Genomics of Mesolithic Scandinavia reveal colonization routes and high-latitude adaptation

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29 Abstract

30Scandinavia was one of the last geographic areas in Europe to become habitable for humans after 31the last glaciation. However, the origin(s) of the first colonizers and their migration routes remain 32unclear. We sequenced the genomes, up to 57x coverage, of seven hunter-gatherers excavated 33across Scandinavia and dated to 9,500-6,000 years before present. Surprisingly, among the 34Scandinavian Mesolithic individuals, the genetic data display an east-west genetic gradient that 35opposes the pattern seen in other parts of Mesolithic Europe. This result suggests that 36Scandinavia was initially colonized following two different routes: one from the south, the other 37from the northeast. The latter followed the ice-free Norwegian north Atlantic coast, along which 38novel and advanced pressure-blade stone-tool techniques may have spread. These two groups met 39and mixed in Scandinavia, creating a genetically diverse population, which shows patterns of 40genetic adaptation to high latitude environments. These adaptations include high frequencies of 41low pigmentation variants and a gene-region associated with physical performance, which shows 42strong continuity into modern-day northern Europeans. Finally, we were able to compute a 3D 43facial reconstruction of a Mesolithic woman from her high-coverage genome, giving a glimpse 44into an individual's physical appearance in the Mesolithic.
45

46 Main text

47As the ice-sheet retracted from northern Europe after the Last Glacial Maximum (LGM), around 4823,000 years ago, new habitable areas emerged (1) allowing plants (2, 3) and animals (4) to 49recolonize the Scandinavian peninsula (hereafter Scandinavia). There is consistent evidence of 50human presence in the archaeological record from c. 11,700 years before present (BP), both in 51southern and northern Scandinavia (5–8). At this time, the ice-sheet was still dominating the 52interior of Scandinavia (8) (Fig. 1A, Supplementary Information 1), but recent climate modeling 53shows that the Arctic coast of (modern-day) northern Norway was ice-free (9). Similarities in 54late-glacial lithic technology (direct blade percussion technique) of western Europe and the oldest 55counterparts of northernmost Scandinavia (10) (Supplementary Information 1) have been used to 56argue for a postglacial colonization of Scandinavia from southwestern Europe. However, studies 57of a new lithic technology, 'pressure blade' technique, which first occurred in the northern parts 58of Scandinavia, indicates contacts with groups in the east and possibly an eastern origin of the 59colonizers (6, 11, 12) (Supplementary Information 1). The first genetic studies of Mesolithic 60human remains from central and eastern Scandinavia (SHGs) revealed similarities to two 61different Mesolithic European populations, the 'western hunter-gatherers' (WHGs) from western, 62central and southern Europe and the 'eastern hunter-gatherers' (EHGs) from northeastern Europe 63(13–19). Archaeology, climate modeling, and genetics, suggest several possibilities for the 64colonization of Scandinavia, including migrations from the south, southeast, northeast and 65combinations of these, however, the early post-glacial peopling of Scandinavia remains elusive 66(1–12, 14–17, 20, 21). In this study, we contrast genome sequence data and stable isotopes from 67Mesolithic human remains from western, northern, and eastern Scandinavia to infer the post-

68glacial colonization of Scandinavia – from where people came, what routes they followed, how 69they were related to other Mesolithic Europeans – and to investigate human adaptation to high-70latitude environments.

71**Results and Discussion**

72We sequenced the genomes of seven hunter-gatherers from Scandinavia (Table 1 and 73Supplementary Information 1-3) ranging from 57.8× to 0.1× genome coverage, of which four 74individuals had a genome coverage above 1×. The remains were directly dated to between 9,500 75BP and 6,000 BP, and were excavated in southwestern Norway (Hum1, Hum2), northern Norway 76(Steigen), and the Baltic islands of Stora Karlsö and Gotland (SF9, SF11, SF12 and SBj) and 77represent 18% (6 of 33) of all known human remains in Scandinavia older than 8,000 (22). All 78samples displayed fragmentation and cytosine deamination at fragment termini characteristic for 79ancient DNA (Supplementary Information 3). Mitochondrial (mt) DNA-based contamination 80estimates were <6% for all individuals and autosomal contamination was <1% for all individuals 81except for SF11, which showed c. 10% contamination (Table 1, Supplementary Information 4). 82Four of the seven individuals were inferred to be males, three were females. All the western and 83northern Scandinavian individuals and one eastern Scandinavian carried U5a1 mitochondrial 84haplotypes while the remaining eastern Scandinavians carried U4a haplotypes (Table 1, 85Supplementary Information 5). These individuals represent the oldest U5a1 and U4 lineages 86detected so far. The Y chromosomal haplotype was determined for three of the four males, all 87carried I2 haplotypes, which were common in pre-Neolithic Europe (Table 1, Supplementary 88Information 5).

89The high coverage and Uracil-DNA-glycosylase (UDG) treated genome (to reduce the effects of 90post-mortem DNA damage) of SF12 allowed us to confidently discover new and hitherto 91unknown variants at sites with 55x or higher sequencing depth (Supplementary Information 3). 92Based on SF12's high-coverage and high-quality genome, we estimate the number of single 93nucleotide polymorphisms (SNPs) hitherto unknown (that are not recorded in dbSNP (v142)) to 94be c. 10,600. This is almost twice the number of unique variants (c. 6,000) per Finnish individual 95(Supplementary Information 3) and close to the median per European individual in the 1000 96Genomes Project (23) (c. 11,400, Supplementary Information 3). At least 17% of these SNPs that 97are not found in modern-day individuals, were in fact common among the Mesolithic 98Scandinavians (seen in the low coverage data conditional on the observation in SF12), suggesting 99that a substantial fraction of human variation has been lost in the past 9,000 years 100(Supplementary Information 3). In other words, the SHGs (as well as WHGs and EHGs) have no 101direct descendants, or a population that show direct continuity with the Mesolithic populations 102(Supplementary Information 6) (13–17). Thus, many genetic variants found in Mesolithic 103individuals have not been carried over to modern-day groups. Among the novel variants in SF12, 104four (all heterozygous) are predicted to affect the function of protein coding genes (24) 105(Supplementary Information 3). The 'heat shock protein' *HSPA2* in SF12 carries an unknown 106mutation that changes the amino acid histidine to tyrosine at a protein-protein interaction site,

107which likely disrupts the function of the protein (Supplementary Information 3). Defects in
108*HSPA2* are known to drastically reduce fertility in males (25). Although SF12 herself would not
109be affected by this variant, her male offspring could carry the reduced fertility variant, and it will
110be interesting to see how common this variant was among Mesolithic groups as more genome
111sequence data become available. The high-quality diploid genotype calls further allowed us to
112genetically predict physical appearance, including pigmentation, and to use a model-based
113approach trained on modern-day faces and genotypes (26) to create a 3D model of SF12's face
114(Supplementary Information 9). This represents a new way of reconstructing an ancient
115individual's facial appearance from genetic information, which is especially informative in cases
116such as for SF12, where only post-cranial fragments were available, and future archaeogenetic
117studies will have the potential to many individuals appearance from past times.

118***Demographic history of Mesolithic Scandinavians***
119In order to compare the genomic data of the seven SHGs to genetic information from other
120ancient individuals and modern-day groups, data was merged with six published Mesolithic
121individuals from Motala in central Scandinavia, 47 published Upper Paleolithic, Mesolithic and
122Early Neolithic individuals from other parts of Eurasia (Supplementary Information 6), as well as
123with a world-wide set of 203 modern-day populations (15, 23). All 13 SHGs – regardless of
124geographic sampling location and age – display genetic affinities to both WHGs and EHGs (Fig.
1251A, B, Supplementary Information 6). This is consistent with a scenario in which SHGs represent
126a mixed group tracing parts of their ancestry to both the WHGs and the EHGs (14–16, 19, 27).

127To investigate the postglacial colonization of Scandinavia, we explored four hypothetical
128migration routes (primarily based on natural geography) linked to WHGs and EHGs, respectively
129(Supplementary Information 11); a) a migration of WHGs from the south, b) a migration of
130EHGs from the east across the Baltic Sea, c) a migration of EHGs from the east and along the
131north-Atlantic coast, d) a migration of EHGs from the east and south of the Baltic Sea, and
132combinations of these four migration routes. These scenarios allow us to formulate expected
133genetic affinities for northern, western, eastern, and central SHGs (Supplementary Information
13411). The SHGs from northern and western Scandinavia show a distinct and significantly stronger
135affinity to the EHGs compared to the central and eastern SHGs (Fig. 1). Conversely, the SHGs
136from eastern and central Scandinavia were genetically more similar to WHGs compared to the
137northern and western SHGs (Fig. 1). Using a model-based approach (15, 16), the EHG genetic
138component of northern and western SHGs was estimated to 55% on average (43-67%) and
139significantly different (Wilcoxon test, p=0.014) from the average 35% (22-44%) in eastern and
140south-central SHGs. This average is similar to eastern Baltic hunter-gatherers from Latvia (28)
141(average 33%, Fig. 1A, Supplementary Information 6). These patterns of genetic affinity within
142SHGs are in direct contrast to the expectation based on geographic proximity with EHGs and
143WHGs and do not correlate with age of the sample (Supplementary Information 11).

144The archaeological record in Scandinavia shows early evidence of human presence in northern
145coastal Atlantic areas (12). Stable isotope analysis of northern and western SHGs revealed an

146extreme marine diet, suggesting a maritime subsistence, in contrast to the more mixed 147terrestrial/aquatic diet of eastern and central SHGs (Supplementary Information 1). Combining 148these isotopic results with the patterns of genetic variation, we suggest an initial colonization 149from the south, likely by WHGs. A second migration of people who were related to the EHGs – 150that brought the new pressure blade technique to Scandinavia and that utilized the rich Atlantic 151coastal marine resources –entered from the northeast moving southwards along the ice-free 152Atlantic coast where they encountered WHG groups. The admixture between the two colonizing 153groups created the observed pattern of a substantial EHG component in the northern and the 154western SHGs, contrary to the higher levels of WHG genetic component in eastern and central 155SHGs (Fig. 1, Supplementary Information 11).

156By sequencing complete ancient genomes, we can compute unbiased estimates of genetic 157diversity, which are informative of past population sizes and population history. Here, we restrict 158the analysis to WHGs and SHGs, since only SNP capture data is available for EHGs 159(Supplementary Information 7). In current-day Europe, there is greater genetic diversity in the 160south compared to the north. During the Mesolithic, by contrast, we find higher levels of genetic 161diversity (Supplementary Information 7) as well as lower levels of runs of homozygosity (Fig. 1622A) and linkage disequilibrium (Fig. 2B) in SHGs compared to WHGs (represented by 163Loschbour and Bichon, (15, 29)) and Caucasus hunter-gatherers (CHG, represented by Kotias 164and Satsurblia, (29)). Using a sequential-Markovian-coalescent approach (30) for the high-165coverage, high quality genome of SF12, we find that right before the SF12 individual lived, the 166effective population size of SHGs was similar to that of WHGs (Fig. 2C). At the time of the LGM 167and back to c. 50,000 years ago, both the WHGs and SHGs go through a bottleneck, but the 168ancestors of SHGs retained a greater population size in contrast to the ancestors of WHGs who 169went through a more severe bottleneck (Fig. 2c). Around 50,000-70,000 years ago, the effective 170population sizes of the ancestors of SHGs, WHGs, Neolithic groups (represented by Stuttgart 171(15)) and Paleolithic Eurasians (represented by Ust-Ishim (31)) align, suggesting that these 172diverse groups all trace their ancestry back to a common ancestral group which likely represents 173the early migrants out-of-Africa, who likely share a common ancestry outside of Africa.

174*Adaptation to high-latitude environments*
175With the aim of detecting signs of adaptation to high-latitude environments and selection during 176and after the Mesolithic, we employed three different approaches that utilize the Mesolithic 177genomic data. In the first approach, we assumed that SHGs adapted to high-latitude environments 178of low temperatures and seasonally low levels of light, and searched for gene variants that carried 179over to modern-day people in northern Europe. As we have already noted, modern-day northern 180Europeans trace limited amount of genetic material back to the SHGs (due to the many additional 181migrations during later periods), and any genomic region that displays extraordinary genetic 182continuity would be a strong candidate for adaptation in people living in northern Europe across 183time. We designed a statistic, D_{sel} (Supplementary Information 10), that captures this specific 184signal and scanned the whole genome for gene-variants that show strong continuity (little

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185 differentiation) between SHGs and modern-day northern Europeans while exhibiting large 186 differentiation to modern-day southern European populations (32) (Fig. 3A; Supplementary 187 Information 10). Six of the top ten SNPs with greatest D_{sel} values were located in the *TMEM131* 188 gene that has been found to be associated with physical performance (33), which could make it 189 part of the physiological adaptation to cold (34). This genomic region was more than 200kbp 190 long and showed the strongest haplotypic differentiation between modern-day Tuscans and Finns 191 (Supplementary Information 10). The particular haplotype was relatively common in SHGs, it is 192 even more common among today's Finnish population (Supplementary Information 10), and 193 showed a strong signal of local adaptation (Supplementary Information 10). Other top hits 194 included genes associated with a wide range of metabolic, cardiovascular, developmental and 195 psychological traits (Supplementary Information 10) potentially linked to physiological (34).

196 In addition to performing this genome-wide scan, we studied the allele frequencies in three 197 pigmentation genes (*SLC24A5*, *SLC45A2*, having a strong effect on skin pigmentation, and 198 *OCA2/HERC2*, having a strong effect on eye pigmentation) where the derived alleles are virtually 199 fixed in northern Europeans today. The differences in allele frequencies of those three loci are 200 among the highest between human populations, suggesting that selection was driving the 201 differences in eye color, skin and hair pigmentation as part of the adaptation to different 202 environments (35–37). The SHGs show a combination of eye and skin pigmentation that was 203 unique in Mesolithic Europe, with light skin pigmentation and varied blue to light-brown eye 204 color. This is strikingly different from the WHGs – who have been found to have the specific 205 combination of blue-eyes and dark-skin (15, 17, 18) (Fig. 3B) – and EHGs – who have been 206 suggested to be brown eyed and light-skinned (16, 17) (Fig. 3B). The unique configuration of the 207 SHGs is not fully explained by the fact that SHGs are a mixture of EHGs and WHGs as the 208 frequencies of the blue-eye and one light-skin variant are significantly higher in SHGs than 209 expected from their genome-wide admixture proportions (Fig. 3B, Supplementary Information 210 10). This could be explained by a continued increase of the allele frequencies after the admixture 211 event, likely caused by adaptation to high-latitude environments (35, 37).

Conclusion

213 By combining information from climate modeling, archaeology and Mesolithic human genomes, 214 we were able to reveal the complexity of the early colonization process of Scandinavia and 215 human adaptation to high-latitude environments. We disentangled migration routes and linked 216 them to particular archaeological patterns, demonstrate greater genetic diversity in northern 217 Europe compared to southern Europe – in contrast to modern-day patterns – and show that many 218 genetic variants that were common in the Mesolithic have been lost today. These finds reiterate 219 the importance of human migration for dispersal of novel technology in human prehistory (13– 220 16, 21, 27, 38–45) and the many partial population turnovers in our past.
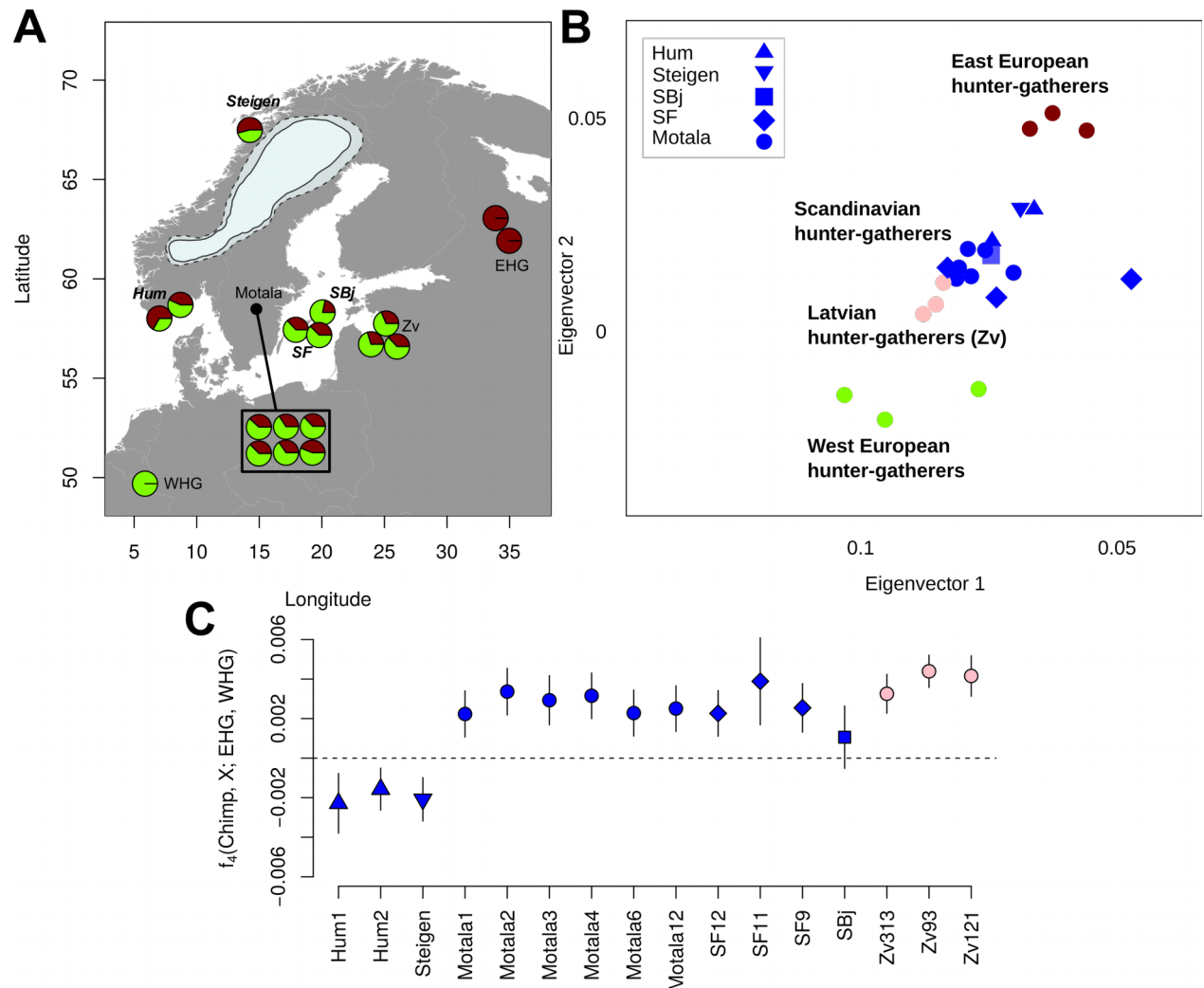
Acknowledgements

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236 Materials and Methods

237 All samples were processed in designated clean labs and sequenced on Illumina HiSeq machines.
238 Sequences were mapped to the human reference genome. More details on the data processing and
239 the population genomic analyses can be found in Supplementary Information.

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240 **Figure legends and Table 1**

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243 **Figure 1: Mesolithic samples and their genetic affinities** – (A) Map of the Mesolithic
244 European samples used in this study. The pie charts show the model-based (15, 16) estimates of
245 genetic ancestry for each SHG individual. The map also displays the ice sheet covering
246 Scandinavia 10,000 BP (most credible (solid line) and maximum extend (dashed line) following
247 (9)). Newly sequenced sites are shown in bold and italics, SF11 is excluded from this map due to
248 its low coverage (0.1x). Additional European EHG and WHG individuals used in this study
249 derive from sites outside this map. (B) Magnified section of genetic similarity among ancient and
250 modern-day individuals using PCA featuring only the Mesolithic European samples (see
251 Supplementary Information 6 for the full plot). (C) Allele sharing between the SHGs, Latvian
252 Mesolithic hunter-gatherers (28) and EHGs vs WHGs measured by f_4(Chimpanzee, SHG; EHG,
253 WHG) calculated for the captured SNPs for the EHGs (17). Error bars show two block-jackknife
254 standard errors.
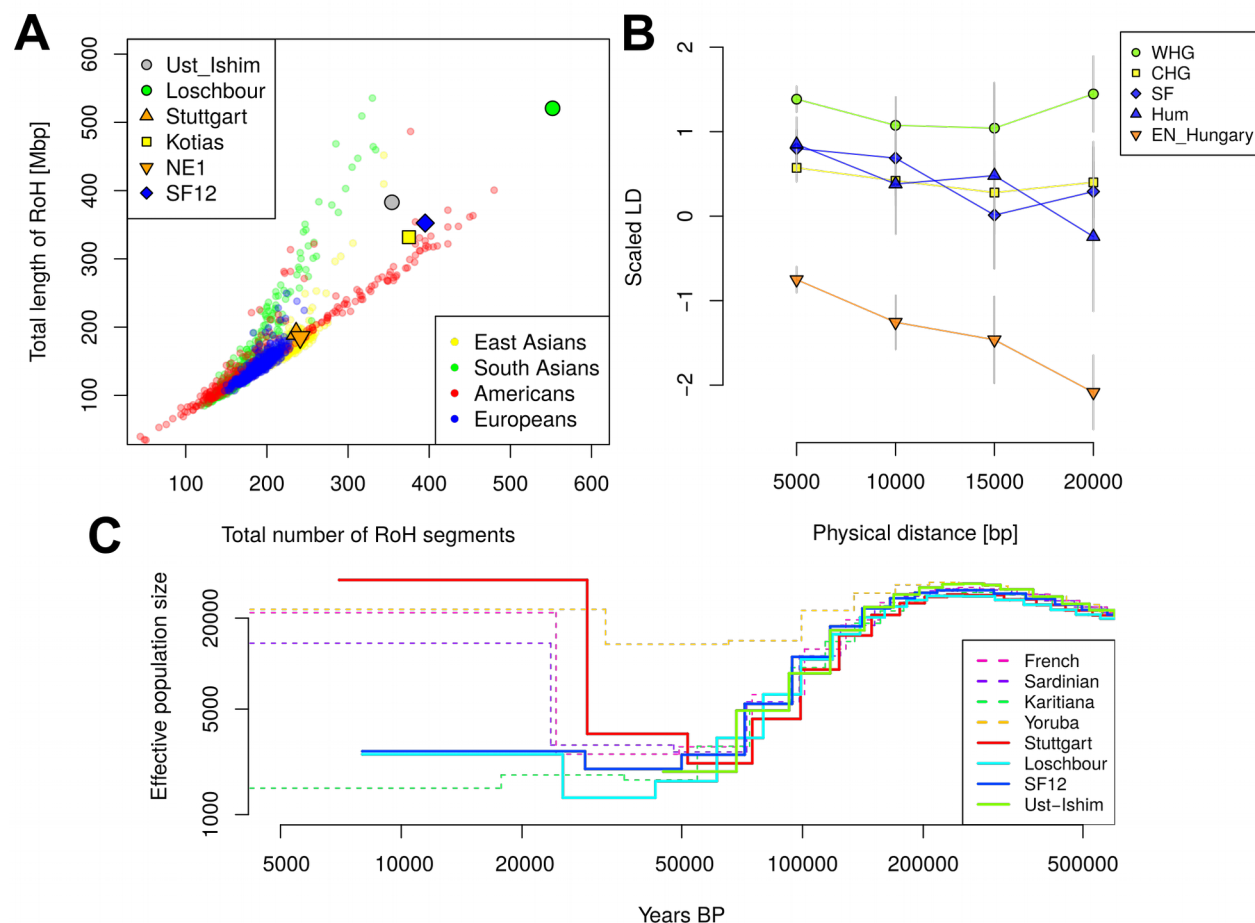
Figure 2: Genetic diversity in prehistoric Europe – (A) Runs of Homozygosity (RoH) for the six prehistoric humans that have been sequenced to >20x genome coverage, (Kotias is a hunter-gatherer from the Caucasus region (29), NE1 is an early Neolithic individual from modern-day Hungary(38), the other individuals are described in the text), compared to all modern-day non-African individuals from the 1000 genomes project (23). (B) Linkage disequilibrium (LD) decay for five prehistoric populations each represented by two individuals (eastern SHGs: SF (SF9 and SF12), western SHGs: Hum (Hum1 and Hum2), Caucasus hunter-gatherers (29): CHG (Kotias and Satsurblia), WHGs (15, 29) (Loschbour and Bichon), and early Neolithic Hungarians(38): EN_Hungary (NE1 and NE6). LD was scaled in each distance bin by using the LD for two modern populations (23) as 1 (modern-day Tuscan, TSI) and as 0 (modern-day Peruvians, PEL). LD was calculated from the covariance of derived allele frequencies of two haploid individuals per population (Supplementary Information 7). Error bars show two standard errors estimate during 100 bootstraps across SNP pairs. (C) Effective population size over time as inferred by MSMC' for four prehistoric humans with high genome coverage. The dashed lines show the effective population sizes for modern-day populations. All curves for prehistoric individuals were shifted along the X axis according to their radiocarbon date.

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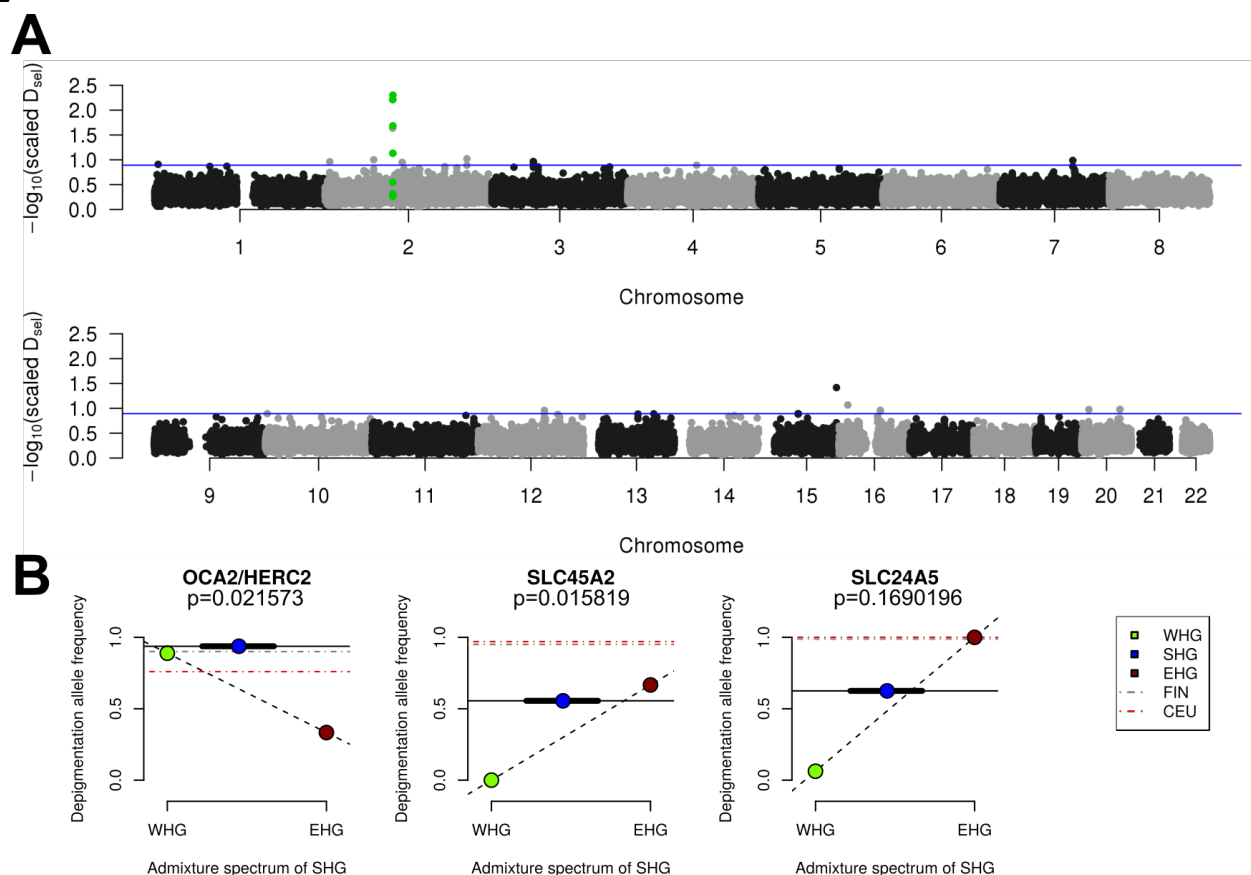
274**Figure 3: Adaptation to high-latitude climates** – (A) Manhattan plot of similarity between 275Mesolithic allele-frequency and modern-day Finnish (FIN) allele-frequency in contrast to 276difference to (TSI) allele-frequency using the statistic D_{sel}. The green-highlighted SNPs are all 277located in the *TMEM131* gene. The horizontal blue line depicts the top 0.01% D_{sel} SNPs across 278the genome. (B) Derived allele frequencies for three pigmentation associated SNPs (*SLC24A5,* 279*SLC45A2*, associated with skin pigmentation and *OCA2/HERC2* associated with eye 280pigmentation). The dashed line connecting EHG and WHG represents potential allele frequencies 281if SHG were a linear combination of admixture between EHG and WHG. The solid horizontal 282line represents the derived allele frequency in SHG. The blue symbols representing SHGs were 283set on the average genome-wide WHG/EHG mixture proportion (on x-axis) across all SHGs, the 284thick black line represents the minimum and maximum admixture proportions across all SHGs. 285Dashed horizontal lines represent modern European populations (CEU=Utah residents with 286Central European ancestry). The p-values were estimated from simulations of SHG allele 287frequencies based on their genome-wide ancestry proportions (Supplementary Information 10). 288

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Individual	Calibrated date (cal BP, 2 sigma)	Genome coverage	mt coverage	Sex	mt haplo-group	Y haplo-group	Contamination estimate		
							based on mt	based on X	based on autosomes
Hum1	9452-9275$^\$$	0.71	597	XX	U5a1	-	0.29%	-	0.00%
Hum2	9452-9275$^\$$	4.05	432	XY	U5a1d	I2	0.15%	0.63%	0.73%
Steigen	5950-5764	1.24	277	XY	U5a1d	I2a1b	0.00%	0.4%	0.00%
SF9	9300-8988	1.15	93	XX	U4a2	-	5.36%	-	0.00%
SF11	9023-8760	0.10	45	XY	U5a1	*	3.42%	*	10.16%
SF12	9033-8757	57.79	9774	XX	U4a1	-	0.34%	-	0.932%
SBj	8963-8579	0.43	102	XY	U4a1	I2	3.72%	1.4%	0.06%

290**Table 1**: Information on the seven Scandinavian hunter-gatherers investigated in this study, 291including calibrated date before present (cal BP) corrected for the marine reservoir effect, given 292as a range of two standard deviations, average genome coverage, average mitochondrial (mt) 293coverage, mt and Y chromosome haplogroups and contamination estimates based on the mt, the 294X-chromosome for males and the autosomes.

295$^\$$ combined probability for the Hummervikholmen samples
296* not enough genome coverage
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