6FQvz))

We identified the presence of 31 of the hard sweeps (Table S2) within the five samples from the Oceanic group, with 28 being detected in multiple groups or multiple individuals (90%), and just three detected in only one individual (1 each in Vanuatu, Australia, and the Andaman Island specimen). The number of sweeps detected in Australia (*n* = 21), Papua New Guinea (*n* = 20), and Vanuatu (*n* = 22)

was highly consistent (i.e. around two thirds of the 31 sweep loci) despite the very different number of samples in each area (from two in Australia versus 28 in PNG), in contrast to 12 within the Andaman Island sample. The latter may relate to the high false negative rate for heterozygote loci in the single sample available for this area, and/or the very small long-term population size of the Andaman Islands leading to higher rates of genetic drift. The number of shared sweeps between each Oceanic area is consistent their known phylogenetic relationships, with the greatest similarity between Papua New Guinea and Vanuatu (16 shared out of 26 total, or 62%), followed by Australia and Vanuatu (16/27, 59%) and Australia and Papua New Guinea (13/28, 46%), with the most distant being Andaman Islands versus the others (Vanuatu 9/25, Papua New Guinea 9/23, Australia 8/25, average 35%) (Tables S2).

These patterns suggest that while relatively few of the sweeps were fixed within the initial AMH population moving into ISEA (potentially *DOK5*, *LIN28B* and *GTSE1*), many were at high frequency and as a result 23 (74%) have ended up in more than one geographic area. Due to the 31 sweeps being present immediately after the Main Eurasian dispersal, but not being of Neandertal origin (see [section](#page-43-0) [4\)](#page-43-0), we designated them as originating during the AS and therefore likely arising somewhere between \sim 80-55ka (Fig. 5, see also Fig. S11).

The oldest group of AMH samples are those of the Eurasian Initial Upper Paleolithic (IUP) groups which were broadly distributed from eastern Europe, across eastern Eurasia to Mongolia. The origin of these groups appears to be within the Levant Emiran culture [\(88\).](https://paperpile.com/c/UfkLXS/H6tVC) The four available IUP genomic sequences were from Bacho Kiro, Bulgaria (*n* = 3, CC7-335, BB7-240, F6-620, dated 45-43ka), and Zlaty kun, Czechia ($n = 1$, with poor genomic coverage and an approximate date of 45ka). The Bacho Kiro genomic studies demonstrated a close relationship between the eastern Chinese Tianyuan specimen (40ka) and the European IUP specimens [\(38\),](https://paperpile.com/c/UfkLXS/H5LT2) and this is consistent with the pattern of shared hard sweeps. While the three Bacho Kiro specimens shared an average of 17% of their hard sweep signals with each other (reflecting the small number of samples, and lack of fixed loci in the Main Eurasian dispersal), the Tianyuan specimen shared an average of 19% with each individual, and 11 of the 32 (34%) hard sweeps observed across all the Bacho Kiro specimens. This pattern suggests a much more diverse origin for the IUP samples than those from the Oceanic group, and potentially relates to additional local Neandertal admixture events detected in the recent ancestry of many IUP samples [\(38\),](https://paperpile.com/c/UfkLXS/H5LT2) or potential population bottlenecks involved in AMH settlement of Oceania.

While the other very old specimen, Ust'-Ishim (45ka), had no associated archaeological evidence so could not be positively associated with the IUP, genomic data suggests it diverged from the IUP genetic lineage or perhaps separated from the Main Eurasians shortly before the IUP group [\(38\).](https://paperpile.com/c/UfkLXS/H5LT2) In this regard, while the Ust'-Ishim specimen only had eight hard sweeps, seven were shared with the IUP or Tianyuan specimens, and seven with the Oceanic group samples. However, Ust'-Ishim possessed only one of the IUP-Tianyuan specific sweeps (*LINC00293*), suggesting a separate origin. As a result, it has been depicted with a dashed line on Figure 4 indicating these uncertain origins. The Czechia Zlaty kun specimen has similarly uncertain origins and placement [\(37\).](https://paperpile.com/c/UfkLXS/PDeTe)

Interestingly, one hard sweep (*DOK5*) was fixed across all Oceanic and IUP samples (including Tianyuan) and the Ust'-Ishim specimen. This appears to be the closest to a fixed loci in the AS/Main Eurasian dispersal detected in the study, although it was subsequently absent in some of the younger European samples.

The four IUP samples at Bacho Kiro and Zlaty kun [\(37, 38\)](https://paperpile.com/c/UfkLXS/H5LT2+PDeTe) were published after the first phase of analyses in this paper had been completed. As a result of their early age within the Main Eurasian dispersal, they effectively provide an independent test of the approach of using the Oceanic group samples to define the sweeps occurring within the AS. The IUP samples (including Tianyuan) contained 24 of the 30 (80%) AS hard sweeps defined by the Oceanic group samples, which is consistent with the small number of samples in both datasets, and elevated false negative detection rate. The remaining six AS hard sweeps absent from the IUP were detected in the next youngest Eurasian samples, suggesting they were indeed present in Europe/Eurasia but simply remained undetected in the IUP dataset.

In total, the IUP/Tianyuan/Ust'-Ishim specimens (45-40ka) contained eight hard sweeps that were not detected in the Oceanic group samples (*CCDC7, DHODH, DOCK3, LINC00293, METTL6, PAX1, WWOX, ZMYM6*) and so we assume these originated on the Levant (Emiran)/West Eurasian/IUP lineage somewhere between ~51ka and 45ka (or potentially as late as 40ka for *WWOX* and *CCDC7,* which are first detected in the Tianyuan specimen). Alternatively, it is possible that some of these hard sweeps may have been present in the Arabian Standstill population but simply were not present in the founders of the southern dispersal into ISEA and Sahul or were lost by drift early in the process.

Following the IUP/Tianyuan/Ust'-Ishim group, a distinct group of nine new hard sweeps are observed for the first time in two slightly younger western European samples, the 38ka Kostenki14 specimen in western Russia (*ANKS6*, *BAIAP2L1*, *DNAH7*, *FANCD2*, *TBC1D7*) and 35ka Goyet 116 specimen from Belgium (*BAIAP2L1, DNAH7, ELMO1, ENAM, FANCD2, OIT3, MARS*). These individuals are associated with the Aurignacian Upper Paleolithic culture (~43/42-35ka; [\(89\)\)](https://paperpile.com/c/UfkLXS/QR70o), one of the earliest pan-European technocomplexes which evolved out of the widely distributed Proto-Aurignacian AMH groups, who were the successors to the IUP populations on the landscape [\(38\).](https://paperpile.com/c/UfkLXS/H5LT2) Both European Early Upper Paleolithic populations appear to result from distinct dispersal waves stemming from the Levant area. The initial IUP (ca. 47-43ka, expressed as localized cultures e.g. Bohunician in Ukraine) are thought to have descended from the Levant Emiran culture, while the following more widespread Proto-Aurignacian cultures (ca \sim 43-41k; [\(90\)\)](https://paperpile.com/c/UfkLXS/1lUbq) descended from a separate movement related to the Levant Ahmarian culture [\(88\).](https://paperpile.com/c/UfkLXS/H6tVC) The initial movements into Europe are observed around 54ka, immediately before the extended severe cold periods of GS13/Heinrich Event 5 (Fig. 4), but successful settlement of Europe by the IUP was delayed until 47ka following this intense cold period and appears to have entered through southeastern Europe, where the earliest archaeological evidence in Bulgaria and Romania suggests a point of entry [\(69\).](https://paperpile.com/c/UfkLXS/BWXxl) The simplistic pattern shown in Figure 4 depicts two separate movements descended in some fashion from the stem lineage of western Main Eurasians originating from around the Levant area.

Only two samples with sufficient genomic coverage are available for the Aurignacian culture, although the geographic sampling is broad (Belgium and western Russia; Fig. 4). Given the small number of samples, it is perhaps surprising to see nine sweeps appear for the first time in this group. However, we can be reasonably sure this is accurate due to the widespread sampling of the period immediately after

the AS, comprising more than 41 samples (i.e. IUP/Tianyuan/Ust'-Ishim, Oceanic group samples) in which these nine sweeps are not detected. The distinct pattern of Aurignacian hard sweeps is consistent with genomic studies that indicate a near-complete population replacement between the IUP and Aurignacian [\(71\).](https://paperpile.com/c/UfkLXS/uMA3g) Therefore, we assume that the above nine sweeps occurred somewhere in the period \sim 51-38ka in the Levant (Ahmiran) or Western Eurasian Proto-Aurignacian populations during the movement into southeastern Europe. This is marked by the number 3 box in Figure 4.

Genomic analyses suggest the European Aurignacian technocomplex was relatively rapidly replaced \sim 35ka by the Gravettian technocomplex (which spanned from 35ka to \sim 25ka [\(89, 91, 92\)\)](https://paperpile.com/c/UfkLXS/QR70o+xBpAd+ghPVc), and which is suggested to have originated around the Danube River Valley and initially spread across eastern Europe. There are several ancient AMH samples during the Gravettian with sufficient genomic coverage for analysis, notably Sunghir 1-4 ($n = 4$) and Vestonice 16 ($n = 1$), along with other specimens in the Gravettian period from northern Siberia (e.g. Yana, $n = 2$). The potential route for this group is shown in Figure 4 and reflects the location of Sunghir (and Crimea) in western Russia as the earliest sampling points. While only one hard sweep (*SMCO2*) is detected for the first time in the Gravettian individuals (in the oldest Sunghir specimen, 34.6ka), the Gravettian specimens have a distinct pattern of hard sweeps that appears to be a unique combination of those seen earlier in the IUP and Aurignacian individuals (Tables S2, S9). For example, four of the eight IUP-unique hard sweeps, and five of the nine Aurignacian hard sweeps appear within the Gravettians. This pattern is consistent with genomic analyses that have suggested that Sunghir individuals and Vestonice-16 share a significant amount of ancestry with the Aurignacian Kostenki14 and Goyet 116 lineages [\(93\).](https://paperpile.com/c/UfkLXS/9YloN) The pattern of hard sweeps is similar to that seen in the Yana individuals, although the latter have been identified as a local regional culture.

The sweep signals suggest that while the Gravettian represented a significant new genetic input, the source lineage was related to that of the Aurignacian lineage and the two had perhaps not been diverged for long as only one new hard sweep (*SMCO2*) is detected (Fig. 4, Tables S2, S9). An alternative model is that a large degree of genetic admixture occurred between the early Gravettian and late surviving Aurignacian individuals, and that on-going selective pressure was sufficient to return the Aurignacian sweeps to a high enough frequency in the Sunghir individuals for detection in our tests. However, given the very short time period between the end of the Aurignacian $(\sim 35k)$ and the early Sunghir 2 and 3 specimens (\sim 34.6ka and \sim 34.5ka) there does not appear to be sufficient time or generations for selection to act across all the loci as required for the latter model, and an abrupt population replacement seems much more consistent with the results, and matches existing genomic analyses [\(89, 91, 92\).](https://paperpile.com/c/UfkLXS/QR70o+xBpAd+ghPVc)

Interestingly, the Gravettian hard sweep patterns suggest that a younger specimen recovered from excavations in the 1970's at Bacho Kiro (BK-1653, 35.3-34.6ka) is potentially also Gravettian (Tables S2, S9). This specimen was found in layers with sparse artifacts, which were attributed to be Aurignacian and hence the specimen was as well [\(38, 71\).](https://paperpile.com/c/UfkLXS/H5LT2+uMA3g) However, the hard sweep pattern in BK-1653 shows the characteristic combination of IUP and Aurignacian hard sweeps seen in the other Gravettian samples. The age of the specimen is exactly at the transition from the Aurignacian to the

Gravettian, although like other Upper Paleolithic replacements the process is spatiotemporally complex.

It has been pointed out that the end of the IUP and onset of the Aurignacian (or Proto-Aurignacian at some sites), occurs around the time of major environmental changes that have been attributed to atmospheric effects associated with the Laschamps Geomagnetic Event around 42-41ka [\(90\).](https://paperpile.com/c/UfkLXS/1lUbq) Similarly, the end of the Aurignacian and onset of the Gravettian (~35ka) also occurs at the next largest geomagnetic excursion - Mono Lake at 35ka [\(90\).](https://paperpile.com/c/UfkLXS/1lUbq) Lastly, genetic and some archaeological estimates place the end of the Gravettian close to a further geomagnetic excursion, Rockall at \sim 26ka [\(94\).](https://paperpile.com/c/UfkLXS/vbW4g) While neither the end of the Gravettian or the Rockall excursion are well defined in time, the overall pattern of correlations raises the possibility that climatic shifts or other changes associated with major geomagnetic events have negative impacts on Upper Paleolithic European human cultures [\(90\).](https://paperpile.com/c/UfkLXS/1lUbq) Recent studies on three European small mammal species have identified similar major genetic transitions also occur at these three points in time, suggesting environmentally widespread impacts [\(95\).](https://paperpile.com/c/UfkLXS/pRbZN)

The last Upper Paleolithic sweep we detect is *FBXO15*, which appears in the Magdalenian culture El Miron specimen (19ka), towards the end of the Last Glacial Maximum (LGM). The El Miron genetic group [\(52\)](https://paperpile.com/c/UfkLXS/54xGg) has been shown to be genetically related to the Goyet-116 lineage and indeed they share 13/34, or 38%, of their combined sweeps. The Magdalenian culture is a western European culture at the end of the LGM, which was superseded by the Azilian culture in western Europe during the Epipaleolithic period (represented by the 13.7ka Bichon specimen from Switzerland).

After the LGM (i.e. <18ka), three sweeps (*CCDC138*, *FBN1*, *PPARD*) appear in European populations of eastern hunter gatherers, of which *PPARD* was also detected in the older 24.3ka Mal'ta specimen (Irkutsk, eastern Russia). As a result of this observation and known gene flow from eastern areas at this time, we have designated these sweeps as likely originating in eastern Eurasia, and largely outside of our sampling area. This makes it difficult to ascertain the actual age of first appearance, although the oldest observation of any sweep in this group is 24.3ka with the Mal'ta specimen.

The last group of three sweeps (*GABBR1*, *MIR662*, *SLC7A1*) all appear in a 15.4ka Anatolian Hunter Gatherer specimen [\(96\)](https://paperpile.com/c/UfkLXS/KLRvB) known to have \sim 25% genomic ancestry from the Basal Eurasians (who diverged from the Main Eurasians prior to the main phase of Neandertal admixture). Given the long separate evolutionary history of the Basal Eurasian lineage, we designate these sweeps as potentially Basal Eurasian in origin, having presumably originated at some point after the divergence from the Main Eurasians. However, they could also represent adaptation in a local Anatolian population or nearby area. It is also interesting that both *GABBR1*, *MIR662* have been detected in modern African populations, raising the question of gene flow between Basal Eurasians and African populations at some point. Again, it is difficult to determine the origin date for these sweeps.

2.9 Potential implications of the reconstructed model of Eurasian dispersals 51ka onwards

It is worth noting that the use of Andaman and Oceanian (Aboriginal, Papuan, Vanuatu) genomes as the closest modern proxy to the AMH population dispersing across Eurasia at \sim 51-54 ka implies that the shared physiological features distributed across these modern groups may also comprise the best approximation of the initial western European populations of the Early Upper Paleolithic. The latter possibility is consistent with the rapid and widespread appearance of similar detailed figurative art cave art from 45-40ka across the breadth of the area covered in the initial Eurasian dispersal [\(90, 97\)](https://paperpile.com/c/UfkLXS/aipId+1lUbq) from southern Europe, to ISEA and Australia, where common themes involve red ochre handprints (negatives and positives), series of red ochre dots, as well as figurative depictions (e.g. animals). The fact that the Andaman and Oceanian populations have remained isolated since the initial dispersal means that the characteristics shared across these groups may provide a useful starting point to conceptualize traits (such as genetic, physiological, and behavioral) of the EUP western Eurasian groups prior to the selection imposed by the cold western Eurasian environment.

Recent studies of early Sri Lankan sites dated as early as ~48ka [\(98\)](https://paperpile.com/c/UfkLXS/SJVMy) have suggested the use of bows and arrows, nets, and advanced symbolism such as ochre bead necklaces. It seems likely that the AMH groups from this site were descendants of the original dispersal through Southeast Asia including the ancestors of the Oceanians, who clearly used advanced deep sea marine voyaging capabilities to cross to Sahul. Similarly, potential arrowhead formation has been recorded in southern France at 54ka [\(69\).](https://paperpile.com/c/UfkLXS/BWXxl) As a result, the implied combined set of technological and symbolic skills held by the dispersing Eurasian groups appears to be much further advanced than is often conceived. Nets in particular would be consistent with a prolonged occupation of the aquatic lower Arabian Gulf environment.

2.10 'Out of Arabia': Climate changes in the Arabian Peninsula and wider region

In contrast to late Pleistocene climate changes recorded in Greenland [\(99\),](https://paperpile.com/c/UfkLXS/r1a6b) hydroclimate and temperatures over northeast Africa, the Levant and Arabia did not mirror the stadial-interstadial cycles of the North Atlantic (the glacial period). Instead, distinctly different regional changes appear to have been driven by orbital variability (most notably precession [\(78\)\)](https://paperpile.com/c/UfkLXS/l22d), Eurasian snow and ice coverage [\(100\),](https://paperpile.com/c/UfkLXS/Fy9eO) lowered atmospheric greenhouse gas concentrations and/or changes in monsoonal intensity and seasonality [\(101\).](https://paperpile.com/c/UfkLXS/c5Kak) To disentangle late Pleistocene hydroclimate and temperature trends, several key reconstructions have been generated from continuous marine records straddling the Gulf of Aden, the upwelling zone of the Arabian Sea and extending towards the southwest Indian Ocean [\(78, 102\).](https://paperpile.com/c/UfkLXS/l22d+NwzuT) Leaf waxes in the Gulf of Aden core RC09-166 are of particular importance. Aerially derived from the Horn of Africa and Afar regions, leaf wax (ice-volume corrected) δD provides a measure of the isotopic composition of precipitation used by higher plants to create their lipids, a proxy for aridity [\(78\).](https://paperpile.com/c/UfkLXS/l22d) Along with stalactite records [\(79, 83, 103\),](https://paperpile.com/c/UfkLXS/dnVl+KHwuo+aUT6n) these show that during MIS 6, while there were large swings in aridity, the region experienced relatively high sustained mean annual temperatures [\(78, 102\).](https://paperpile.com/c/UfkLXS/l22d+NwzuT) Importantly, these relatively warm temperatures persisted through the Last Interglacial (MIS 5) with moist conditions during MIS 5e, 5c and 5a, consistent with relatively high precipitation and lake levels [\(104, 105\),](https://paperpile.com/c/UfkLXS/ZzXRy+WWWDF) creating 'green corridors' across the region [\(78\).](https://paperpile.com/c/UfkLXS/l22d) These brief moist spells have been related

to signs of AMH presence throughout the Arabian Peninsula, especially around 80 ka [\(103\).](https://paperpile.com/c/UfkLXS/aUT6n) Towards the end of MIS 5 (\sim 71 ka), mean annual temperatures dramatically decreased by \sim 4°C, accompanied by increased aridity into the last glacial period. Potentially importantly, AMH populations effectively trapped in the Arabian Peninsula area would have likely been exposed to considerably colder temperatures than these reconstructions suggest. The quantified estimates from the region are derived for alkenones and represent mean annual temperatures [\(106\),](https://paperpile.com/c/UfkLXS/3C7eS) implying the boreal winter was considerably more frigid (*i.e.* this is a conservative estimate of the temperature decline). Under the arid conditions of MIS 4 from 71ka onwards, apart from coastal sites and the Arabian Gulf, the biodiversity-rich mountain ranges >2,000m asl across Arabia (e.g. Shada and Hajar Mountains) [\(107\)](https://paperpile.com/c/UfkLXS/7RPRd) would have provided potential food and water resources, albeit at the cost of exposure to still colder temperatures. Population movements into these interior sites and around the Arabian Gulf during the brief moist phase around 80ka may have resulted in population fragmentation, potentially such as that separating the Main and Basal Eurasians depicted in Figure 4.

Importantly, the eruption of the Toba volcano in northern Sumatra around 74ka, immediately before the onset of MIS 4 may have amplified the impacts of this prolonged cooling phase [\(81\).](https://paperpile.com/c/UfkLXS/uWNC) Tephra-fall deposits from Toba have been identified across Indonesia, southern continental Asia, the Indian Ocean and into the Arabian Sea [\(108–110\).](https://paperpile.com/c/UfkLXS/VndWw+vHfeU+8K0Ze) The Toba eruption was the largest in the last two million years and the associated injection of large quantities of sulfate into the troposphere and stratosphere has been estimated to be10-100 times that of the 1991 Mt Pinatubo eruption, and as a result, likely had a substantial impact on incoming solar radiation [\(111\).](https://paperpile.com/c/UfkLXS/r11OH) While contentious, resulting changes in surface albedo have been used to explain shifts in climate and vegetation patterns around the world at this time including aridification and replacement of woodland by open grassland in India [\(112\),](https://paperpile.com/c/UfkLXS/yjdc3) cooling in the south Atlantic [\(113\),](https://paperpile.com/c/UfkLXS/4iVLz) a weakened Asian Monsoon [\(114\),](https://paperpile.com/c/UfkLXS/NeLU9) and even the onset of MIS 4 [\(115\).](https://paperpile.com/c/UfkLXS/1086k) Analysis of the Greenland ice core records suggest amplified cooling following the eruption [\(116\)](https://paperpile.com/c/UfkLXS/tWEjA) although modeling studies suggest the impacts were highly variable globally, with major decreases in European and Asian temperatures and rainfall in the years following the eruption [\(117\).](https://paperpile.com/c/UfkLXS/ZtiXm) There is considerable debate about the long-term impacts of Toba on AMH populations, with recent studies suggesting minimal changes in Africa, consistent with modeling results of the eruption impacts on African climate and rainfall [\(117\).](https://paperpile.com/c/UfkLXS/ZtiXm) The same modeling study suggests the Arabian Peninsula may have experienced a significant decrease in rainfall (40%) and temperature (2-8˚C) in the years following Toba, but it is unclear how long these impacts may have lasted.

The impacts of the prolonged cold conditions of MIS 4, with or without Toba as an amplifier, have been suggested to have radically changed modern human behavior and cognition by enforcing much greater emphasis of extended social and trading intergroup networks, reflected in changes in stone tool industries in southern Africa [\(81\).](https://paperpile.com/c/UfkLXS/uWNC) The idea that human cognitive ability may have undergone significant selective pressure during MIS 4 is provocative given the large number of neural hard sweeps (9/31 functional genes) observed during the Arabian Standstill, especially since many of the loci are associated with mental developmental variation in modern studies.

From 57-50ka (MIS 3), reconstructions suggest a relatively brief moist period across the region, accompanied by sustained cool conditions, providing a potential green corridor for migration

northwards from the Arabian Peninsula [\(53, 54, 75, 78\),](https://paperpile.com/c/UfkLXS/l22d+vvOi+Zv06+5q0d) very closely matched to the timing of the subsequent main phase of admixture with Neandertals ~54-50 ka, and estimated movement through the region and subsequent Eurasian dispersal 54-51ka.

Supplemental Materials 3. Functional classification and analyses of candidate genes

3.1 Refining the targets of selection

Because 52 of the 57 detected sweeps contained two or more genes, we attempted to refine the putative target of selection to a single gene in each of the 52 multigene sweeps using the iSAFE metho[d \(118\).](https://paperpile.com/c/UfkLXS/tv8se) iSAFE quantifies the evidence for selection at each SNP within a predefined window that can be used to identify the underlying causal mutation. Using simulated 5Mb regions, the iSAFE developers showed that the selected SNP was among the top 20 ranked SNPs in 94% of case[s \(118\).](https://paperpile.com/c/UfkLXS/tv8se) Accordingly, the proportion of top 20 ranked iSAFE SNPs carried by a gene provides a coarse estimate of the probability that the gene contains the causal allele somewhere within the annotated gene boundaries. Thus, for all 52 multigene sweeps, we searched for instances where a single gene had a majority $(\geq 50\%)$ of the top iSAFE SNPs in phased genomes from five modern European populations and five modern African populations from phase 3 of the 1,000 genomes dataset (which included samples from populations used our SweepFinder2 assays, i.e. CEU, FIN, TSI, and YRI). African samples were included in the iSAFE estimation in order to provide a sample of non-sweep haplotypes, as this has been shown to increase power to identify the causal allele when the sweep haplotype is at high frequencie[s \(118\).](https://paperpile.com/c/UfkLXS/tv8se) We also extended the boundaries of each sweep by 250kb on each side, as the inclusion of sweep shoulders and flanking regions also improves the power of iSAFE [\(118\).](https://paperpile.com/c/UfkLXS/tv8se)

Application of the iSAFE method to the 52 multigene sweeps resulted in 25 sweeps where a single gene could be identified that contained at least 50% of the top 20 iSAFE alleles (Table S5). Among these 25 sweeps, three sweep regions had at least one other gene that carried a moderate $(\geq 20\%)$ proportion of iSAFE SNPs (i.e. sweeps *CCDC138*, *ARFGEF1*, and *COL4A3BP*; Table S5). Because such sweeps provided less convincing evidence for a single focal driver gene overall, these were flagged as edge cases. Three additional sweeps (*PNLIPRP3*, *TP53BP1*, and *FMO2*) were also included as edge cases on the basis that these regions had a single gene with ≥30% of the top 20 iSAFE SNPs, but no other gene in the sweep contained any of these top ranked iSAFE SNPs (Table S5). The resulting 28 sweeps were combined with four sweeps containing single genes (*LINCO1153* being omitted due to having too few marker SNPs and lacking functional information in the biomedical literature; Table S6) to create a set of candidate genes that were used in functional analyses described in this section.

3.2 Comparative candidate gene sets

Population migrations and range expansions often place organisms in unique conditions that pose new physiological challenges, like those experienced by contemporary human populations that have recently moved from low to high altitude environments and suffer increased perinatal mortality and morbidity compared to high altitude-adapted populations [\(119–121\).](https://paperpile.com/c/UfkLXS/1kP3C+DrNrs+eefHd) Similarly, the OoA migration by

AMH is thought to have led to a variety of adaptations to the cool arid environments of Pleistocene Eurasia [\(122\).](https://paperpile.com/c/UfkLXS/I48U6) Previous investigations of mammalian adaptation to cold environments have reported a number of putatively adaptive changes to organismal temperature regulation, including neurocranial restructuring (face structure in cold living nonhuman primates [\(123\)\)](https://paperpile.com/c/UfkLXS/OUmgt), as well as changes to the volume and distribution of fat tissue and modifications in energy expenditure [\(124–126\),](https://paperpile.com/c/UfkLXS/UsbEk+xW2KJ+FjoyX) and selection for skin traits [\(127\).](https://paperpile.com/c/UfkLXS/6nVWG) Cold temperatures are also known to affect respiratory health and sensitivity to infection [\(128, 129\).](https://paperpile.com/c/UfkLXS/tgvsh+hYETE)

To determine if our driver loci were potentially part of an adaptive response to living in cold climates during the AMH occupation of Arabian Peninsula and Eurasia, we compared the functional characteristics of the 32 candidate genes with additional candidate loci identified in five previous studies of positive selection in contemporary Arctic human populations living in Greenland [\(130\),](https://paperpile.com/c/UfkLXS/TsnYm) Siberia [\(131, 132\),](https://paperpile.com/c/UfkLXS/8C7bq+dEU7p) and North America [\(133, 134\).](https://paperpile.com/c/UfkLXS/iNlUU+cuD5O) We obtained a previously curated set of 58 candidate genes from refs. [\(130\)](https://paperpile.com/c/UfkLXS/TsnYm) and [\(131\)](https://paperpile.com/c/UfkLXS/8C7bq) from a recent meta-analysis of mammalian cold adaptation [\(135\),](https://paperpile.com/c/UfkLXS/Ox8Q8) adding six, three, and 15 candidate genes from refs. [\(132\),](https://paperpile.com/c/UfkLXS/dEU7p) [\(133\),](https://paperpile.com/c/UfkLXS/iNlUU) and [\(134\),](https://paperpile.com/c/UfkLXS/cuD5O) respectively. To reduce potential false positives, candidate loci from ref. [\(132\)](https://paperpile.com/c/UfkLXS/dEU7p) that were situated outside of annotated gene regions or contained multiple annotated genes were excluded. Similarly for ref. [\(134\),](https://paperpile.com/c/UfkLXS/cuD5O) the reported candidate list of ~80 genes was reduced by first removing all genes that did not contain any non-synonymous, splicing, or UTR-based variants, and then removing any remaining genes that were within 1Mb of another outlier gene. Compiling the candidate genes from all five studies resulted in a set of 82 candidate adaptive genes from modern Arctic human groups that were considered for functional analyses (Table S6).

Additionally, previous studies have demonstrated that historical admixture events involving Neandertal and Denisovan lineages have left a large number of introgressed hominin loci segregating in modern human populations [\(63, 136–139\).](https://paperpile.com/c/UfkLXS/ri7DT+ZcwUQ+VIulE+ORdNo+UAu6i) While many of these archaic loci are thought to have survived simply due to being in selectively neutral areas of the genome, a small number exhibit signs of positive selection suggesting they have conferred an adaptive advantage in some human populations – e.g. the Denisovan variant of the *EPAS1* gene which confers high-altitude tolerance in modern Tibetans [\(140\)](https://paperpile.com/c/UfkLXS/Av0Js) and another introgressed Denisovan region comprising two genes (*WARS2* and *TBX15*) suggested to have a role in human cold adaptation [\(130, 141\).](https://paperpile.com/c/UfkLXS/Vc4Us+TsnYm) Given the potential advantage of cold-adapted Neandertal and Denisovan genes to the AMH population spreading across Eurasia, we also compiled a set of candidate hominin adaptively introgressed (HAI) genes from three studies that performed explicit tests for HAI loci, namely refs. [\(142–144\).](https://paperpile.com/c/UfkLXS/9dq6Z+Et8hK+Q5Hu1) To ensure that the likely driver gene was identified, we restricted our analyses to HAI regions comprising a single gene that did not lie within 1Mb of a neighboring adaptively-introgressed region from the same study. Further, due to the large number of reported HAI loci in ref. [\(143\),](https://paperpile.com/c/UfkLXS/Et8hK) we restricted HAI regions from this study to those with an FDR < 0.2. This resulted in a set of 56 HAI loci, which were further supplemented with a five additional loci that had been specifically singled out for further functional examination in a recent genomic study [\(139\),](https://paperpile.com/c/UfkLXS/ORdNo) producing in a final set of 61 candidate HAI loci that were considered in further functional analyses (Table S6).

3.3 Sweeps are enriched with genes intolerant of deletion in present day populations

The availability of large genomic datasets across multiple human populations has allowed for rigorous assessment of the 'essentiality' of all annotated human genes [\(145\).](https://paperpile.com/c/UfkLXS/vSEj2) In contrast to genes with high levels of redundancy, such as olfactory genes, that exhibit large numbers of segregating putative loss of function alleles (pLoF) in the human populations [\(145, 146\),](https://paperpile.com/c/UfkLXS/VodnX+vSEj2) genes with essential functions are expected to be less tolerant of such inactivating mutations and subsequently should carry fewer pLoF alleles on average [\(145\).](https://paperpile.com/c/UfkLXS/vSEj2) Following this logic, a recent study used pLoF variants identified among >140,000 worldwide human exomes to develop a measure, LOEUF (for loss-of-function observed/expected upper bound fraction), that quantifies the robustness of human genes to pLoF variants [\(145\).](https://paperpile.com/c/UfkLXS/vSEj2) Genes with low LOEUF scores tend to have fewer pLoF variants than expected and also tend to be more likely to be haploinsufficient (i.e. heterozygotes do not produce the wild-type phenotype and tend to be lethal when heterozygous in mice and human cell lines) [\(145\).](https://paperpile.com/c/UfkLXS/vSEj2) Additionally, segregating variants are more likely to be deleterious in genes with low LOEUF scores in general, regardless of their population frequency [\(145\),](https://paperpile.com/c/UfkLXS/vSEj2) and LOEUF scores are correlated with two codon-based measures of gene conservation in human and vertebrate lineages (called synRVIS and synGREP, respectively [\(147\)\)](https://paperpile.com/c/UfkLXS/LG34b). Thus, genes with low LOEUF scores tend to be intolerant of new variants in general, and preservation of their core functionality appears to be a crucial determinant in maintaining human health.

We used the LOEUF scores for \sim 20,000 annotated human genes to test if any of the candidate gene sets (i.e. HAI, Arctic modern human, and driver genes from the present study) were more essential than expected by chance, by contrasting the LOEUF scores in each candidate set against all non-candidate genes using a Wilcoxon Sign Rank Test. The LOEUF scores were significantly lower for all three candidate gene sets (all $p \le 0.0009$; Fig. S12), and this result remained significant after removing the six edge cases from the Eurasian candidate genes ($p \le 0.0009$), indicating that these candidate gene sets tend to be less permissive to pLoF mutations in human lineages than expected by chance.

Notably, it is possible that the observed tendency toward low LOEUF scores for three putative selected gene sets was a result of positive selection removing pLoF variation at these loci. To test this scenario, we compared another pLoF-based metric that is correlated with LOEUF that was also calculated in ref [\(145\)](https://paperpile.com/c/UfkLXS/vSEj2) – namely *p,* the probability that a haplotype carries a pLoF mutation at a particular gene *–* for genomes from African and non-African populations. Specifically, we computed a modified value of *p* that captures changes that followed OoA movement out of Africa, by performing a LOESS regression of *p*EUR (i.e. *p* derived from individuals with non-Finnish European ancestry) upon *p*AFR (i.e. *p* calculated for individuals with African or African American ancestry) using the loess function provided by the R statistical programming language with default parameter settings [\(49\).](https://paperpile.com/c/UfkLXS/Sp8IW) All *p* values were logarithmically transformed (base 10), which required adding a small random number uniformly distributed between 10⁻⁵ and 10⁻⁶ to account for *p* values equal to 0. After computing the LOESS model on these log-transformed *p* values, we obtained corrected values, *p*_{corr}, for each gene by subtracting the observed *p*_{EUR} from the predicted value in the LOESS model (i.e. the corrected value is the residual score for each gene, whereby positive p_{corr} values indicate that a gene has fewer LoF mutations than expected following the movement of AMH into Eurasia, and vice versa for negative values). We then

used a one-sided Wilcoxon Signed Rank Test to determine if the mean p_{corr} was significantly inflated across any of the three categories of candidate genes (i.e. HAI, Arctic modern human, and ancient Eurasian genes) relative to the remaining 'null' set of genes. The observed mean p_{corr} values did not differ from expectations for any of the three candidate gene sets (HAI genes: $p \le 0.40$; Arctic modern human genes: $p \le 0.96$; ancient Eurasian genes: $p \le 0.16$; Fig. S12). Indeed, the deleterious nature of LoF variants imply that most will have evolutionarily recent origins due to the high probability that new LoF mutants are quickly removed by purifying selection. Our results are consistent with this expectation and indicate that the LOEUF scores for our driver genes are probably only weakly impacted by the positive selection events that largely occurred >10,000 years ago, and therefore should still provide a robust measure of the essentiality of genes putatively affected by positive selection following the OoA movements.

3.4 Functional characterization of ancient Eurasian candidate genes

The biological function of the 32 putative ancient Eurasian candidate genes identified within our hard sweeps was assessed by multiple complementary methods. We evaluated gene function through a systematic review of human disease literature, as well as animal and cell knockout phenotypic data sets available on OMIM, PubMed, and GeneCards databases, and through utilization of available online bioinformatic functional annotation tools, e.g. STRING (see [section 3.8\).](#page-39-0) This combined approach, which takes particular advantage of current human genomic and clinical data sets, allowed us to define a biological function and assign a physiological process for 32 ancient Eurasian candidate genes (as well as candidate genes identified in modern Arctic human populations and among adaptively introgressed archaic hominin loci; see [section 3.5\)](#page-35-0). A key component in our functional classification approach that differs from related methods employed in evolutionary studies is that we sought to assign primary gene function based on phenotypic data observed in human carriers of crippling or haploinsufficient alleles, or from animal studies investigating the impact of deletions or loss-offunction mutations in orthologous genes. Most of these animal studies were rodent 'knock-out' assays, though zebra fish and *Drosophila* studies were also included in some cases (Table S6). For the 11 ancient Eurasian candidate genes lacking this type of phenotypic information, 10 were assigned functions via genome-wide association trait studies (GWAS) or biochemical and cell-based studies human and or other animals (Table S6), with one gene, *LINCO1153*, being excluded from all functional analyses due to a lack of suitable classificatory data (see Table S6 and [section 3.1\)](#page-31-1).

Using this approach, 32 Eurasian driver genes could be assigned a clear functional role under a surprisingly small number of higher-level categories: Neurological Processes (31% of total genes); Development Processes (34%); Metabolic Processes (28%); and Reproductive Fitness (6%); while no genes were overtly associated with immune function (Table S6). Further, just over half of all the selected genes (59%) were associated with a major physiological impact in humans and animals when mutated, with phenotypes including premature lethality (e.g. *GTSE1*, *FBN1*), spontaneous neurodevelopmental defects (e.g. *ARFGEF1*, *NFASC*), premature aging, skeletal and organ malformations and rearrangements (e.g. *TBC1D7*, *DNAH7*) and other whole body defects (e.g. absence of a vascular

network, *BCAS3;* reduced sperm output and fertility defects *ELMO1*) (Table S6). Further evidence for the biological importance of the driver genes is provided by their significantly reduced LOEUF scores (see [section 3.2\)](#page-31-2) and the observation that 25% are associated with a lethal phenotype when functionally crippled (Tables 1, S6). These properties point to the selected genes having relatively high biological significance and performing non-redundant functions in human physiology.

A second striking observation is that most of the driver genes (~88%) encode intracellular proteins (Table S6), and many of these are involved in related evolutionary conserved processes or gene regulatory networks. For example, *CAND1* and *FBXO15* are both components of the Skp1-cullin-F-box (*SCF*) complex [\(148\)](https://paperpile.com/c/UfkLXS/VJ7jj) – a cellular E3 ligase machine conserved across yeast, plants, nematodes, drosophila and humans – which is critical to regulation of cell cycle progression [\(149\).](https://paperpile.com/c/UfkLXS/melHT) Other highly conserved genes include *TP53BP1* [\(150, 151\),](https://paperpile.com/c/UfkLXS/VnRdZ+hoTDM) which was first identified in yeast, which together with *GTSE1* [\(152\)](https://paperpile.com/c/UfkLXS/ro7Mw) and *FANCD2* [\(153\)](https://paperpile.com/c/UfkLXS/c5IJg) regulate components of the evolutionarily-ancient DNA damage response and repair pathways. Further, the driver gene *TAF15* is an evolutionary conserved transcription factor (related to the *Drosophila melanogaster* homologue *cabeza/SARFH* associated factor [\(154\)\)](https://paperpile.com/c/UfkLXS/FMmRq) that cooperates with the RNA polymerase II complex to regulate gene transcription, including regulating the expression of the selected gene *DNAH7* [\(155\)](https://paperpile.com/c/UfkLXS/7Iawn) (Fig. 2D). This suggests that recent human evolution has included repeated adaptive modifications of proteins involved in core cellular functions. Notably, cell cycle progression and DNA repair are intertwined processes, implying that our driver genes not only fall within a relatively small set of high-level functional classifications, but also share mechanistic associations at the subcellular functional level.

3.5 Candidate genes form coordinated functional pathways

Adopting the same criteria and analyses that were used to functionally characterize the ancient Eurasian candidate genes identified in this study, we were able to assign a function to 54 of the 61 HAI candidate genes and 58 of the 82 Arctic human candidate genes, resulting in a set of 112 additional loci that were subjected to further functional investigation (Table S6). Intriguingly, the high-order functional classifications identified for the HAI and Arctic human candidate genes closely align with the distribution of functions observed for the ancient Eurasian candidate genes: overall, the three sets of candidate genes group with marked concordance around neurological (31%, 35% and 35%, for ancient Eurasian, HAI, and Arctic human candidates, respectively), developmental (34%, 32% and 28%, respectively) and metabolic (28%, 24% and 22%, respectively) processes (Tables 1, S6). The remaining genes are distributed across two distinct physiological functions – reproductive fitness and immunity – with reproductive fitness genes only found within the ancient Eurasian $(6%)$ and HAI $(2%)$ candidates, whereas immune genes are specific to the HAI (7%) and Arctic human (16%) candidates (Table S6). Moreover, many of the candidate genes within either group were associated with severe physiological phenotypes (i.e. lethality and or Mendelian disease) when disrupted (60% and 63% of all HAI and Arctic human candidate genes, respectively; Table S6).

Strikingly, several of the Eurasian candidate genes also formed parts of larger integrated molecular networks that included both HAI and Arctic human candidate genes. Comparing the functions across
the three datasets revealed distinct interacting gene networks involved in fat synthesis and adipocyte formation, cilia formation and function, and skin physiology (including melanocyte formation). Notably, each produced a phenotype with a potentially adaptive advantage in cold conditions, which are discussed in the main text and accompanying figure (Fig. 2, Table S6). For instance, *EDAR* is an Arctic human candidate gene that also sits within a large ancient Eurasian sweep in the present study, which results in ectodermal dysplasia when mutated (characterized by primary defects in hair, nails, teeth as well as sweat glands and skin) [\(156\).](https://paperpile.com/c/UfkLXS/SNHLN) Two additional Arctic human candidate genes also regulate skin and ectodermal properties: *SREBF2*, which associates with impaired skin wound repair and cataracts [\(157\),](https://paperpile.com/c/UfkLXS/8J4Qr) and *DSP,* which regulates skin thickness and the 'wooly-hair' phenotype in mammals [\(158\).](https://paperpile.com/c/UfkLXS/JvCIJ) Further cases of functions coordinately regulated by genes from different candidate gene sets are outlined in the main text (also see Fig. 2).

3.6 Neurological function as an underappreciated adaptive target in humans

Around one third of the 32 ancient Eurasian candidate genes that could be assigned a clear physiological role are associated with neurological function (Tables 1, S6). Our temporal analyses indicate that most of those neuronal genes (82%; 9/11) were under selection during the Arabian Standstill period of ~80-50ka, with the remaining two genes (*WWOX* and *DOCK3)* arising immediately afterwards during the Initial Upper Paleolithic (~47-43ka). Neuronal adaptations therefore appear to have been essential components of the selective environment during the Arabian Standstill and during the early phase of AMH dispersal across Eurasia. Again, this is provocative given archaeological suggestions of rapid cognitive development during this period [\(81\)](https://paperpile.com/c/UfkLXS/uWNC)*.*

Selection for neurological function stands in apparent contrast to previous evidence of positive selection in humans where the link between the selective pressure and adaptive response are more readily obvious (e.g. changes in diet resulted in selection for genes controlling lactose tolerance, infectious disease resulted in selection for genes controlling malaria resistance, changes in climate resulted in selection for genes controlling pigmentation [\(122\)\)](https://paperpile.com/c/UfkLXS/I48U6). While neurological functions initially appear surprising, it is possible that this observation mostly relates to the critical role the nervous system and brain play in coordinating, integrating, and subsequently regulating diverse physiological processes, which are impacted by cold environments. A key influence of the brain in this context is its ability to synthesize immediate environmental contextual cues and integrate these with the present physiological state. This is exemplified by evidence that the brain plays a central role in adjusting fuel metabolism and appetite to food resource availability [\(159\),](https://paperpile.com/c/UfkLXS/xrGwk) regulating blood flow in response to changed external conditions (e.g. cold) for thermal homeostasis [\(160\),](https://paperpile.com/c/UfkLXS/jI239) directly aids immune defense against infection and injury [\(161\),](https://paperpile.com/c/UfkLXS/2n7Nj) and ensures the fetus is protected, safely delivered, and cared for to facilitate successful pregnancy [\(162\).](https://paperpile.com/c/UfkLXS/8Q4zA) Indeed, both cognitive performance [\(163–166\)](https://paperpile.com/c/UfkLXS/9bpJN+ZJ7yE+w4ztP+ghf4e) and multiple aspects of neural physiology [\(167–170\)](https://paperpile.com/c/UfkLXS/F2q2A+ngloe+RaOg5+igKcv) are sensitive to thermal variation, suggesting that sustained occupation of cold environments by AMH may have required recalibration of many essential neurological processes towards new optimal settings, potentially leading to some of the adaptive changes observed in this study. Thus, the Eurasian candidate genes point to the brain as a central

mechanism facilitating human adaptation to changing environmental conditions where cold temperatures are a stressor, a hypothesis that is further supported by our finding that neurological genes also represent one third of candidate genes observed in modern Arctic human groups and HAI genes from putatively cold-adapted archaic groups.

It is intriguing to speculate that neurological adaptation may have played a key role in facilitating the spread of AMH through the colder Eurasian environments ~54-51ka. Future investigation of this hypothesis will benefit from targeted approaches that directly investigate how human cold response is modulated by candidate neuronal genes identified in ancient Eurasians, Arctic humans, and among HAI loci, by recording their singular and combined physiological activity in response to cold stimuli. Exemplar studies of this type have previously revealed how temperature information is relayed to the brain by synaptic firing in nerves regulated by cold-sensitive voltage-gated membrane channels [\(171,](https://paperpile.com/c/UfkLXS/LALtK+wBFYt) [172\).](https://paperpile.com/c/UfkLXS/LALtK+wBFYt) Model organisms offer a further source of mechanistic insights into the candidate neuronal genes, as demonstrated by gene knock-out studies in mice that have revealed the central role of two nerve receptor genes, *TRPM2* and *TRPM8,* in the sensation of warm [\(173\)](https://paperpile.com/c/UfkLXS/eVHXO) and cold temperatures [\(174, 175\)](https://paperpile.com/c/UfkLXS/isV8X+uTmnp) (reviewed in refs. [\(176, 177\)\).](https://paperpile.com/c/UfkLXS/u6xfV+NARew) Notably, *TRPM2* is one of the candidate genes identified in modern Arctic human populations [\(131\),](https://paperpile.com/c/UfkLXS/8C7bq) and *TRPM8* is regulated by a variant with a clinal distribution across modern Eurasian populations suggestive of adaptation to cold conditions [\(178\).](https://paperpile.com/c/UfkLXS/GrLRN) Further, the Eurasian candidate gene *MPP6* is involved in formation of nerve myelin sheaths [\(179\)](https://paperpile.com/c/UfkLXS/wkEgz) and myelination levels display plasticity with respect to environmental stimuli [\(180\),](https://paperpile.com/c/UfkLXS/zSAtU) suggesting another possible route for neuronal adaptation in new environments. Accordingly, while the role of metabolic and thermogenic processes are well described components of the adaptive mammalian cold response [\(181, 182\),](https://paperpile.com/c/UfkLXS/asmgd+PeP28) these studies suggest that neuronal processes are also plausible targets of selection that appear to have played a previously underappreciated role in AMH adaptation.

3.7 Confirming functional concordance through analyses of protein-protein interactions

Functional classification of the 32 candidate genes from our study revealed strong concordance with the inferred functions of candidate genes reported in selection studies of Arctic human populations and introgressed from archaic hominins [\(section 3.4\)](#page-34-0). Further, by drawing upon previously published molecular studies we were able to identify several cases where genes from each of these three groups contribute to known molecular networks (Fig. 2). These results suggest that the candidate genes from all three sets may have been targeted by one or more common selection pressures that have acted across much of western Eurasian population history.

To provide independent evidence on the degree of the interrelationships between the ancient Eurasian, HAI, and Arctic human candidate gene sets, we used human protein-protein interaction (PPI) data from the STRING database (version 11.5; ref. [\(183\)\)](https://paperpile.com/c/UfkLXS/50XVR) to test if the number of PPIs observed between the three different candidate gene sets exceeded chance expectations. Specifically, we performed a series of permutation tests in which all genes from one of the three groups were replaced with the same number of genes randomly selected from all human genes represented in the STRING database, with the number of PPIs among genes from these randomized gene sets being compared to the observed PPI

count. By repeating this process 10,000 times for each of the three gene sets, we calculated an empirical *p* value by evaluating the number of random gene sets that had more PPIs than in the observed case. Further, to account for the variable levels of evidence among the STRING PPIs, which are denoted by an associated score (0.15 being the minimum value required for reporting a PPI, with 1 being the maximum possible evidence), we performed separate tests after excluding PPIs with scores falling below specific thresholds (i.e. the score quartiles, or 25th, 50th and 75th percentiles, relating to scores of 0.175, 0.216 and 0.309, respectively).

The PPI analyses provide quantitative support for the strong functional concordance observed among the three different candidate gene sets from our bespoke functional annotations: all pairwise combinations of the three gene sets tend to have more pairwise PPIs than expected (Fig. S6 and Table S7), with Artic human and HAI genes showing the most significant inflation in PPIs overall $(p <$ 0.0011 for all tests; Table S7). Ancient Eurasian candidate genes also have significantly more PPIs with Arctic human genes than expected for several tests, though this signal was comparatively weaker at the most stringent PPI score threshold (i.e. when removing PPIs in the bottom 75% of scores), albeit with the excess of PPIs still being relatively high $(\sim 15\%;$ Table S7). The ancient Eurasian candidate genes also do not have significant levels of PPIs among themselves, which contrasts with the significant inflation in PPIs observed within the Arctic human and HAI candidate genes. Notably, when comparing results from the two permutation tests performed for each pair of candidate gene sets, *p* values were generally lower when replacing genes from the smaller of the two gene sets (Table S7). This result suggests that the ancient Eurasian candidate gene set, which had approximately 50% to 60% fewer genes than the HAI and Arctic human candidates respectively, may have had comparatively less statistical power than the two larger gene sets, which may have been further exacerbated when using more stringent PPI score thresholds.

Intriguingly, each of the ancient Eurasian, Arctic human, and HAI candidate gene sets exhibit a significant excess of PPIs when compared to remaining genes from the STRING database (Wilcoxon sign rank test $p \le 0.039$ for all three gene sets across all PPI score thresholds; Fig. S8). This result complements findings from a recent study, which showed that genes with high levels of PPIs, also known as 'hub' genes, are also significantly more likely to exhibit signals of positive selection in humans [\(184\).](https://paperpile.com/c/UfkLXS/JW1Os) Moreover, hub genes were also found to be among the most evolutionary constrained genes in both human and mammalian evolutionary histor[y \(184\),](https://paperpile.com/c/UfkLXS/JW1Os) a result that also broadly aligns with the deficit of loss of function alleles observed for among the three candidate gene sets analyzed in the present study. These results suggest positively selected genes in human history may share a core set of common features that include elevated levels of protein connectivity and a general intolerance to protein altering mutations; though we note that determining the influence of PPI and other potentially causal factors in gene evolution remains a complex and contentious topic [\(185, 186\)](https://paperpile.com/c/UfkLXS/Zk7G0+14DoW) and further unraveling these factors is beyond the scope of the current manuscript.

3.8 Quantitative evaluation of functional annotations

To assess the accuracy of our functional annotations across candidate genes identified in ancient Eurasians, Arctic humans, and introgressed from hominins (HAI genes), we examined if any of the functionally distinct sets of genes identified through our annotation protocol (see sections [3.4,](#page-34-0) [3.5](#page-35-0) and [3.6\)](#page-36-0) were enriched for Gene Ontologies (GO) or other biomedical annotations with similar functions. We used the STRING online enrichment tool (v. 11.5; [https://string-db.org/\)](https://string-db.org/) to perform separate enrichment tests for candidate genes classified into the four most common broad functional categories – i.e. Neurological, Development, Metabolism, and Immune (Table S6), with additional testing on four functionally distinct subcategories identified in our analyses – i.e. Adipocyte and free fatty acid synthesis, Skin physiology (which combines Skin properties and Melanogenesis; see Fig. 2), Cilia formation, and DNA damage repair (see sections [3.4,](#page-34-0) [3.5](#page-35-0) and [3.6,](#page-36-0) and Table S6). All tests were limited functional groups with more than five genes, with non-candidate genes shown in Fig. 2 also being included in the subcategory tests. All enrichment test results are reported in the main text and Table S8.

3.9 Generality of functional annotations beyond hard sweeps

We also investigated the generality of our functional annotations to positively selected loci in ancient Eurasians beyond hard sweeps. We used outFLANK to identify SNPs with elevated divergence between the 12 ancient Eurasian populations (*i.e.* those with $n_{\text{eff}} \ge 10$; see [section 1.6\)](#page-6-0) and a modern African population (*i.e.* YRI), and submitted these to enrichment testing using the STRING [\(183\)](https://paperpile.com/c/UfkLXS/50XVR) online GO testing facilities. Specifically, we evaluated frequencies at each ~1.1M ascertained SNPs in the YRI samples and the combined samples from all ancient populations (i.e. creating a single ancient Eurasian group), and calculated *F*st for each SNP using the standard Weir-Cockerham estimator [\(187\).](https://paperpile.com/c/UfkLXS/pI0mD) After excluding SNPs with heterozygosity less than 0.1, we then used OutFLANK to estimate the probability that each SNP was more divergent than expected under neutrality (i.e. assuming a null χ^2 distribution with parameters estimated from putatively neutral SNPs [\(188\);](https://paperpile.com/c/UfkLXS/AS7xN) see Dataset S57 [\[https://doi.org/10.25909/22359874\]](https://doi.org/10.25909/22359874) for results from all evaluated SNPs). This divergence-based method should in principle capture modes of positive selection leaving less distinctive genetic signals than hard sweeps, including soft and partial sweep signals. Further, OutFLANK is robust to nonequilibrium demographic models [\(188\),](https://paperpile.com/c/UfkLXS/AS7xN) including rapid range expansions that are thought to have resulted in highly divergent alleles observed in modern human populations (*i.e.* through allele surfing; [\(189\)\)](https://paperpile.com/c/UfkLXS/Ky0Xp).

The outFLANK analyses support the authenticity of the 57 hard sweep signals, with 49 sweeps (~86%) having significantly elevated F_{ST} values relative to the remaining background genome ($p < 0.05$, Wilcoxon Rank Sum Test; see ref. [\(1\)\)](https://paperpile.com/c/UfkLXS/fbXtc). To obtain a complementary set of outFLANK candidate loci for functional classification, we compiled a set of 423 candidate selected genes that contained at least one outlier SNP $(q < 0.05)$ within the annotated gene boundaries, excluding all ambiguous genes where outlier SNPs were situated between two or more overlapping genes. We then applied the same candidate selection criteria after extending gene boundaries by 50kb on either side, identifying a further 111 candidate genes with one or more outlier SNP located in proximal flanking regions (and more than

50kb of all other genes), and submitted the final list of 534 unique OutFLANK candidate genes to STRING for functional analysis (Table S8). Notably, around 8% of the OutFLANK candidate genes (44/534) are also found within the 57 sweep regions, suggesting that the OutFLANK candidate set likely captured additional positively selected loci that have left less pronounced genomic signals in ancient Eurasians.

The OutFLANK candidate genes were significantly enriched in more than 100 of biological categories across a range of different ontologies (FDR < 0.05) – with neurological, developmental, and cell adhesion/signaling categories being particularly abundant – and also had significantly more PPIs than expected (Table S7). Applying the same STRING enrichment analyses to the complete set of 175 candidate genes from ancient Eurasians, Arctic humans, and HAI loci, also resulted in enriched neurological and cell adhesion categories, suggesting that these broad functions were targeted by multiple modes of positive selection in ancient Eurasians. Further, these results also highlight that statistical analyses of aggregated gene sets that combine functionally diverse genes can overlook signals that were evident in our functional characterization of individual candidate genes. This result emphasizes the value of the gene-centric approach adopted in this study for gaining a more complete understanding of the targets of historical selection.

3.10 Arctic human candidate genes likely had local selection pressures

No genes were shared between the 32 ancient Eurasian candidate genes identified in this study and the combined set of 82 candidate genes from the five studies of modern Arctic human adaptation (though the Arctic human candidate gene *EDAR* sits within an ancient Eurasian sweep), suggesting that selection has utilized different sets of genes to adaptively modify common functional targets (see [section 3.5\)](#page-35-0). However, this lack of overlap was partly by design, as we preferentially chose candidate genes having 'local' selection signals – i.e. where the adaptive event most likely arose only after the settlement of Arctic regions – to increase the probability that the underlying selection pressures were a consequence of human occupation of the cold arid Arctic environment.

For instance, ref. [\(132\)](https://paperpile.com/c/UfkLXS/dEU7p) applied a combination of haplotype-based analyses (i.e. iHS [\(190\)](https://paperpile.com/c/UfkLXS/hqP8x) and XP-EHH [\(191\)\)](https://paperpile.com/c/UfkLXS/WJuUm) to eight populations from the Russian Arctic region, which could potentially recover adaptive loci resulting from both recent (i.e. XP-EHH with either European [CEU] or East Asian populations [CHB] as contrasts) and older (i.e. XP-EHH with an African population [YRI] contrast) selection events. Indeed, three Eurasian driver genes (i.e. *BCAS3*, *TMEM232*, *PPARD*) and another gene from a multi-gene sweep (*EDAR*) were among the candidate loci reported in ref. [\(132\)](https://paperpile.com/c/UfkLXS/dEU7p) when an African population was used as the contrast in XP-EHH testing; however, these loci were typically not outliers when either European or East Asian population contrasts were used instead (1/32 significant population tests across all three loci using either CHB or CEU as the population contrast, cf. 22/32 significant tests when using the YRI population contrast; see table 2 in ref[. \(132\)\)](https://paperpile.com/c/UfkLXS/dEU7p). These results clearly point to these three loci having an ancient antiquity, replicating the findings in our study. Accordingly, to better discriminate loci under local Arctic selection, we excluded all candidate genes reported in ref[. \(132\)](https://paperpile.com/c/UfkLXS/dEU7p) that were among the outliers reported for XP-EHH tests using an African population contrast.

Our preference for local Arctic selection signals was further enabled by the remaining four Arctic human studies (i.e. refs. [\(130, 131, 133, 134\)\)](https://paperpile.com/c/UfkLXS/cuD5O+TsnYm+iNlUU+8C7bq), using selection criteria that favored the detection of genomic regions under local selection in the Arctic populations. Specifically, two of these studies (refs. [\(130, 133\)\)](https://paperpile.com/c/UfkLXS/TsnYm+iNlUU) used the population branch statistic (PBS [\(192\)\)](https://paperpile.com/c/UfkLXS/BcmeM) to test for genomic regions showing excessive differentiation relative to modern Han Chinese (CHB) populations, with Northern Europeans (CEU) as an outgroup. Two further studies used PBS tests and another statistic that scans for regions with depleted haplotype diversity in the focal populations (iHS [\(190\)\)](https://paperpile.com/c/UfkLXS/hqP8x), with ref. [\(131\)](https://paperpile.com/c/UfkLXS/8C7bq) also using a further divergence statistic XP-EHH [\(191\)](https://paperpile.com/c/UfkLXS/WJuUm) that contrasts haplotype diversity in the focal population with a Eurasian group (in this case an ethnic Vietnamese population). Notably, while the iHS statistic should in principle be capable of detecting sweeps that arose before the separation of each Arctic populations from other Mainland Eurasian groups, both studies use post-test filtering strategies that greatly reduce the chances of observing such sweeps – ref. [\(131\)](https://paperpile.com/c/UfkLXS/8C7bq) ignores the top 5% of iHS windows from the ethnic Vietnamese population, and ref. [\(134\)](https://paperpile.com/c/UfkLXS/cuD5O) only reports outliers in the top 1% of PBS and iHS statistics, favoring the detection of locally selected regions over ancient sweep loci reported in the present study.

While these criteria should enrich the AAH gene set for loci selected within Arctic environments, it is possible that there is still some statistical correspondence between the selection scans from these studies and our own sweep regions when looking at more general signals beyond the candidate loci. Further, the extensive Holocene admixture suggested in the present study has likely reduced the sweep haplotype frequencies in many modern European populations, making it possible that some of these sweeps might have moderate PBS signals if they remained at high frequencies in the Arctic populations. To examine these scenarios in more detail, we used the permutation framework outlined in [section 1.8](#page-7-0) to test if the outlier windows reported for the Arctic populations in ref. [\(131\)](https://paperpile.com/c/UfkLXS/8C7bq) were enriched within the sweep regions detected in the present study, with separate tests performed for each of the three statistics employed in this study (i.e. PBS, XP-EHH, and iHS) as well as the combined set of results from all three statistics.

Intriguingly, while the outlier iHS windows were found to be marginally enriched across our 57 sweeps for both unscaled (observed overlap = 7 sweeps; expected overlap = 3.71 sweeps; $p \le 0.0701$) and recombination-scaled (expected overlap = 3.96 sweeps; $p \le 0.0905$) genomes, we also observed an significant enrichment for XP-EHH outliers in both scenarios (Unscaled: observed overlap = 11 sweeps; expected overlap = 4.51 sweeps; $p \le 0.0028$; Scaled: expected overlap = 4.77 sweeps; $p \le$ 0.0051), but not for PBS outliers (Unscaled: observed overlap = 16 sweeps; expected overlap = 20.06 sweeps; $p \le 0.9197$; Scaled: expected overlap = 19.36 sweeps; $p \le 0.8779$). The PBS result indicates that there were fewer of these outlier regions overlapping with our sweeps than expected – which is consistent with our hypothesis that inclusion of a European population in this statistic has biased it against the sweeps detected in our study. However, the inclusion of the ethnic Vietnamese population as a contrast in the XP-EHH statistic did not produce a similar bias. Both Vietnamese and Siberian populations are descendants of Eurasian lineages that split from Main Eurasians by 40ka [\(193, 194\),](https://paperpile.com/c/UfkLXS/Yprp7+mMJmg) and therefore are expected to have inherited the same subset of the 57 sweeps. Accordingly, the enrichment of outlier XP-EHH signals in Siberian populations suggests that the underlying selection signals have dissipated in modern Vietnamese populations, in comparison to modern European

populations, possibly through one or more admixture events involving a population where these sweeps were less frequent that occurred after their split from Siberian lineages, or perhaps because later occupation of a subtropical climate has resulted in selection against segregating adaptive cold haplotypes in the Vietnamese.

Supplemental Materials 4. Evaluating the hominin source of sweep driver alleles

The growing evidence for adaptively introgressed loci in AMH populations [\(142–144, 195\)](https://paperpile.com/c/UfkLXS/Q5Hu1+qfh9e+9dq6Z+Et8hK) suggests that some of the 57 ancient Eurasian sweeps could have been driven by introgressed hominin-derived variants. To explore this possibility in more detail we compared the location of the 57 ancient Eurasian sweeps with putative hominin adaptively introgressed (HAI) loci reported in four recent publications [\(142–144, 195\),](https://paperpile.com/c/UfkLXS/Q5Hu1+qfh9e+9dq6Z+Et8hK) and tested if there was an significant excess of HAI loci overlapping our sweeps. Note that these HAI loci include genomic regions that either harbor multiple annotated genes or lack any annotated genes, and therefore represent a much broader class of loci than the HAI gene set outlined in section 3.2 (which comprise selected loci containing only one gene).

Combining all reported outlier loci in these four studies resulted in 2267 distinct HAI loci, which were further refined by combining all loci with identical chromosomal positions from the same study into a single locus, resulting in a final set of 862 distinct HAI loci. We compared our 57 sweep regions with the combined set of 862 HAI loci, identifying 25 distinct loci that overlapped 14 different hard sweeps $(-25\%$ of all sweeps) (Fig. S7). Note that because only central positions were reported in candidate loci in ref[. \(144\),](https://paperpile.com/c/UfkLXS/Q5Hu1) we created intervals for each locus by adding 100kb flanking regions either side of this reported position (100kb being the approximate mean size of adaptively introgressed loci in ref. [\(143\)\).](https://paperpile.com/c/UfkLXS/Et8hK) We tested if the observed number of sweeps that overlap one or more adaptively introgressed locus was greater than expected by chance, applying the permutation test procedure outlined in [section 1.8](#page-7-0) to the complete set of 862 HAI loci, with additional testing also performed for the HAI loci specific to each study. These tests confirmed that our sweeps were significantly more likely to overlap the combined set of 862 adaptively introgressed regions than expected for both the standard genome ($p \le 0.0092$) and the recombination rescaled genome ($p \le 0.0113$) analyses. Moreover, excluding adaptively introgressed loci with Denisovan or ambiguous origins from these analyses showed that our hard sweeps were also more likely to overlap Neandertal-specific adaptively introgressed loci than expected (*p* ≤ 0.0364 and 0.0475 for standard and recombining genome tests, respectively). The number of HAI loci overlapping the ancient Eurasian sweeps consistently exceeded expectations across all four studies, though these were only significant ($p < 0.05$) or marginally significant ($p < 0.10$) for the loci from refs[. \(142, 144\).](https://paperpile.com/c/UfkLXS/9dq6Z+Q5Hu1) Notably, these two studies also reported much fewer adaptively introgressed loci overall, suggesting that these significant patterns may partly relate to the higher ratio of true positives to false positives in these two studies.

Next, we examined if any of the nine previously published hominin genomes available on AADR v42.4 closely matched alleles at marker SNPs in each overlapping adaptively introgressed region, extending the marker alleles in each sweep to include all SNPs that exceeded the 80th percentile of mean neutral *F*st values (se[e section 2.1\)](#page-9-0) in order to provide a reasonable amount of SNPs for this calculation. Among the set of 25 adaptively introgressed regions that overlapped a sweep, 18 also overlapped at least one marker SNP across 12 separate sweeps, though many only covered a handful of marker SNPs (Fig. S7). When considering adaptively introgressed regions overlapping at least 4 marker SNPs (after accounting for missingness), the maximum proportion of matching marker alleles at an adaptively introgressed locus for any hominin genome was ~82%, with most cases having less than half the total

number of marker alleles (median proportion of shared marker alleles ~40%, dependent on the hominin allele being present; Fig. S7).

Our results indicate that adaptively introgressed variants are more common among our hard sweeps than expected, but that available hominin genomes do not provide particularly close matches for the putative causal haplotypes when a reasonable number of marker SNPs are available, suggesting that the causal HAI haplotype may have come from a lineage that had diverged from the nine sequenced hominins. However, closer inspection of the HAI loci showed that they were typically located on the periphery of the sweep regions that they overlapped, often at a considerable distance from the peak selection signals from SweepFinder2 CLR scores (Fig. S7). This finding suggests that an introgressed hominin variant is unlikely to be the causal allele for any of the 57 Eurasian sweeps, and that the enrichment of HAI loci proximal to the hard sweep signals may instead be caused by introgressed hominin variants hitchhiking on a beneficial human-derived haplotype.

To further investigate this hypothesis, we applied the recently published admixfro[g \(196\)](https://paperpile.com/c/UfkLXS/PZQKy) method to the 27 Anatolian EF samples to investigate if any introgressed hominin haplotypes were segregating at high frequencies near to the CLR peaks in our sweeps. We chose the Anatolian samples for this test as this population had the most significant hard sweep signals among the three ancestral populations that make up modern European ancestry (WHG and Steppe being the other two), and causal allele frequencies in this population are unaffected by subsequent Holocene admixture events. To identify Neandertal introgressed segments in the Anatolian EF genomes we used admixfrog version 0.6.2.dev6 [\(https://github.com/BenjaminPeter/admixfrog/;](https://github.com/BenjaminPeter/admixfrog/) [\(196\)\)](https://paperpile.com/c/UfkLXS/PZQKy) applying the parameters used in ref. [\(38\).](https://paperpile.com/c/UfkLXS/H5LT2) In short, we used three high-coverage Neandertal genomes [\(197–199\)](https://paperpile.com/c/UfkLXS/USNDL+pn2TX+QONug) and 46 African genomes from the Simons Genome Diversity Project [\(85\)](https://paperpile.com/c/UfkLXS/gajBe) as reference genomes, and the panTro4 chimpanzee genome to assign the ancestral hominin allele state for each of the ~1.1 million probe SNPs used in this study.

Among the 28 Anatolian EF samples, we detected thousands of small to moderate length introgressed hominin loci (mean introgressed locus length = 69.6kb, each sample having around 3,890 individual introgressed loci at least 10kb in length on average), all inferred to have a Neandertal origin. We calculated the frequency of the introgressed loci overlapping our sweep regions by counting the number of introgressed hominin alleles at each site in a sweep (noting that when multiple regions overlapped in a single individual, we kept only the highest scoring introgressed region from the overlapping set of loci). Several introgressed loci were found to be segregating at intermediate frequencies – 34 of 56 (-60%) sweeps had a segregating introgressed locus above 20% frequency – with the maximum frequency observed at any introgressed site that overlapped a sweep being ~78% (*MLPH* and *ZMYM6*; Figs. 3, S8). However, all introgressed loci segregating at intermediate frequencies (>20%) tended to be hundreds of thousands of base pairs distant from the maximum CLR score within any sweep (Figs. 3, S8), echoing the patterns we observe among adaptively introgressed loci reported in other studies. Moreover, the frequency of introgressed loci was significantly reduced near to the peak CLR score in each sweep relative to regions >100kb from this peak (i.e. the mean frequency of introgressed fragments minus two times the local standard error exceeds the mean frequency of introgressed fragments at the peak CLR score), which is consistent with positive selection on human-derived variants resulting in the removal of introgressed hominin loci near to the selected site (purifying

selection on introgressed variants not expected to show the same relationship with the peak CLR score). Accordingly, we find no strong support that any of our sweeps are caused by introgressed archaic hominin variants and posit that the majority of these overlapping adaptively introgressed regions may instead be artifacts created by introgressed neutral alleles hitchhiking upon beneficial AMH-derived loci.

Supplemental Figures

Figure S2. **Effect of SNP missingness on gene scores.** Linear regression analyses revealed a weak correlation between gene scores and the mean proportion of SNP missingness per gene (i.e. number of samples with missing data per SNP) for each ancient population used to determine sweeps in this study. Accordingly, our sweep signals are unlikely to be artifacts caused by high levels of SNP missingness. Red lines show the estimated linear fit for each population. Data points are aggregated into hexagonal bins (counts indicated by blue shading, see key).

Figure S3. The impact of parameter choice on sweep haplotype accumulation through time. The dynamics of sweep aggregation were assessed by fitting a LOESS regression of sweep haplotype counts against radiocarbon estimates for three sets of regionally bounded Holocene samples (different columns) and a common set of samples from the Eurasian Upper Paleolithic. To examine the robustness of specific trends identified by the fit (e.g. reductions in sweep haplotype presence during periods of the Anatolian and Steppe-related introgression during the Holocene), we ran separate regressions for different haplotype selection criteria (different rows; see Methods) using three plausible span settings (i.e. 0.35, 0.5, 0.65 indicated by green, red, and purple lines respectively) and also the optimal span (blue line; values in upper right corner of each panel) estimated using general cross validation. Separate loess regressions were performed for results from each of the three haplotype detection criteria (different rows; Supplemental Materials 2). Most trends were reasonably robust to these different parameter choices, with inconsistencies being largely consigned to temporal spans with negligible sampling (e.g. between 6 to 10 ka in the British Isles). The mean sweep count in modern samples sourced from compatible regions is indicated by horizontal black dashed lines, which suggest that Iberian populations experienced an additional period of admixture-related sweep haplotype loss in the past 1,000 years prior to rebounding closer to the present. Note that the values on the x-axis have been square rooted to better highlight trends occurring in the Holocene period.

Figure S4. Sweep aggregation correcting for SNP missingness across samples. (A) The number of SNPs present in the 456 ancient samples used in the sweep aggregation analysis varied between ~500k and ~1.2M, with the number of sweeps detected in each sample being weakly positively associated with SNP presence (regression slope coefficient $p \sim 0.05$). **(B)** Correcting data for differential SNP missingness across samples (i.e. using residuals from the linear regression) had negligible impact on the fit of the LOESS regression lines (Residuals panel; cf. original data displayed in the Raw panel), indicating that this did not impact the temporal cumulative sweep patterns observed in our analyses (noting that span was set to 0.5 for both regression analyses).

Figure S5. Sweep haplotype frequencies in modern human populations. Sweep haplotypes were enumerated in 2,506 phased samples from the 1,000 Genomes Project. The distribution of frequencies is shown for each population (violins), with mean frequency and associated standard error indicated with red cross and lines. Notably, many sweep haplotypes occur at intermediate frequencies in many contemporary non-African populations. Results are shown for different sweep haplotype detection criteria (separate columns), with the intermediate value (no. significant tests \geq 3) being used for all results discussed in this study.

Figure S6. Protein-protein interactions within and between the candidate gene sets. (A) Proteinprotein interactions (PPIs) were quantified for the three candidate gene sets used in the current study (i.e. 32 ancient Eurasian [Driver] genes in hard sweeps, 82 adaptive Arctic human [AAH] genes, and 61 hominin adaptively introgressed [HAI] genes) and compared to expected values using permutation tests where genes from one set were replaced by randomly chosen genes. For each pair of candidate gene sets, separate tests were performed where genes were randomly replaced for one set (separate panels) while remaining fixed for the other (x-axis). Tests were performed using three different PPI score thresholds (based on score quartiles and indicated by different point shapes; see key). PPIs exceeded expectations in all cases with the majority being significant (point colors, see key; error bars indicating 95% confidence intervals), with tests involving the replacement of larger gene sets (i.e. AAH and HAI candidates) potentially having more statistical power. **(B)** Distribution of the number PPIs among genes in each of the three candidate sets. Regardless of which PPI score threshold was used (separate panels), genes in each candidate set have significantly more PPIs on average relative to all remaining genes (mean and median values shown as blue and gray crosses, respectively; dashed lines are included to facilitate comparison of expected to observed values, with *p* values from Wilcoxon signed rank tests shown to the right of each distribution).

Figure S7. Allelic state of archaic hominin sequences homologous to Eurasian sweeps. To examine if archaic hominin species were a potential source of the beneficial alleles at sweeps, nine previously published pseudohaploid hominin genomes were examined for evidence of the sweep haplotype. The allelic state of diagnostic marker SNPs in each hominin genome were compared to the inferred sweep haplotype allele in 12 sweep regions where a previously reported adaptively introgressed hominin region overlaps at least one marker SNP (orange = same allele as inferred sweep allele, gray = alternate allele from inferred sweep allele, black = no allele called in sample). Hominin introgressed regions are indicated by colored boxes, with different colors used for each study where the hominin region was reported (see key); boxes with solid lines depict introgressed loci observed in Neandertals, dashed lines indicate introgressed loci observed in Denisovans or where the identity of the hominin donor was ambiguous.

Figure S8. Introgressed archaic hominin sequences in the vicinity of Eurasian hard sweeps.

Similar to Fig. 3 but showing results for all 56 sweeps that were used in dating analyses. See Fig 3. for a full explanation of the plot items. As with Figure S7, the colored boxes indicate the position of introgressed hominin sequences, with different colors for each study (see key).

Figure S11. Model-based estimates of the onset of selection. (A) Linear regression of the proportion of the 56 sweeps observed in select samples upon sample date. Radiocarbon dates were used for all ancient Eurasian samples, with Andamanese and Oceanian samples assigned a single date that coincides with their point of separation from Main Eurasians (i.e. ~51ka; see Supplementary Materials 2). The diagonal blue line shows the best fitting linear relationship, with the associated 95% confidence interval indicated by the surrounding light blue shading. The predicted x-intercept in the regression model at ~83ka provides an approximate lower bound for the onset of selection, with a 95% confidence interval between ~72-97ka. **(B)** Results from a population genetic model where sweeps were simulated under a demographically informed coalescent model and the resulting trajectories aggregated across time. Simulated patterns were compared to sweep haplotype patterns among the same set of samples used in the linear regression analysis, excluding the Mesolithic samples (these have >30% fewer sweeps than expected assuming sweeps aggregate at the constant rate across time, likely reflecting population structure that is not included in our model; see Supplemental Materials 2). The best fitting trajectory is shown as a blue line, which predicts that selection commenced around 79ka (red point; red bar beneath shows the 95% confidence interval [74ka to 91ka]). Note that the expected probability of sweep presence does not decrease below 6%, as this is the FPR for sweep detection that was directly incorporated into the model.

Figure S12. Candidate genes are less tolerant of loss of function mutations than expected. (A) The distribution of two statistics measuring intolerance to loss of function mutations (see Supplemental Materials 3) for each candidate set (i.e. 32 ancient Eurasian [Driver] genes, 82 adaptive Arctic human [AAH] genes, and 61 hominin adaptively introgressed [HAI] genes; orange violins) relative to the scores on all remaining genes (gray violins). Notably, LOEUF scores are significantly lower in each of three categories (*p* values from permutation tests are shown at the top of each violin), but this is not observed for the corrected *p*lof statistic, suggesting that the significant LOEUF scores are not due to the erasure of deleterious variation following positive selection at each sweep locus (see Supplemental Materials 3). **(B)** Raw *p*lof statistics for European populations relative to African populations (right panel). Corrected *p*lof values were calculated for Europeans (left panel) by taking residuals from a regression against African *p*lof values. Corrected *p*lof values should be a proxy for changes in this statistic following the separation of ancestral Eurasian and African AMH lineages. The red and green lines highlight the best fitting linear and LOESS regression trends for the raw and residual datasets.

Figure S13. Age and genetically determined sex of pre-Holocene AMH and archaic hominin specimens. All pre-Holocene AMH samples from the Allen Ancient DNA Resource version 42.4 with sufficient genomic coverage to pass the quality filtering criteria. Most are western Eurasian in origin, and include specimens associated with IUP, Aurignacian, Gravettian, and Magdalenian cultures. Samples are arranged along the x-axis by radiocarbon date (sequential number indicated). There is a marked dominance of males (blue dots) relative to females (purple dots) in the pre-Holocene AMH specimens, whereas in comparison available archaic hominins with sufficient genomic coverage appear to show the reverse pattern. Several of the older hominid ages are mid-point estimates from a sizable range.

Supplemental Tables

Table S1. Ancient western Eurasian samples used for hard sweep detection. Summarized metadata includes (across successive columns) sample identifier, population assignment, geographic sampling coordinates, mean sample ages (largely calibrated with IntCal13), source publication, and raw genetic data type. Note that not all samples were able to be assigned to sufficiently large and genetically homogenous groups to be used in the analyses.

Table S2. Sweep haplotype presence in ancient and modern genomic datasets. Sweep haplotypes were quantified for pseudohaploid ancient samples and modern populations for each of the 56 sweeps, after adjusting for missing data (see Supplemental Materials 2). For individual ancient samples, sweep haplotype presence is indicated using a binary indicator (i.e. present $= 1$ and absent $= 0$), whereas sweep frequencies were calculated for modern populations. Ancient samples with missing data are indicated with a blank cell. Results are shown for the three different sweep haplotype detection criteria (Criteria column; see Supplemental Materials 2). For each sample, broad geographical origin (Region column) and abbreviated labels are provided (Sample / Pop. column). For ancient samples, archaeological metadata (Group column), and sample ages (Date; largely calibrated with IntCal13) from the Allen Ancient DNA Resource version 42.4 are listed. For modern data, population labels (Sample / Pop.) and dataset source (Group) are provided instead.

Table S3. Sweep haplotype data used to estimate selection onset and Eurasian migrations.

Summary of samples and metadata, which include (over successive columns) abbreviated and full sample IDs, sampling region and country, sample age (largely calibrated with IntCal13), SNP count (among 1.2M probe set), and number of sweeps (adjusted for missing data; see Supplemental Materials 2). All metadata was obtained from the Allen Ancient DNA Resource version 42.4.

Table S4. Summary of 57 sweeps. Information includes (across successive columns) chromosomal location, sweep labels used throughout the manuscript, functional classification (possible for sweeps that contained only a single gene or where candidate genes were inferred using iSAFE), estimated sweep onset (based on age of oldest sample sweep was observed in and binned into broad spatiotemporal / archaeological categories), and list of all genes situated within the sweep boundaries.

Table S5. Summary of iSAFE analyses. For each sweep, genes with at least one of the top 20 ranked iSAFE SNPs (i.e. those with the highest 20 iSAFE scores) are indicated (maximum of five genes shown for each sweep). Genes are ranked according to the number of the top 20 iSAFE SNPs they carry. The proportion of top ranked iSAFE SNPs carried by each gene are shown on the left-hand columns. Gene names are listed in the right-hand columns, with the fraction of the top 20 iSAFE SNPs (numerator) relative to the total number of SNPs found in each gene (denominator) also shown in square parentheses.

Table S6A. Functional classifications of candidate genes identified within Eurasian hard sweeps.

Genes were assigned into a broad functional category and subclass (first two columns) via a systematic review of human disease literature, as well as animal and cell knockout phenotypic data sets, available on GnomAD, OMIM, PubMed and GeneCards databases. Additional information is provided in the footnotes located at base of table (see Supplemental Materials 3).

FOOTNOTES:

1 Single gene sweep; gene name from OMIM
2 Constraint definition based on LOUEF score w

2 Constraint definition based on LOUEF score whereby < 0.3 highly constrained (intolerant of deletion); 0.3-0.5 intermediate constraint; 0.5-1.0 moderate constraint; >1.0 no constraint [PMID: 32461654]
3 Sourced from OMIM

3 Sourced from OMIM & PubMed search

4 Sourced from PubMed search
5 Human haploinsufficiency data

5 Human haploinsufficiency data sourced from OMIM & PubMed search

6 Animal and or cell data sourced from OMIM & PubMed search

7 Sourced from GWAS Central and PubMed

8 Sourced from PubMed

ND No data

Table S6B. Functional classifications of candidate genes identified within adaptively introgressed

hominin loci. Genes were assigned into a broad functional category and subclass (first two columns) via a systematic review of human disease literature, as well as animal and cell knockout phenotypic data sets, available on GnomAD, OMIM, PubMed and GeneCards databases. The final three columns successively show the study source for each gene, population(s) where the AI variant was observed, and the reported hominin source. Additional information is provided in the footnotes located at base of table (see Supplemental Materials 3).

FOOTNOTES:

1 Single gene sweep; gene name from OMIM
2 Constraint definition based on LOUEF score w 2 Constraint definition based on LOUEF score whereby < 0.3 highly constrained (intolerant of deletion); 0.3-0.5 intermediate constraint; 0.5-1.0 moderate constraint; >1.0 no constraint [PMID: 32461654]
Sourced from OMIM &

3 Sourced from OMIM & PubMed search
4 Sourced from PubMed search

4 Sourced from PubMed search
5 Human haploinsufficiency data

5 Human haploinsufficiency data sourced from OMIM & PubMed search

6 Animal and or cell data sourced from OMIM & PubMed search

7 Sourced from GWAS Central and PubMed
8 Sourced from PubMed

8 Sourced from PubMed
ND No data

No data

Table S6C. Functional classifications of candidate genes identified within contemporary Arctic human populations. Genes were assigned into a broad functional category and subclass (first two columns) via a systematic review of human disease literature, as well as animal and cell knockout phenotypic data sets, available on GnomAD, OMIM, PubMed and GeneCards databases. The study source for each gene is shown in the final column. Additional information is provided in the footnotes located at base of table (see Supplemental Materials 3).

FOOTNOTES:
1
|2

Single gene sweep; gene name from OMIM

2 Constraint definition based on LOUEF score whereby < 0.3 highly constrained (intolerant of deletion); 0.3-0.5 intermediate constraint; 0.5-1.0 moderate constraint; >1.0 no constraint [PMID: 32461654]

Table S6D. Summary of functional classifications of candidate genes across all datasets.

Counts (N) and proportion of genes per function (after removing genes with no known function) for each of the three candidate sources (first column).

Table S7A. Protein-protein interaction (PPI) test results. Results from permutation tests evaluating if there were more interactions between putatively adaptive genes from three different sources: i.e. driver genes from the current study (Driver) and candidate genes from Arctic human groups (AAH) and hominin adaptively introgressed (HAI) loci. Genes were randomly replaced from one of the three groups (Test group column) and the number of PPIs compared to another group where the genes were not changed (Fixed group column). Observed and expected numbers of PPIs are shown, along with the percentage excess and associated empirical *p* values (based on 10,000 permutations). Results are shown for different quantiles based on minimum PPI scores (first two columns).

Table S7B. Protein-protein interaction (PPI) test results. PPI enrichment test results for the combined set of candidate genes and for candidate genes assigned to a predefined functional class. Results for three different PPI thresholds shown in separate columns. The original STRING categories are reproduced, whereby nodes denote genes and edges indicate an interaction between two proteins (PPI) encoded by genes in a functional class.

Table S8. STRING Enrichment test results. Results are collated for combined candidate genes and for subsets of candidate genes in each predefined functional class. Results are provided in original STRING categories (see https://string-db.org for more details).

Table S9. Sweep haplotype patterns used to reconstruct Eurasian migrations. For each named sample(s) or population, sweep haplotype presence is indicated with an 'X', absence with a blank, and inability to call due to lack of data with a '?'. The upper table contains sweeps inferred for the Arabian Standstill phase, based on their broad presence across ISEA/Oceania as well as early Paleolithic Europe. The lower table contains sweeps that are only identified in western Eurasian samples and are grouped according to sample archaeological designations. Where multiple samples exist (e.g. for the IUP, Sunghir 1-4, Yana 1-2) the individual specimens are listed, rather than a simple X. Disjunct groupings of sweeps can be seen between the IUP (light blue) and Aurignacian (red). For the BK-1653 specimen which falls at the Aurignacian/Gravettian boundary, the suite of sweeps is more consistent with the Gravettian specimens (mauve and pink) than the Aurignacian, although the signal is not completely clear. The Gravettian and Magdalenian contain many sweeps identified in earlier archaeological periods, and only a few novel sweeps (e.g. *SMCO2* and *FBX015*).

Table S10. Radiocarbon ages of key ancient Eurasian samples recalibrated with IntCal20.

Key [samples used for the quantification of sweep dynamics were recalibrated with IntCal20 \(41\)](https://paperpile.com/c/UfkLXS/bWLVT), with mean age estimates and associated uncertainty (calculated at one and two standard deviations) provided.

References

- 1. [Y. Souilmi, et al., Admixture has obscured signals of historical hard sweeps in humans. Nat Ecol Evol](http://paperpile.com/b/UfkLXS/fbXtc) [\(2022\)](http://paperpile.com/b/UfkLXS/fbXtc) [https:/doi.org/](http://paperpile.com/b/UfkLXS/fbXtc)[10.1038/s41559-022-01914-9.](http://dx.doi.org/10.1038/s41559-022-01914-9)
- 2. [W. Haak, et al., Massive migration from the steppe was a source for Indo-European languages in Europe. Nature](http://paperpile.com/b/UfkLXS/UdaTS) [522,](http://paperpile.com/b/UfkLXS/UdaTS) [207–211 \(2015\).](http://paperpile.com/b/UfkLXS/UdaTS)
- 3. [I. Mathieson, et al., Genome-wide patterns of selection in 230 ancient Eurasians. Nature](http://paperpile.com/b/UfkLXS/uplme) [528, 499–503 \(2015\).](http://paperpile.com/b/UfkLXS/uplme)
- 4. [I. Mathieson, et al., The genomic history of southeastern Europe. Nature](http://paperpile.com/b/UfkLXS/zNJEb) [555, 197–203 \(2018\).](http://paperpile.com/b/UfkLXS/zNJEb)
- 5. [S. Eisenmann, et al., Reconciling material cultures in archaeology with genetic data: The nomenclature of clusters](http://paperpile.com/b/UfkLXS/6DuKi) [emerging from archaeogenomic analysis. Sci. Rep.](http://paperpile.com/b/UfkLXS/6DuKi) [8, 13003 \(2018\).](http://paperpile.com/b/UfkLXS/6DuKi)
- 6. [J. M. Smith, J. Haigh, The hitch-hiking effect of a favourable gene. Genetical Research](http://paperpile.com/b/UfkLXS/cQaKJ) [23, 23–35 \(1974\).](http://paperpile.com/b/UfkLXS/cQaKJ)
- 7. [J. Hermisson, P. S. Pennings, Soft sweeps and beyond: Understanding the patterns and probabilities of selection](http://paperpile.com/b/UfkLXS/UlgdI) [footprints under rapid adaptation. Methods in Ecology and Evolution](http://paperpile.com/b/UfkLXS/UlgdI) [8, 700–716 \(2017\).](http://paperpile.com/b/UfkLXS/UlgdI)
- 8. [I. Höllinger, P. S. Pennings, J. Hermisson, Polygenic adaptation: From sweeps to subtle frequency shifts. PLoS Genet.](http://paperpile.com/b/UfkLXS/wEWpQ) [15, e1008035 \(2019\).](http://paperpile.com/b/UfkLXS/wEWpQ)
- 9. [W. Stephan, Signatures of positive selection: from selective sweeps at individual loci to subtle allele frequency](http://paperpile.com/b/UfkLXS/vwMBK) [changes in polygenic adaptation. Mol. Ecol.](http://paperpile.com/b/UfkLXS/vwMBK) [25, 79–88 \(2016\).](http://paperpile.com/b/UfkLXS/vwMBK)
- 10. [S. Chen, Y. Zhou, Y. Chen, J. Gu, fastp: an ultra-fast all-in-one FASTQ preprocessor. Bioinformatics](http://paperpile.com/b/UfkLXS/s9Hkq) [34, i884–i890](http://paperpile.com/b/UfkLXS/s9Hkq) [\(2018\).](http://paperpile.com/b/UfkLXS/s9Hkq)
- 11. [H. Li, Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM. arXiv \[q-bio.GN\]](http://paperpile.com/b/UfkLXS/35QS5) [\(2013\).](http://paperpile.com/b/UfkLXS/35QS5)
- 12. [H. Li, et al., The Sequence Alignment/Map format and SAMtools. Bioinformatics](http://paperpile.com/b/UfkLXS/3iD4C) [25, 2078–2079 \(2009\).](http://paperpile.com/b/UfkLXS/3iD4C)
- 13. [A. McKenna, et al., The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA](http://paperpile.com/b/UfkLXS/3S8Li) [sequencing data. Genome Res.](http://paperpile.com/b/UfkLXS/3S8Li) [20, 1297–1303 \(2010\).](http://paperpile.com/b/UfkLXS/3S8Li)
- 14. [H. Jónsson, A. Ginolhac, M. Schubert, P. L. F. Johnson, L. Orlando, mapDamage2.0: fast approximate Bayesian](http://paperpile.com/b/UfkLXS/FvOrc) [estimates of ancient DNA damage parameters. Bioinformatics](http://paperpile.com/b/UfkLXS/FvOrc) [29, 1682–1684 \(2013\).](http://paperpile.com/b/UfkLXS/FvOrc)
- 15. [M. Kircher, "Analysis of High-Throughput Ancient DNA Sequencing Data" in Ancient DNA: Methods and Protocols,](http://paperpile.com/b/UfkLXS/1UpR1) [B. Shapiro, M. Hofreiter, Eds. \(Humana Press, 2012\), pp. 197–228.](http://paperpile.com/b/UfkLXS/1UpR1)
- 16. [G. Jun, M. K. Wing, G. R. Abecasis, H. M. Kang, An efficient and scalable analysis framework for variant extraction](http://paperpile.com/b/UfkLXS/HINEx) [and refinement from population-scale DNA sequence data. Genome Res.](http://paperpile.com/b/UfkLXS/HINEx) [25, 918–925 \(2015\).](http://paperpile.com/b/UfkLXS/HINEx)
- 17. [H. Li, A statistical framework for SNP calling, mutation discovery, association mapping and population genetical](http://paperpile.com/b/UfkLXS/5HsUt) [parameter estimation from sequencing data. Bioinformatics](http://paperpile.com/b/UfkLXS/5HsUt) [27, 2987–2993 \(2011\).](http://paperpile.com/b/UfkLXS/5HsUt)
- 18. [A. L. Price, et al., Principal components analysis corrects for stratification in genome-wide association studies. Nat.](http://paperpile.com/b/UfkLXS/viNdO) [Genet.](http://paperpile.com/b/UfkLXS/viNdO) [38, 904–909 \(2006\).](http://paperpile.com/b/UfkLXS/viNdO)
- 19. [N. Patterson, A. L. Price, D. Reich, Population structure and eigenanalysis. PLoS Genet.](http://paperpile.com/b/UfkLXS/VeGSI) [2, e190 \(2006\).](http://paperpile.com/b/UfkLXS/VeGSI)
- 20. [C. C. Chang, et al., Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience](http://paperpile.com/b/UfkLXS/Dnxs7) [4, 7](http://paperpile.com/b/UfkLXS/Dnxs7) [\(2015\).](http://paperpile.com/b/UfkLXS/Dnxs7)
- 21. [S. Purcell, et al., PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum.](http://paperpile.com/b/UfkLXS/3J8lJ) [Genet.](http://paperpile.com/b/UfkLXS/3J8lJ) [81, 559–575 \(2007\).](http://paperpile.com/b/UfkLXS/3J8lJ)
- 22. [C. D. Huber, M. DeGiorgio, I. Hellmann, R. Nielsen, Detecting recent selective sweeps while controlling for mutation](http://paperpile.com/b/UfkLXS/xxu9W) [rate and background selection. Mol. Ecol.](http://paperpile.com/b/UfkLXS/xxu9W) [25, 142–156 \(2016\).](http://paperpile.com/b/UfkLXS/xxu9W)
- 23. [M. DeGiorgio, C. D. Huber, M. J. Hubisz, I. Hellmann, R. Nielsen, S weep F inder 2: increased sensitivity, robustness](http://paperpile.com/b/UfkLXS/tQHiA) [and flexibility. Bioinformatics](http://paperpile.com/b/UfkLXS/tQHiA) [32, 1895–1897 \(2016\).](http://paperpile.com/b/UfkLXS/tQHiA)
- 24. [1000 Genomes Project Consortium, et al., A global reference for human genetic variation. Nature](http://paperpile.com/b/UfkLXS/0VsCz) [526, 68–74 \(2015\).](http://paperpile.com/b/UfkLXS/0VsCz)
- 25. [R. Nielsen, et al., Genomic scans for selective sweeps using SNP data. Genome Res.](http://paperpile.com/b/UfkLXS/FQvA4) [15, 1566–1575 \(2005\).](http://paperpile.com/b/UfkLXS/FQvA4)
- 26. [R. J. Kinsella, et al., Ensembl BioMarts: a hub for data retrieval across taxonomic space. Database](http://paperpile.com/b/UfkLXS/UlrjD) [2011, bar030–](http://paperpile.com/b/UfkLXS/UlrjD) [bar030 \(2011\).](http://paperpile.com/b/UfkLXS/UlrjD)
- 27. [J. D. Storey, The positive false discovery rate: a Bayesian interpretation and the q -value. The Annals of Statistics](http://paperpile.com/b/UfkLXS/LFrsy) [31,](http://paperpile.com/b/UfkLXS/LFrsy) [2013–2035 \(2003\).](http://paperpile.com/b/UfkLXS/LFrsy)
- 28. [S. Durinck, P. T. Spellman, E. Birney, W. Huber, Mapping identifiers for the integration of genomic datasets with the](http://paperpile.com/b/UfkLXS/uuXJ5) [R/Bioconductor package biomaRt. Nature Protocols](http://paperpile.com/b/UfkLXS/uuXJ5) [4, 1184–1191 \(2009\).](http://paperpile.com/b/UfkLXS/uuXJ5)
- 29. [B. Iglewicz, D. C. Hoaglin, How to Detect and Handle Outliers](http://paperpile.com/b/UfkLXS/tpaRA) [\(Asq Press, 1993\).](http://paperpile.com/b/UfkLXS/tpaRA)
- 30. [J. T. Daub, et al., Evidence for Polygenic Adaptation to Pathogens in the Human Genome. Molecular Biology and](http://paperpile.com/b/UfkLXS/q333K) [Evolution](http://paperpile.com/b/UfkLXS/q333K) [30, 1544–1558 \(2013\).](http://paperpile.com/b/UfkLXS/q333K)
- 31. [A. Ferrer-Admetlla, M. Liang, T. Korneliussen, R. Nielsen, On detecting incomplete soft or hard selective sweeps](http://paperpile.com/b/UfkLXS/TEYxV) [using haplotype structure. Mol. Biol. Evol.](http://paperpile.com/b/UfkLXS/TEYxV) [31, 1275–1291 \(2014\).](http://paperpile.com/b/UfkLXS/TEYxV)
- 32. [A. Choudhury, et al., High-depth African genomes inform human migration and health. Nature](http://paperpile.com/b/UfkLXS/qiJub) [586, 741–748 \(2020\).](http://paperpile.com/b/UfkLXS/qiJub)
- 33. [B. Gel, et al., regioneR: an R/Bioconductor package for the association analysis of genomic regions based on](http://paperpile.com/b/UfkLXS/6yy9l) [permutation tests. Bioinformatics](http://paperpile.com/b/UfkLXS/6yy9l) [32, 289–291 \(2016\).](http://paperpile.com/b/UfkLXS/6yy9l)
- 34. [C. Bhérer, C. L. Campbell, A. Auton, Refined genetic maps reveal sexual dimorphism in human meiotic](http://paperpile.com/b/UfkLXS/8fPLj) [recombination at multiple scales. Nat. Commun.](http://paperpile.com/b/UfkLXS/8fPLj) [8, 14994 \(2017\).](http://paperpile.com/b/UfkLXS/8fPLj)
- 35. [A. Bergström, C. Stringer, M. Hajdinjak, E. M. L. Scerri, P. Skoglund, Origins of modern human ancestry. Nature](http://paperpile.com/b/UfkLXS/8Lch1) [590, 229–237 \(2021\).](http://paperpile.com/b/UfkLXS/8Lch1)
- 36. [G. Bhatia, N. Patterson, S. Sankararaman, A. L. Price, Estimating and interpreting FST: The impact of rare variants.](http://paperpile.com/b/UfkLXS/75UoE) [Genome Res.](http://paperpile.com/b/UfkLXS/75UoE) [23, 1514 \(2013\).](http://paperpile.com/b/UfkLXS/75UoE)
- 37. [K. Prüfer, et al.](http://paperpile.com/b/UfkLXS/PDeTe)[, A genome sequence from a modern human skull over 45,000 years old from Zlatý kůň i](http://paperpile.com/b/UfkLXS/PDeTe)n Czechia. [Nat Ecol Evol](http://paperpile.com/b/UfkLXS/PDeTe) [5, 820–825 \(2021\).](http://paperpile.com/b/UfkLXS/PDeTe)
- 38. [M. Hajdinjak, et al., Initial Upper Palaeolithic humans in Europe had recent Neanderthal ancestry. Nature](http://paperpile.com/b/UfkLXS/H5LT2) [592, 253–](http://paperpile.com/b/UfkLXS/H5LT2) [257 \(2021\).](http://paperpile.com/b/UfkLXS/H5LT2)
- 39. [I. Olalde, et al., The genomic history of the Iberian Peninsula over the past 8000 years. Science](http://paperpile.com/b/UfkLXS/2DG9v) [363, 1230–1234](http://paperpile.com/b/UfkLXS/2DG9v) [\(2019\).](http://paperpile.com/b/UfkLXS/2DG9v)
- 40. [A. Bergström, et al., Insights into human genetic variation and population history from 929 diverse genomes. Science](http://paperpile.com/b/UfkLXS/3b8FY) [367, 674986 \(2020\).](http://paperpile.com/b/UfkLXS/3b8FY)
- 41. [P. J. Reimer, et al., The IntCal20 Northern Hemisphere Radiocarbon Age Calibration Curve \(0–55 cal kBP\).](http://paperpile.com/b/UfkLXS/bWLVT) [Radiocarbon](http://paperpile.com/b/UfkLXS/bWLVT) [62, 725–757 \(2020\).](http://paperpile.com/b/UfkLXS/bWLVT)
- 42. [G. Gower, et al., Widespread male sex bias in mammal fossil and museum collections. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/paPSU) [116, 19019–19024 \(2019\).](http://paperpile.com/b/UfkLXS/paPSU)
- 43. [M. Petr, et al., The evolutionary history of Neanderthal and Denisovan Y chromosomes. Science](http://paperpile.com/b/UfkLXS/rSoi4) [369, 1653–1656](http://paperpile.com/b/UfkLXS/rSoi4) [\(2020\).](http://paperpile.com/b/UfkLXS/rSoi4)
- 44. [Canty, Ripley, Others, boot: Bootstrap R \(S-Plus\) functions. R package version](http://paperpile.com/b/UfkLXS/7jxaw) [1, 3–20 \(2017\).](http://paperpile.com/b/UfkLXS/7jxaw)
- 45. [X. Wang, fANCOVA: Nonparametric Analysis of Covariance](http://paperpile.com/b/UfkLXS/NVuRl) [\(2020\).](http://paperpile.com/b/UfkLXS/NVuRl)
- 46. [A. Mittnik, et al., The genetic prehistory of the Baltic Sea region. Nat. Commun.](http://paperpile.com/b/UfkLXS/4wtl4) [9, 442 \(2018\).](http://paperpile.com/b/UfkLXS/4wtl4)
- 47. [T. Günther, et al., Ancient genomes link early farmers from Atapuerca in Spain to modern-day Basques. Proc. Natl.](http://paperpile.com/b/UfkLXS/Uree8) [Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/Uree8) [112, 11917–11922 \(2015\).](http://paperpile.com/b/UfkLXS/Uree8)
- 48. [D. M. Fernandes, et al., A genomic Neolithic time transect of hunter-farmer admixture in central Poland. Sci. Rep.](http://paperpile.com/b/UfkLXS/PG7W8) [8,](http://paperpile.com/b/UfkLXS/PG7W8) [14879 \(2018\).](http://paperpile.com/b/UfkLXS/PG7W8)
- 49. [R Core Team, R: A Language and Environment for Statistical Computing](http://paperpile.com/b/UfkLXS/Sp8IW) [\(R Foundation for Statistical Computing,](http://paperpile.com/b/UfkLXS/Sp8IW) [2021\).](http://paperpile.com/b/UfkLXS/Sp8IW)
- 50. [J. Kamm, J. Terhorst, R. Durbin, Y. S. Song, Efficiently inferring the demographic history of many populations with](http://paperpile.com/b/UfkLXS/r6N7y) [allele count data. J. Am. Stat. Assoc.](http://paperpile.com/b/UfkLXS/r6N7y) [115, 1472–1487 \(2020\).](http://paperpile.com/b/UfkLXS/r6N7y)
- 51. [G. Ewing, J. Hermisson, MSMS: a coalescent simulation program including recombination, demographic structure and](http://paperpile.com/b/UfkLXS/EoGqe) [selection at a single locus. Bioinformatics](http://paperpile.com/b/UfkLXS/EoGqe) [26, 2064–2065 \(2010\).](http://paperpile.com/b/UfkLXS/EoGqe)
- 52. [Q. Fu, et al., The genetic history of Ice Age Europe. Nature](http://paperpile.com/b/UfkLXS/54xGg) [534, 200–205 \(2016\).](http://paperpile.com/b/UfkLXS/54xGg)
- 53. [R. M. Beyer, M. Krapp, A. Eriksson, A. Manica, Climatic windows for human migration out of Africa in the past](http://paperpile.com/b/UfkLXS/Zv06) [300,000 years. Nat. Commun.](http://paperpile.com/b/UfkLXS/Zv06) [12, 4889 \(2021\).](http://paperpile.com/b/UfkLXS/Zv06)
- 54. [J. I. Rose, An Introduction to Human Prehistory in Arabia: The Lost World of the Southern Crescent](http://paperpile.com/b/UfkLXS/5q0d) [\(Springer](http://paperpile.com/b/UfkLXS/5q0d) [International Publishing, 2022\) \(December 1, 2022\).](http://paperpile.com/b/UfkLXS/5q0d)
- 55. [I. Hershkovitz, et al., A Middle Pleistocene Homo from Nesher Ramla, Israel. Science](http://paperpile.com/b/UfkLXS/aB2Qz) [372, 1424–1428 \(2021\).](http://paperpile.com/b/UfkLXS/aB2Qz)
- 56. [P. Moorjani, et al., A genetic method for dating ancient genomes provides a direct estimate of human generation](http://paperpile.com/b/UfkLXS/XrMro) [interval in the last 45,000 years. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/XrMro) [113, 5652–5657 \(2016\).](http://paperpile.com/b/UfkLXS/XrMro)
- 57. [L. N. M. Iasi, H. Ringbauer, B. M. Peter, An extended admixture pulse model reveals the limitations to Human-](http://paperpile.com/b/UfkLXS/PRXuj)[Neandertal introgression dating. bioRxiv, 2021.04.04.438357 \(2021\).](http://paperpile.com/b/UfkLXS/PRXuj)
- 58. [R. Tobler, et al., Aboriginal mitogenomes reveal 50,000 years of regionalism in Australia. Nature](http://paperpile.com/b/UfkLXS/gX1LT) [544, 180–184](http://paperpile.com/b/UfkLXS/gX1LT) [\(2017\).](http://paperpile.com/b/UfkLXS/gX1LT)
- 59. [B. David, et al., 45,610–52,160 years of site and landscape occupation at Nawarla Gabarnmang, Arnhem Land plateau](http://paperpile.com/b/UfkLXS/ShE0F) [\(northern Australia\). Quat. Sci. Rev.](http://paperpile.com/b/UfkLXS/ShE0F) [215, 64–85 \(2019\).](http://paperpile.com/b/UfkLXS/ShE0F)
- 60. [T. Maloney, S. O'Connor, R. Wood, K. Aplin, J. Balme, Carpenters Gap 1: A 47,000 year old record of indigenous](http://paperpile.com/b/UfkLXS/OrR6h) [adaption and innovation. Quat. Sci. Rev.](http://paperpile.com/b/UfkLXS/OrR6h) [191, 204–228 \(2018\).](http://paperpile.com/b/UfkLXS/OrR6h)
- 61. [Y. Kaifu, et al., Modern human teeth unearthed from below the](http://paperpile.com/b/UfkLXS/j9dX7) ∼128,000-year-old level at Punung, Java: A case [highlighting the problem of recent intrusion in cave sediments. J. Hum. Evol.](http://paperpile.com/b/UfkLXS/j9dX7) [163, 103122 \(2022\).](http://paperpile.com/b/UfkLXS/j9dX7)
- 62. [J. F. O'Connell, et al., When did Homo sapiens first reach Southeast Asia and Sahul? Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/6FQvz) [115, 8482–8490 \(2018\).](http://paperpile.com/b/UfkLXS/6FQvz)
- 63. [J. C. Teixeira, A. Cooper, Using hominin introgression to trace modern human dispersals. Proc. Natl. Acad. Sci. U. S.](http://paperpile.com/b/UfkLXS/UAu6i) [A.](http://paperpile.com/b/UfkLXS/UAu6i) [116, 15327–15332 \(2019\).](http://paperpile.com/b/UfkLXS/UAu6i)
- 64. [T. A. Surovell, Early Paleoindian women, children, mobility, and fertility. Am. Antiq.](http://paperpile.com/b/UfkLXS/73tFG) [65, 493–508 \(2000\).](http://paperpile.com/b/UfkLXS/73tFG)
- 65. [J. Allen, J. F. O'Connell, A different paradigm for the initial colonisation of Sahul. Archaeol. Ocean.](http://paperpile.com/b/UfkLXS/rmxXJ) [55, 1–14 \(2020\).](http://paperpile.com/b/UfkLXS/rmxXJ)
- 66. [S. O'Connor, S. Kealy, C. Reepmeyer, S. C. Samper Carro, C. Shipton, Terminal Pleistocene emergence of maritime](http://paperpile.com/b/UfkLXS/D2p4d) [interaction networks across Wallacea. World Archaeol., 1–20 \(2023\).](http://paperpile.com/b/UfkLXS/D2p4d)
- 67. [J. I. Rose, New Light on Human Prehistory in the Arabo-Persian Gulf Oasis. Curr. Anthropol.](http://paperpile.com/b/UfkLXS/BF57) [51, 849–883 \(2010\).](http://paperpile.com/b/UfkLXS/BF57)
- 68. [E. K. F. Chan, e](http://paperpile.com/b/UfkLXS/bIuhF)t [al., Human origins in a southern African palaeo-wetland and first migrations. Nature](http://paperpile.com/b/UfkLXS/bIuhF) [575, 185–189](http://paperpile.com/b/UfkLXS/bIuhF) [\(2019\).](http://paperpile.com/b/UfkLXS/bIuhF)
- 69. [L. Slimak, et al., Modern human incursion into Neanderthal territories 54,000 years ago at Mandrin, France. Sci Adv](http://paperpile.com/b/UfkLXS/BWXxl) [8, eabj9496 \(2022\).](http://paperpile.com/b/UfkLXS/BWXxl)
- 70. [H. Fewlass, et al., A 14C chronology for the Middle to Upper Palaeolithic transition at Bacho Kiro Cave, Bulgaria.](http://paperpile.com/b/UfkLXS/w3i5e) [Nat Ecol Evol](http://paperpile.com/b/UfkLXS/w3i5e) [4, 794–801 \(2020\).](http://paperpile.com/b/UfkLXS/w3i5e)
- 71. [J.-J. Hublin, et al., Initial Upper Palaeolithic Homo sapiens from Bacho Kiro Cave, Bulgaria. Nature](http://paperpile.com/b/UfkLXS/uMA3g) [581, 299–302](http://paperpile.com/b/UfkLXS/uMA3g) [\(2020\).](http://paperpile.com/b/UfkLXS/uMA3g)
- 72. [K. Harris, R. Nielsen, The Genetic Cost of Neanderthal Introgression. Genetics](http://paperpile.com/b/UfkLXS/wIcEX) [203, 881–891 \(2016\).](http://paperpile.com/b/UfkLXS/wIcEX)
- 73. [M. Petr, S. Pääbo, J. Kelso, B. Vernot, Limits of long-term selection against Neandertal introgression. Proc. Natl.](http://paperpile.com/b/UfkLXS/H1rVy) [Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/H1rVy) [116, 1639–1644 \(2019\).](http://paperpile.com/b/UfkLXS/H1rVy)
- 74. [M. J. Shoaee, H. Vahdati Nasab, M. D. Petraglia, The Paleolithic of the Iranian Plateau: Hominin occupation history](http://paperpile.com/b/UfkLXS/1MhC) [and implications for human dispersals across southern Asia. Journal of Anthropological Archaeology](http://paperpile.com/b/UfkLXS/1MhC) [62, 101292](http://paperpile.com/b/UfkLXS/1MhC) [\(2021\).](http://paperpile.com/b/UfkLXS/1MhC)
- 75. [H. S. Groucutt, et al., Multiple hominin dispersals into Southwest Asia over the past 400,000 years. Nature](http://paperpile.com/b/UfkLXS/vvOi) [597, 376–](http://paperpile.com/b/UfkLXS/vvOi) [380 \(2021\).](http://paperpile.com/b/UfkLXS/vvOi)
- 76. [M. Stewart, et al., Human footprints provide snapshot of last interglacial ecology in the](http://paperpile.com/b/UfkLXS/rRne) Arabian interior[. Sci Adv](http://paperpile.com/b/UfkLXS/rRne) [6](http://paperpile.com/b/UfkLXS/rRne) [\(2020\).](http://paperpile.com/b/UfkLXS/rRne)
- 77. [S. J. Armitage, et al., The Southern Route "Out of Africa": Evidence for an Early Expansion of Modern Humans into](http://paperpile.com/b/UfkLXS/Lqq1) [Arabia. Science](http://paperpile.com/b/UfkLXS/Lqq1) [331, 453–456 \(2011\).](http://paperpile.com/b/UfkLXS/Lqq1)
- 78. [J. E. Tierney, P. B. deMenocal, P. D. Zander, A climatic context for the out-of-Africa migration. Geology](http://paperpile.com/b/UfkLXS/l22d) [45, 1023–](http://paperpile.com/b/UfkLXS/l22d) [1026 \(2017\).](http://paperpile.com/b/UfkLXS/l22d)
- 79. [M. D. Petraglia, P. S. Breeze, H. S. Groucutt, "Blue Arabia, Green Arabia: Examining Human Colonisation and](http://paperpile.com/b/UfkLXS/dnVl) [Dispersal Models" in Geological Setting, Palaeoenvironment and Archaeology of the Red Sea, N. M. A. Rasul, I. C. F.](http://paperpile.com/b/UfkLXS/dnVl) [Stewart, Eds. \(Springer International Publishing, 2019\), pp. 675–683.](http://paperpile.com/b/UfkLXS/dnVl)
- 80. [M. D. Petraglia, Archaeology: Trailblazers across Arabia. Nature](http://paperpile.com/b/UfkLXS/Hul4) [470, 50–51 \(2011\).](http://paperpile.com/b/UfkLXS/Hul4)
- 81. [S. H. Ambrose, Chronological calibration of Late Pleistocene modern human dispersals, climate change and](http://paperpile.com/b/UfkLXS/uWNC) [archaeology with geochemical isochrons. S](http://paperpile.com/b/UfkLXS/uWNC)ahle [Yonatan, Reyes-Centeno Hugo, Bentz Christian, Sahle Y, Reyes-](http://paperpile.com/b/UfkLXS/uWNC)[Centeno H, Bentz C, editors. Modern Human Origins and Dispersal. Tübingen: Kerns Verlag, 171–213 \(2017\).](http://paperpile.com/b/UfkLXS/uWNC)
- 82. [J. C. Ferreira, et al., Projecting Ancient Ancestry in Modern-Day Arabians and Iranians: A Key Role of the Past](http://paperpile.com/b/UfkLXS/zbEWX) [Exposed Arabo-Persian Gulf on Human Migrations. Genome Biol. Evol.](http://paperpile.com/b/UfkLXS/zbEWX) [13](http://paperpile.com/b/UfkLXS/zbEWX) [\(2021\).](http://paperpile.com/b/UfkLXS/zbEWX)
- 83. [P. S. Breeze, et al., Palaeohydrological corridors for hominin dispersals in the Middle East 250--70,000 years ago.](http://paperpile.com/b/UfkLXS/KHwuo) [Quat. Sci. Rev.](http://paperpile.com/b/UfkLXS/KHwuo) [144, 155–185 \(2016\).](http://paperpile.com/b/UfkLXS/KHwuo)
- 84. [J. V. Moreno-Mayar, et al., Early human dispersals within the Americas. Science](http://paperpile.com/b/UfkLXS/P4IOV) [362](http://paperpile.com/b/UfkLXS/P4IOV) [\(2018\).](http://paperpile.com/b/UfkLXS/P4IOV)
- 85. [S. Mallick, et al., The Simons Genome Diversity Project: 300 genomes from 142 diverse populations. Nature](http://paperpile.com/b/UfkLXS/gajBe) [538,](http://paperpile.com/b/UfkLXS/gajBe) [201–206 \(2016\).](http://paperpile.com/b/UfkLXS/gajBe)
- 86. [M. Lipson, et al., Population Turnover in Remote Oceania Shortly after Initial Settlement. Curr. Biol.](http://paperpile.com/b/UfkLXS/e5GdN) [28, 1157–](http://paperpile.com/b/UfkLXS/e5GdN) [1165.e7 \(2018\).](http://paperpile.com/b/UfkLXS/e5GdN)
- 87. [X.-F. Sun, et al., Ancient DNA and multimethod dating confirm the late arrival of anatomically modern humans in](http://paperpile.com/b/UfkLXS/BpLAc) [southern China. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/BpLAc) [118, e2019158118 \(2021\).](http://paperpile.com/b/UfkLXS/BpLAc)
- 88. [J. F. Hoffecker, Out of Africa: modern human origins special feature: the spread of modern humans in Europe. Proc.](http://paperpile.com/b/UfkLXS/H6tVC) [Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/H6tVC) [106, 16040–16045 \(2009\).](http://paperpile.com/b/UfkLXS/H6tVC)
- 89. [T. Higham, et al., Precision dating of the Palaeolithic: a new radiocarbon chronology for the Abri Pataud \(France\), a](http://paperpile.com/b/UfkLXS/QR70o) [key Aurignacian sequence. J. Hum. Evol.](http://paperpile.com/b/UfkLXS/QR70o) [61, 549–563 \(2011\).](http://paperpile.com/b/UfkLXS/QR70o)
- 90. [A. Cooper,](http://paperpile.com/b/UfkLXS/1lUbq) [et al., A global environmental crisis 42,000 years ago. Science](http://paperpile.com/b/UfkLXS/1lUbq) [371, 811–818 \(2021\).](http://paperpile.com/b/UfkLXS/1lUbq)
- 91. [W. E. Banks, et al., An application of hierarchical Bayesian modeling to better constrain the chronologies of Upper](http://paperpile.com/b/UfkLXS/xBpAd) Paleolithic archaeological cultures in France [between ca. 32,000–21,000 calibrated years before present. Quat. Sci.](http://paperpile.com/b/UfkLXS/xBpAd) [Rev.](http://paperpile.com/b/UfkLXS/xBpAd) [220, 188–214 \(2019\).](http://paperpile.com/b/UfkLXS/xBpAd)
- 92. [E. Andrew Bennett, et al., The origin of the Gravettians: genomic evidence from a 36,000-year-old Eastern European.](http://paperpile.com/b/UfkLXS/ghPVc) [Cold Spring Harbor Laboratory, 685404 \(2019\).](http://paperpile.com/b/UfkLXS/ghPVc)
- 93. [I. Lazaridis, The evolutionary history of human populations in Europe. Curr. Opin. Genet. Dev.](http://paperpile.com/b/UfkLXS/9YloN) [53, 21–27 \(2018\).](http://paperpile.com/b/UfkLXS/9YloN)
- 94. [J. E. T. Channell, B. S. Singer, B. R. Jicha, Timing of Quaternary geomagnetic reversals and excursions in volcanic](http://paperpile.com/b/UfkLXS/vbW4g) [and sedimentary archives. Quat. Sci. Rev.](http://paperpile.com/b/UfkLXS/vbW4g) [228, 106114 \(2020\).](http://paperpile.com/b/UfkLXS/vbW4g)
- 95. [M. Baca, et al., Ancient DNA of narrow-headed vole reveal common features of the Late Pleistocene population](http://paperpile.com/b/UfkLXS/pRbZN) [dynamics in cold-adapted small mammals. Proc. Biol. Sci.](http://paperpile.com/b/UfkLXS/pRbZN) [290, 20222238 \(2023\).](http://paperpile.com/b/UfkLXS/pRbZN)
- 96. [M. Feldman, et al., Late Pleistocene human genome suggests a local origin for the first farmers of central Anatolia.](http://paperpile.com/b/UfkLXS/KLRvB) [Nat. Commun.](http://paperpile.com/b/UfkLXS/KLRvB) [10, 1218 \(2019\).](http://paperpile.com/b/UfkLXS/KLRvB)
- 97. [D. L. Hoffmann, et al., U-Th dating of carbonate crusts reveals Neandertal origin of Iberian cave art. Science](http://paperpile.com/b/UfkLXS/aipId) [359,](http://paperpile.com/b/UfkLXS/aipId) [912–915 \(2018\).](http://paperpile.com/b/UfkLXS/aipId)
- 98. [M. C. Langley, et al., Bows and arrows and complex symbolic displays 48,000 years ago in the South Asian tropics.](http://paperpile.com/b/UfkLXS/SJVMy) [Sci Adv](http://paperpile.com/b/UfkLXS/SJVMy) [6, eaba3831 \(2020\).](http://paperpile.com/b/UfkLXS/SJVMy)
- 99. [S. O. Rasmussen, et al., A stratigraphic framework for abrupt climatic changes during the Last Glacial period based on](http://paperpile.com/b/UfkLXS/r1a6b) [three synchronized Greenland ice-core records: refining and extending the INTIMATE event stratigraphy. Quaternary](http://paperpile.com/b/UfkLXS/r1a6b) [Science Reviews](http://paperpile.com/b/UfkLXS/r1a6b) [106, 14–28 \(2014\).](http://paperpile.com/b/UfkLXS/r1a6b)
- 100. [H. Paeth, et al., Comparison of climate change from Cenozoic surface uplift and glacial-interglacial episodes in the](http://paperpile.com/b/UfkLXS/Fy9eO) [Himalaya-Tibet region: Insights from a regional climate model and proxy data. Global and Planetary Change](http://paperpile.com/b/UfkLXS/Fy9eO) [177, 10–](http://paperpile.com/b/UfkLXS/Fy9eO) [26 \(2019\).](http://paperpile.com/b/UfkLXS/Fy9eO)
- 101. [J. E. Kutzbach, et al., African climate response to orbital and glacial forcing in 140,000-y simulation with implications](http://paperpile.com/b/UfkLXS/c5Kak) [for early modern human environments. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/c5Kak) [117, 2255–2264 \(2020\).](http://paperpile.com/b/UfkLXS/c5Kak)
- 102. [F. Rostek, E. Bard, L. Beaufort, C. Sonzogni, G. Ganssen, Sea surface temperature and productivity records for the](http://paperpile.com/b/UfkLXS/NwzuT) [past 240 kyr in the Arabian Sea. Deep Sea Research Part II: Topical Studies in Oceanography](http://paperpile.com/b/UfkLXS/NwzuT) [44, 1461–1480 \(1997\).](http://paperpile.com/b/UfkLXS/NwzuT)
- 103. [H. S. Groucutt, et al., Homo sapiens in Arabia by 85,000 years ago. Nat Ecol Evol](http://paperpile.com/b/UfkLXS/aUT6n) [2, 800–809 \(2018\).](http://paperpile.com/b/UfkLXS/aUT6n)
- 104. [P. Scussolini, et al., Agreement between reconstructed and modeled boreal precipitation of the Last Interglacial. Sci](http://paperpile.com/b/UfkLXS/ZzXRy) [Adv](http://paperpile.com/b/UfkLXS/ZzXRy) [5, eaax7047 \(2019\).](http://paperpile.com/b/UfkLXS/ZzXRy)
- 105. [R. P. Jennings, et al., The greening of Arabia: Multiple opportunities for human occupation of the Arabian Peninsula](http://paperpile.com/b/UfkLXS/WWWDF) [during the Late Pleistocene inferred from an ensemble of climate model simulations. Quat. Int.](http://paperpile.com/b/UfkLXS/WWWDF) [382, 181–199 \(2015\).](http://paperpile.com/b/UfkLXS/WWWDF)
- 106. [C. S. M. Turney, et al., A global mean sea surface temperature dataset for the Last Interglacial \(129–116 ka\) and](http://paperpile.com/b/UfkLXS/3C7eS) [contribution of thermal expansion to sea level change. Earth System Science Data](http://paperpile.com/b/UfkLXS/3C7eS) [12, 3341–3356 \(2020\).](http://paperpile.com/b/UfkLXS/3C7eS)
- 107. [L. Al Harthy, R. Grenyer, Classification and ordination of the main plant communities of the Eastern Hajar Mountains,](http://paperpile.com/b/UfkLXS/7RPRd) [Oman. J. Arid Environ.](http://paperpile.com/b/UfkLXS/7RPRd) [169, 1–18 \(2019\).](http://paperpile.com/b/UfkLXS/7RPRd)
- 108. [A. Amonkar, S. D. Iyer, E. V. S. S. K. Babu, S. Manju, Extending the limit of widespread dispersed Toba volcanic](http://paperpile.com/b/UfkLXS/VndWw) [glass shards and identification of new in-situ volcanic events in the Central Indian Ocean Basin. J. Earth Syst. Sci.](http://paperpile.com/b/UfkLXS/VndWw) [129, 175 \(2020\).](http://paperpile.com/b/UfkLXS/VndWw)
- 109. [J. A. Westgate, et al., Tephrochronology of the Toba tuffs: four primary glass populations define the 75-ka Youngest](http://paperpile.com/b/UfkLXS/vHfeU) [Toba Tuff, northern Sumatra, Indonesia. J. Quat. Sci.](http://paperpile.com/b/UfkLXS/vHfeU) [28, 772–776 \(2013\).](http://paperpile.com/b/UfkLXS/vHfeU)
- 110. [M. R. Rampino, S. Self, Volcanic winter and accelerated glaciation following the Toba super-eruption. Nature](http://paperpile.com/b/UfkLXS/8K0Ze) [359,](http://paperpile.com/b/UfkLXS/8K0Ze) [50–52 \(1992\).](http://paperpile.com/b/UfkLXS/8K0Ze)
- 111. [G. S. Jones, J. M. Gregory, P. A. Stott, S. F. B. Tett, R. B. Thorpe, An AOGCM simulation of the climate response to](http://paperpile.com/b/UfkLXS/r11OH) [a volcanic super-eruption. Clim. Dyn.](http://paperpile.com/b/UfkLXS/r11OH) [25, 725–738 \(2005\).](http://paperpile.com/b/UfkLXS/r11OH)
- 112. [M. A. J. Williams, et al., Environmental impact of the 73ka Toba super-eruption in South Asia. Palaeogeogr.](http://paperpile.com/b/UfkLXS/yjdc3) [Palaeoclimatol. Palaeoecol.](http://paperpile.com/b/UfkLXS/yjdc3) [284, 295–314 \(2009\).](http://paperpile.com/b/UfkLXS/yjdc3)
- 113. [E. Camillo, J. P. Quadros, A. C. A. Santarosa, K. B. Costa, F. A. L. Toledo, An abrupt cooling event recorded around](http://paperpile.com/b/UfkLXS/4iVLz) [73 kyr in western South Atlantic. Quat. Int.](http://paperpile.com/b/UfkLXS/4iVLz) [542, 80–87 \(2020\).](http://paperpile.com/b/UfkLXS/4iVLz)
- 114. [W. Du, et al., Timing and structure of the weak Asian Monsoon event about 73,000 years ago. Quat. Geochronol.](http://paperpile.com/b/UfkLXS/NeLU9) [53,](http://paperpile.com/b/UfkLXS/NeLU9) [101003 \(2019\).](http://paperpile.com/b/UfkLXS/NeLU9)
- 115. [M. A. J. Williams, et al., Reply to the comment on "Environmental impact of the 73ka Toba super-eruption in South](http://paperpile.com/b/UfkLXS/1086k) [Asia" by M. A. J. Williams, S. H. Ambrose, S. van der Kaars, C. Ruehlemann, U. Chattopadhyaya, J. Pal, P. R.](http://paperpile.com/b/UfkLXS/1086k) [Chauhan \[Palaeogeography, Palaeoclimatology, Palaeoecology 284 \(2009\) 295–314\]. Palaeogeogr. Palaeoclimatol.](http://paperpile.com/b/UfkLXS/1086k) [Palaeoecol.](http://paperpile.com/b/UfkLXS/1086k) [296, 204–211 \(2010\).](http://paperpile.com/b/UfkLXS/1086k)
- 116. [G. A. Zielinski, et al., Potential atmospheric impact of the Toba Mega-Eruption](http://paperpile.com/b/UfkLXS/tWEjA) ∼71,000 years ago[. Geophys. Res.](http://paperpile.com/b/UfkLXS/tWEjA) [Lett.](http://paperpile.com/b/UfkLXS/tWEjA) [23, 837–840 \(1996\).](http://paperpile.com/b/UfkLXS/tWEjA)
- 117. [B. A. Black, J.-F. Lamarque, D. R. Marsh, A. Schmidt, C. G. Bardeen, Global climate disruption and regional climate](http://paperpile.com/b/UfkLXS/ZtiXm) [shelters after the Toba supereruption. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/ZtiXm) [118](http://paperpile.com/b/UfkLXS/ZtiXm) [\(2021\).](http://paperpile.com/b/UfkLXS/ZtiXm)
- 118. [A. Akbari, et al., Identifying the favored mutation in a positive selective sweep. Nat. Methods](http://paperpile.com/b/UfkLXS/tv8se) [15, 279–282 \(2018\).](http://paperpile.com/b/UfkLXS/tv8se)
- 119. [L. G. Moore, Human genetic adaptation](http://paperpile.com/b/UfkLXS/1kP3C) to high altitude[. High Alt. Med. Biol.](http://paperpile.com/b/UfkLXS/1kP3C) [2, 257–279 \(2001\).](http://paperpile.com/b/UfkLXS/1kP3C)
- 120. [L. G. Moore, et al., Maternal adaptation to high-altitude pregnancy: an experiment of nature--a review. Placenta](http://paperpile.com/b/UfkLXS/DrNrs) [25](http://paperpile.com/b/UfkLXS/DrNrs) Suppl A, S60-71 (2004).
- 121. [X. Zhang, et al., The history and evolution of the Denisovan- haplotype in Tibetans. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/eefHd) [118](http://paperpile.com/b/UfkLXS/eefHd) [\(2021\).](http://paperpile.com/b/UfkLXS/eefHd)
- 122. [J. S. Rees, S. Castellano, A. M. Andrés, The Genomics of Human Local Adaptation. Trends Genet.](http://paperpile.com/b/UfkLXS/I48U6) [36, 415–428](http://paperpile.com/b/UfkLXS/I48U6) [\(2020\).](http://paperpile.com/b/UfkLXS/I48U6)
- 123. [L. T. Buck, et al., Evidence of different climatic adaptation strategies in humans and non-human primates. Sci. Rep.](http://paperpile.com/b/UfkLXS/OUmgt) [9,](http://paperpile.com/b/UfkLXS/OUmgt) [11025 \(2019\).](http://paperpile.com/b/UfkLXS/OUmgt)
- 124. [H. J. Grav, A. S. Blix, Brown adipose tissue-a factor in the survival of harp seal pups. Can. J. Physiol. Pharmacol.](http://paperpile.com/b/UfkLXS/UsbEk) [54,](http://paperpile.com/b/UfkLXS/UsbEk) [409–412 \(1976\).](http://paperpile.com/b/UfkLXS/UsbEk)
- 125. [A. A. J. J. van der Lans, et al., Cold acclimation recruits human brown fat and increases nonshivering thermogenesis.](http://paperpile.com/b/UfkLXS/xW2KJ) [J. Clin. Invest.](http://paperpile.com/b/UfkLXS/xW2KJ) [123, 3395–3403 \(2013\).](http://paperpile.com/b/UfkLXS/xW2KJ)
- 126. [J. Sanchez-Gurmaches, et al., Brown Fat AKT2 Is a Cold-Induced Kinase that Stimulates ChREBP-Mediated De](http://paperpile.com/b/UfkLXS/FjoyX) [Novo Lipogenesis to Optimize Fuel Storage and Thermogenesis. Cell Metab.](http://paperpile.com/b/UfkLXS/FjoyX) [27, 195–209.e6 \(2018\).](http://paperpile.com/b/UfkLXS/FjoyX)
- 127. [Z. Yang, et al., Darwinian Positive Selection on the Pleiotropic Effects of KITLG Explain Skin Pigmentation and](http://paperpile.com/b/UfkLXS/6nVWG) [Winter Temperature Adaptation in Eurasians. Mol. Biol. Evol.](http://paperpile.com/b/UfkLXS/6nVWG) [35, 2272–2283 \(2018\).](http://paperpile.com/b/UfkLXS/6nVWG)
- 128. [H. O. Koskela, Cold air-provoked respiratory symptoms: the mechanisms and management. Int. J. Circumpolar Health](http://paperpile.com/b/UfkLXS/tgvsh) [66, 91–100 \(2007\).](http://paperpile.com/b/UfkLXS/tgvsh)
- 129. [T. M. Mäkinen, et al., Cold temperature and low humidity are associated with increased occurrence of respiratory tract](http://paperpile.com/b/UfkLXS/hYETE) [infections. Respir. Med.](http://paperpile.com/b/UfkLXS/hYETE) [103, 456–462 \(2009\).](http://paperpile.com/b/UfkLXS/hYETE)
- 130. [M. Fumagalli, et al., Greenlandic Inuit show genetic signatures of diet and climate adaptation. Science](http://paperpile.com/b/UfkLXS/TsnYm) [349, 1343–](http://paperpile.com/b/UfkLXS/TsnYm) [1347 \(2015\).](http://paperpile.com/b/UfkLXS/TsnYm)
- 131. [A. Cardona, et al., Genome-wide analysis of cold adaptation in indigenous Siberian populations. PLoS One](http://paperpile.com/b/UfkLXS/8C7bq) [9, e98076](http://paperpile.com/b/UfkLXS/8C7bq) [\(2014\).](http://paperpile.com/b/UfkLXS/8C7bq)
- 132. [A. V. Khrunin, G. V. Khvorykh, A. N. Fedorov, S. A. Limborska, Genomic landscape of the signals of positive natural](http://paperpile.com/b/UfkLXS/dEU7p) [selection in populations of Northern Eurasia: A view from Northern Russia. PLoS One](http://paperpile.com/b/UfkLXS/dEU7p) [15, e0228778 \(2020\).](http://paperpile.com/b/UfkLXS/dEU7p)
- 133. [S. Zhou, et al., Genetic architecture and adaptations of Nunavik Inuit. Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/iNlUU) [116, 16012–](http://paperpile.com/b/UfkLXS/iNlUU) [16017 \(2019\).](http://paperpile.com/b/UfkLXS/iNlUU)
- 134. [A. W. Reynolds, et al., Comparing signals of natural selection between three Indigenous North American populations.](http://paperpile.com/b/UfkLXS/cuD5O) [Proc. Natl. Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/cuD5O) [116, 9312–9317 \(2019\).](http://paperpile.com/b/UfkLXS/cuD5O)
- 135. [N. S. Yudin, D. M. Larkin, E. V. Ignatieva, A compendium and functional characterization of mammalian genes](http://paperpile.com/b/UfkLXS/Ox8Q8) [involved in adaptation to Arctic or Antarctic environments. BMC Genet.](http://paperpile.com/b/UfkLXS/Ox8Q8) [18, 111 \(2017\).](http://paperpile.com/b/UfkLXS/Ox8Q8)
- 136. [M. Mondal, J. Bertranpetit, O. Lao, Approximate Bayesian computation with deep learning supports a third archaic](http://paperpile.com/b/UfkLXS/ri7DT) [introgression in Asia and Oceania. Nat. Commun.](http://paperpile.com/b/UfkLXS/ri7DT) [10, 246 \(2019\).](http://paperpile.com/b/UfkLXS/ri7DT)
- 137. [S. Sankararaman, S. Mallick, N. Patterson, D. Reich, The Combined Landscape of Denisovan and Neanderthal](http://paperpile.com/b/UfkLXS/ZcwUQ) [Ancestry in Present-Day Humans. Curr. Biol.](http://paperpile.com/b/UfkLXS/ZcwUQ) [26, 1241–1247 \(2016\).](http://paperpile.com/b/UfkLXS/ZcwUQ)
- 138. [B. Vernot, et al., Excavating Neandertal and Denisovan DNA from the genomes of Melanesian individuals. Science](http://paperpile.com/b/UfkLXS/VIulE) [352, 235–239 \(2016\).](http://paperpile.com/b/UfkLXS/VIulE)
- 139. [G. S. Jacobs, et al., Multiple Deeply Divergent Denisovan Ancestries in Papuans. Cell](http://paperpile.com/b/UfkLXS/ORdNo) [177, 1010–1021.e32 \(2019\).](http://paperpile.com/b/UfkLXS/ORdNo)
- 140. [E. Huerta-Sánchez, et al., Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. Nature](http://paperpile.com/b/UfkLXS/Av0Js) [512,](http://paperpile.com/b/UfkLXS/Av0Js) [194–197 \(2014\).](http://paperpile.com/b/UfkLXS/Av0Js)
- 141. [F. Racimo, et al., Archaic Adaptive Introgression in TBX15/WARS2. Mol. Biol. Evol.](http://paperpile.com/b/UfkLXS/Vc4Us) [34, 509–524 \(2017\).](http://paperpile.com/b/UfkLXS/Vc4Us)
- 142. [G. Gower, P. I. Picazo, M. Fumagalli, F. Racimo, Detecting adaptive introgression in human evolution using](http://paperpile.com/b/UfkLXS/9dq6Z) [convolutional neural networks. eLife](http://paperpile.com/b/UfkLXS/9dq6Z) [\(2021\) https:/doi.org/](http://paperpile.com/b/UfkLXS/9dq6Z)[10.7554/eLife.64669.](http://dx.doi.org/10.7554/eLife.64669)
- 143. R. [M. Gittelman, et al., Archaic Hominin Admixture Facilitated Adaptation to Out-of-Africa Environments. Curr.](http://paperpile.com/b/UfkLXS/Et8hK) [Biol.](http://paperpile.com/b/UfkLXS/Et8hK) [26, 3375–3382 \(2016\).](http://paperpile.com/b/UfkLXS/Et8hK)
- 144. [D. Setter, et al., VolcanoFinder: Genomic scans for adaptive introgression. PLoS Genet.](http://paperpile.com/b/UfkLXS/Q5Hu1) [16, e1008867 \(2020\).](http://paperpile.com/b/UfkLXS/Q5Hu1)
- 145. [K. J. Karczewski, et al., The mutational constraint spectrum quantified from variation in 141,456 humans. Nature](http://paperpile.com/b/UfkLXS/vSEj2) [581,](http://paperpile.com/b/UfkLXS/vSEj2) [434–443 \(2020\).](http://paperpile.com/b/UfkLXS/vSEj2)
- 146. [C. Trimmer, et al., Genetic variation across the human olfactory receptor repertoire alters odor perception. Proc. Natl.](http://paperpile.com/b/UfkLXS/VodnX) [Acad. Sci. U. S. A.](http://paperpile.com/b/UfkLXS/VodnX) [116, 9475–9480 \(2019\).](http://paperpile.com/b/UfkLXS/VodnX)
- 147. [R. S. Dhindsa, B. R. Copeland, A. M. Mustoe, D. B. Goldstein, Natural Selection Shapes Codon Usage in the Human](http://paperpile.com/b/UfkLXS/LG34b) [Genome. Am. J. Hum. Genet.](http://paperpile.com/b/UfkLXS/LG34b) [107, 83–95 \(2020\).](http://paperpile.com/b/UfkLXS/LG34b)
- 148. [W. Zhou, W. Wei, Y. Sun, Genetically engineered mouse models for functional studies of SKP1-CUL1-F-box-protein](http://paperpile.com/b/UfkLXS/VJ7jj) [\(SCF\) E3 ubiquitin ligases. Cell Res.](http://paperpile.com/b/UfkLXS/VJ7jj) [23, 599–619 \(2013\).](http://paperpile.com/b/UfkLXS/VJ7jj)
- 149. [T. Cardozo, M. Pagano, The SCF ubiquitin ligase: insights into a molecular machine. Nat. Rev. Mol. Cell Biol.](http://paperpile.com/b/UfkLXS/melHT) [5,](http://paperpile.com/b/UfkLXS/melHT) [739–751 \(2004\).](http://paperpile.com/b/UfkLXS/melHT)
- 150. [J. C. Morales, et al., Role for the BRCA1 C-terminal repeats \(BRCT\) protein 53BP1 in maintaining genomic stability.](http://paperpile.com/b/UfkLXS/VnRdZ)

[J. Biol. Chem.](http://paperpile.com/b/UfkLXS/VnRdZ) [278, 14971–14977 \(2003\).](http://paperpile.com/b/UfkLXS/VnRdZ)

- 151. [I. M. Ward, K. Minn, J. van Deursen, J. Chen, p53 Binding protein 53BP1 is required for DNA damage responses and](http://paperpile.com/b/UfkLXS/hoTDM) [tumor suppression in mice. Mol. Cell. Biol.](http://paperpile.com/b/UfkLXS/hoTDM) [23, 2556–2563 \(2003\).](http://paperpile.com/b/UfkLXS/hoTDM)
- 152. [M. Monte, et al., Cloning, chromosome mapping and functional characterization of a human homologue of murine](http://paperpile.com/b/UfkLXS/ro7Mw) [gtse-1 \(B99\) gene. Gene](http://paperpile.com/b/UfkLXS/ro7Mw) [254, 229–236 \(2000\).](http://paperpile.com/b/UfkLXS/ro7Mw)
- 153. [Q. Yang, et al., Severe Fanconi Anemia phenotypes in Fancd2 depletion mice. Biochem. Biophys. Res. Commun.](http://paperpile.com/b/UfkLXS/c5IJg) [514,](http://paperpile.com/b/UfkLXS/c5IJg) [713–719 \(2019\).](http://paperpile.com/b/UfkLXS/c5IJg)
- 154. [M. Catinozzi, et al., The Drosophila FUS ortholog cabeza promotes adult founder myoblast selection by Xrp1](http://paperpile.com/b/UfkLXS/FMmRq) [dependent regulation of FGF signaling. PLoS Genet.](http://paperpile.com/b/UfkLXS/FMmRq) [16, e1008731 \(2020\).](http://paperpile.com/b/UfkLXS/FMmRq)
- 155. [M. Ballarino, et al., TAF15 is important for cellular proliferation and regulates the expression of a subset of cell cycle](http://paperpile.com/b/UfkLXS/7Iawn) [genes through miRNAs. Oncogene](http://paperpile.com/b/UfkLXS/7Iawn) [32, 4646–4655 \(2013\).](http://paperpile.com/b/UfkLXS/7Iawn)
- 156. [R. Döffinger, et al., X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF](http://paperpile.com/b/UfkLXS/SNHLN)[kappaB signaling. Nat. Genet.](http://paperpile.com/b/UfkLXS/SNHLN) [27, 277–285 \(2001\).](http://paperpile.com/b/UfkLXS/SNHLN)
- 157. [K. M. Merath, B. Chang, R. Dubielzig, R. Jeannotte, D. J. Sidjanin, A spontaneous mutation in Srebf2 leads to](http://paperpile.com/b/UfkLXS/8J4Qr) [cataracts and persistent skin wounds in the lens opacity 13 \(lop13\) mouse. Mamm. Genome](http://paperpile.com/b/UfkLXS/8J4Qr) [22, 661–673 \(2011\).](http://paperpile.com/b/UfkLXS/8J4Qr)
- 158. I. Juranović, Z. Meić, I. Piantanida, L.-[M. Tumir, M. Žinić, Interactions of phenanthridinium](http://paperpile.com/b/UfkLXS/JvCIJ)–nucleobase conjugates [with polynucleotides in aqueous media. Recognition of poly UElectronic supplementary information \(ESI\) available:](http://paperpile.com/b/UfkLXS/JvCIJ) [materials and methods and CD titrations. See http://www.rsc.org/suppdata/cc/b2/b202615e/. Chem. Commun. , 1432–](http://paperpile.com/b/UfkLXS/JvCIJ) [1433 \(2002\).](http://paperpile.com/b/UfkLXS/JvCIJ)
- 159. [M. J. Krashes, B. B. Lowell, A. S. Garfield, Melanocortin-4 receptor-regulated energy homeostasis. Nat. Neurosci.](http://paperpile.com/b/UfkLXS/xrGwk) [19,](http://paperpile.com/b/UfkLXS/xrGwk) [206–219 \(2016\).](http://paperpile.com/b/UfkLXS/xrGwk)
- 160. [B. L. Houghton, J. R. Meendering, B. J. Wong, C. T. Minson, Nitric oxide and noradrenaline contribute to the](http://paperpile.com/b/UfkLXS/jI239) [temperature threshold of the axon reflex response to gradual local heating in human skin. J. Physiol.](http://paperpile.com/b/UfkLXS/jI239) [572, 811–820](http://paperpile.com/b/UfkLXS/jI239) [\(2006\).](http://paperpile.com/b/UfkLXS/jI239)
- 161. [V. A. Pavlov, K. J. Tracey, Neural regulation of immunity: molecular mechanisms and clinical translation. Nat.](http://paperpile.com/b/UfkLXS/2n7Nj) [Neurosci.](http://paperpile.com/b/UfkLXS/2n7Nj) [20, 156–166 \(2017\).](http://paperpile.com/b/UfkLXS/2n7Nj)
- 162. [P. J. Brunton, J. A. Russell, The expectant brain: adapting for motherhood. Nat. Rev. Neurosci.](http://paperpile.com/b/UfkLXS/8Q4zA) [9, 11–25 \(2008\).](http://paperpile.com/b/UfkLXS/8Q4zA)
- 163. [L. A. Palinkas, Mental and cognitive performance in the cold. Int. J. Circumpolar Health](http://paperpile.com/b/UfkLXS/9bpJN) [60, 430–439 \(2001\).](http://paperpile.com/b/UfkLXS/9bpJN)
- 164. [T. M. Mäkinen, Human cold exposure, adaptation, and](http://paperpile.com/b/UfkLXS/ZJ7yE) performance in high latitude environments. [Am. J. Hum. Biol.](http://paperpile.com/b/UfkLXS/ZJ7yE) [19, 155–164 \(2007\).](http://paperpile.com/b/UfkLXS/ZJ7yE)
- 165. [T. M. Mäkinen, et al., Effect of repeated exposures to cold on cognitive performance in humans. Physiol. Behav.](http://paperpile.com/b/UfkLXS/w4ztP) [87,](http://paperpile.com/b/UfkLXS/w4ztP) [166–176 \(2006\).](http://paperpile.com/b/UfkLXS/w4ztP)
- 166. [L. Taylor, S. L. Watkins, H. Marshall, B. J. Dascombe, J. Foster, The Impact of Different Environmental Conditions](http://paperpile.com/b/UfkLXS/ghf4e) [on Cognitive Function: A Focused Review. Front. Physiol.](http://paperpile.com/b/UfkLXS/ghf4e) [6, 372 \(2015\).](http://paperpile.com/b/UfkLXS/ghf4e)
- 167. [J. C. Montgomery, J. A. Macdonald, Effects of temperature on nervous system: implications for behavioral](http://paperpile.com/b/UfkLXS/F2q2A) [performance. Am. J. Physiol.](http://paperpile.com/b/UfkLXS/F2q2A) [259, R191–6 \(1990\).](http://paperpile.com/b/UfkLXS/F2q2A)
- 168. [C. Städele, S. Heigele, W. Stein, Neuromodulation to the Rescue: Compensation of Temperature-Induced Breakdown](http://paperpile.com/b/UfkLXS/ngloe) [of Rhythmic Motor Patterns via Extrinsic Neuromodulatory Input. PLoS Biol.](http://paperpile.com/b/UfkLXS/ngloe) [13, e1002265 \(2015\).](http://paperpile.com/b/UfkLXS/ngloe)
- 169. [E. de la Peña, et al., The Influence of Cold Temperature on Cellular Excitability of Hippocampal Networks. PLoS One](http://paperpile.com/b/UfkLXS/RaOg5) [7, e52475 \(2012\).](http://paperpile.com/b/UfkLXS/RaOg5)
- 170. [M. J. Van Hook, Temperature effects on synaptic transmission and neuronal function in the visual thalamus. PLoS](http://paperpile.com/b/UfkLXS/igKcv) [One](http://paperpile.com/b/UfkLXS/igKcv) [15, e0232451 \(2020\).](http://paperpile.com/b/UfkLXS/igKcv)
- 171. F. Viana, E. de la Peña, C. Belmonte, Specificity of [cold thermotransduction is determined by differential ionic](http://paperpile.com/b/UfkLXS/LALtK) [channel expression. Nat. Neurosci.](http://paperpile.com/b/UfkLXS/LALtK) [5, 254–260 \(2002\).](http://paperpile.com/b/UfkLXS/LALtK)
- 172. [K. Zimmermann, et al., Sensory neuron sodium channel Nav1.8 is essential for pain at low temperatures. Nature](http://paperpile.com/b/UfkLXS/wBFYt) [447,](http://paperpile.com/b/UfkLXS/wBFYt) [855–858 \(2007\).](http://paperpile.com/b/UfkLXS/wBFYt)
- 173. [C.-H. Tan, P. A. McNaughton, The TRPM2 ion channel is required for sensitivity to warmth. Nature](http://paperpile.com/b/UfkLXS/eVHXO) [536, 460–463](http://paperpile.com/b/UfkLXS/eVHXO) [\(2016\).](http://paperpile.com/b/UfkLXS/eVHXO)
- 174. [W. M. Knowlton, A. Bifolck-Fisher, D. M. Bautista, D. D. McKemy, TRPM8, but not TRPA1, is required for neural](http://paperpile.com/b/UfkLXS/isV8X) [and behavioral responses to acute noxious cold temperatures and cold-mimetics in vivo. Pain](http://paperpile.com/b/UfkLXS/isV8X) [150, 340–350 \(2010\).](http://paperpile.com/b/UfkLXS/isV8X)
- 175. [D. M. Bautista, et al., The menthol receptor TRPM8 is the principal detector of environmental cold. Nature](http://paperpile.com/b/UfkLXS/uTmnp) [448, 204–](http://paperpile.com/b/UfkLXS/uTmnp) [208 \(2007\).](http://paperpile.com/b/UfkLXS/uTmnp)
- 176. [T. J. Buijs, P. A. McNaughton, The Role of Cold-Sensitive Ion Channels in Peripheral Thermosensation. Front. Cell.](http://paperpile.com/b/UfkLXS/u6xfV) [Neurosci.](http://paperpile.com/b/UfkLXS/u6xfV) [14, 262 \(2020\).](http://paperpile.com/b/UfkLXS/u6xfV)
- 177. [Z. A. K. Chan Lek Tan, Regulation of body temperature by the nervous system. Neuron](http://paperpile.com/b/UfkLXS/NARew) [98, 31 \(2018\).](http://paperpile.com/b/UfkLXS/NARew)
- 178. [F. M. Key, et al., Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. PLoS Genet.](http://paperpile.com/b/UfkLXS/GrLRN) [14,](http://paperpile.com/b/UfkLXS/GrLRN) [e1007298 \(2018\).](http://paperpile.com/b/UfkLXS/GrLRN)
- 179. [Y. Saitoh, A. Kamijo, J. Yamauchi, T. Sakamoto, N. Terada, The membrane palmitoylated protein, MPP6, is involved](http://paperpile.com/b/UfkLXS/wkEgz) [in myelin formation in the mouse peripheral nervous system. Histochem. Cell Biol.](http://paperpile.com/b/UfkLXS/wkEgz) [151, 385–394 \(2019\).](http://paperpile.com/b/UfkLXS/wkEgz)
- 180. [T. A. Forbes, V. Gallo, All Wrapped Up: Environmental Effects on Myelination. Trends Neurosci.](http://paperpile.com/b/UfkLXS/zSAtU) [40, 572–587](http://paperpile.com/b/UfkLXS/zSAtU) [\(2017\).](http://paperpile.com/b/UfkLXS/zSAtU)
- 181. [M. M. Saltykova, The Main Physiological Mechanisms of Cold Adaptation in Humans. Neuroscience and Behavioral](http://paperpile.com/b/UfkLXS/asmgd) [Physiology](http://paperpile.com/b/UfkLXS/asmgd) [48, 543–550 \(2018\).](http://paperpile.com/b/UfkLXS/asmgd)
- 182. [O. Keinan, et al., Glycogen metabolism links glucose homeostasis to thermogenesis in adipocytes. Nature](http://paperpile.com/b/UfkLXS/PeP28) [599, 296–](http://paperpile.com/b/UfkLXS/PeP28) [301 \(2021\).](http://paperpile.com/b/UfkLXS/PeP28)
- 183. [D. Szklarczyk, et al., The STRING database in 2021: customizable protein-protein networks, and functional](http://paperpile.com/b/UfkLXS/50XVR) [characterization of user-uploaded gene/measurement sets. Nucleic Acids Res.](http://paperpile.com/b/UfkLXS/50XVR) [49, D605–D612 \(2021\).](http://paperpile.com/b/UfkLXS/50XVR)
- 184. [P. Luisi, et al., Recent Positive Selection Has Acted on Genes Encoding Proteins with](http://paperpile.com/b/UfkLXS/JW1Os) More Interactions within the [Whole Human Interactome. Genome Biol. Evol.](http://paperpile.com/b/UfkLXS/JW1Os) [7, 1141–1154 \(2015\).](http://paperpile.com/b/UfkLXS/JW1Os)
- 185. [D. Enard, L. Cai, C. Gwennap, D. A. Petrov, Viruses are a dominant driver of protein adaptation in mammals. Elife](http://paperpile.com/b/UfkLXS/Zk7G0) [5](http://paperpile.com/b/UfkLXS/Zk7G0) [\(2016\).](http://paperpile.com/b/UfkLXS/Zk7G0)
- 186. [Y.-F. Huang, Dissecting Genomic Determinants of Positive Selection with an Evolution-Guided Regression Model.](http://paperpile.com/b/UfkLXS/14DoW) [Mol. Biol. Evol.](http://paperpile.com/b/UfkLXS/14DoW) (2021) [https:/doi.org/](http://paperpile.com/b/UfkLXS/14DoW)[10.1093/molbev/msab291](http://dx.doi.org/10.1093/molbev/msab291) [\(December 6, 2021\).](http://paperpile.com/b/UfkLXS/14DoW)
- 187. [B. S. Weir, C. C. Cockerham, ESTIMATING F-STATISTICS FOR THE ANALYSIS OF POPULATION](http://paperpile.com/b/UfkLXS/pI0mD) [STRUCTURE. Evolution](http://paperpile.com/b/UfkLXS/pI0mD) [38, 1358–1370 \(1984\).](http://paperpile.com/b/UfkLXS/pI0mD)
- 188. [M. C. Whitlock, K. E. Lotterhos, Reliable Detection of Loci Responsible for Local Adaptation: Inference of a Null](http://paperpile.com/b/UfkLXS/AS7xN) [Model through Trimming the Distribution of F\(ST\). Am. Nat.](http://paperpile.com/b/UfkLXS/AS7xN) [186 Suppl 1, S24–36 \(2015\).](http://paperpile.com/b/UfkLXS/AS7xN)
- 189. [L. Excoffier, N. Ray, Surfing during population expansions promotes genetic revolutions and structuration. Trends](http://paperpile.com/b/UfkLXS/Ky0Xp) [Ecol. Evol.](http://paperpile.com/b/UfkLXS/Ky0Xp) [23, 347–351 \(2008\).](http://paperpile.com/b/UfkLXS/Ky0Xp)
- 190. [B. F. Voight, S. Kudaravalli, X. Wen, J. K. Pritchard, A map of recent positive selection in the human genome. PLoS](http://paperpile.com/b/UfkLXS/hqP8x)

[Biol.](http://paperpile.com/b/UfkLXS/hqP8x) [4, e72 \(2006\).](http://paperpile.com/b/UfkLXS/hqP8x)

- 191. [P. C. Sabeti, et al., Genome-wide detection and characterization of positive selection in human populations. Nature](http://paperpile.com/b/UfkLXS/WJuUm) [449, 913–918 \(2007\).](http://paperpile.com/b/UfkLXS/WJuUm)
- 192. [X. Yi, et al., Sequencing of 50 human exomes reveals adaptation to high altitude. Science](http://paperpile.com/b/UfkLXS/BcmeM) [329, 75–78 \(2010\).](http://paperpile.com/b/UfkLXS/BcmeM)
- 193. [H. McColl, et al., The prehistoric peopling of Southeast Asia. Science](http://paperpile.com/b/UfkLXS/Yprp7) [361, 88–92 \(2018\).](http://paperpile.com/b/UfkLXS/Yprp7)
- 194. [M. A. Yang, et al., 40,000-Year-Old Individual from Asia Provides Insight into Early Population Structure in Eurasia.](http://paperpile.com/b/UfkLXS/mMJmg) [Curr. Biol.](http://paperpile.com/b/UfkLXS/mMJmg) [27, 3202–3208.e9 \(2017\).](http://paperpile.com/b/UfkLXS/mMJmg)
- 195. [F. Racimo, D. Marnetto, E. Huerta-Sánchez, Signatures of Archaic Adaptive Introgression in Present-Day Human](http://paperpile.com/b/UfkLXS/qfh9e) [Populations. Mol. Biol. Evol.](http://paperpile.com/b/UfkLXS/qfh9e) [34, 296–317 \(2017\).](http://paperpile.com/b/UfkLXS/qfh9e)
- 196. [B. M. Peter, 100,000 years of gene flow between Neandertals and Denisovans in the Altai mountains. bioRxiv,](http://paperpile.com/b/UfkLXS/PZQKy) [2020.03.13.990523 \(2020\).](http://paperpile.com/b/UfkLXS/PZQKy)
- 197. [K. Prüfer, et al., The complete genome sequence of a Neanderthal from the Altai Mountains. Nature](http://paperpile.com/b/UfkLXS/USNDL) [505, 43–49](http://paperpile.com/b/UfkLXS/USNDL) [\(2014\).](http://paperpile.com/b/UfkLXS/USNDL)
- 198. [K. Prüfer, et al., A high-coverage Neandertal genome from Vindija Cave in Croatia. Science](http://paperpile.com/b/UfkLXS/pn2TX) [358, 655–658 \(2017\).](http://paperpile.com/b/UfkLXS/pn2TX)
- 199. [F. Mafessoni,](http://paperpile.com/b/UfkLXS/QONug) [et al., A high-coverage Neandertal genome from Chagyrskaya Cave. Proc. Natl. Acad. Sci. U.](http://paperpile.com/b/UfkLXS/QONug) S. A[.](http://paperpile.com/b/UfkLXS/QONug) [117,](http://paperpile.com/b/UfkLXS/QONug) [15132–15136 \(2020\).](http://paperpile.com/b/UfkLXS/QONug)