Skeletal Anomalies in The Neandertal Family of El Sidrón (Spain) Support A Role of Inbreeding in Neandertal Extinction

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Neandertals disappeared from the fossil record around 40,000 bp, after a demographic history of small and isolated groups with high but variable levels of inbreeding, and episodes of interbreeding with other Paleolithic hominins. It is reasonable to expect that high levels of endogamy could be expressed in the skeleton of at least some Neandertal groups. Genetic studies indicate that the 13 individuals from the site of El Sidrón, Spain, dated around 49,000 bp, constituted a closely related kin group, making these Neandertals an appropriate case study for the observation of skeletal signs of inbreeding. We present the complete study of the 1674 identified skeletal specimens from El Sidrón. Altogether, 17 congenital anomalies were observed (narrowing of the internal nasal fossa, retained deciduous canine, clefts of the first cervical vertebra, unilateral hypoplasia of the second cervical vertebra, clefting of the twelfth thoracic vertebra, diminutive thoracic or lumbar rib, os centrale carpi and bipartite scaphoid, tripartite patella, left foot anomaly and cuboid-navicular coalition), with at least four individuals presenting congenital conditions (clefts of the first cervical vertebra). At 49,000 years ago, the Neandertals from El Sidrón, with genetic and skeletal evidence of inbreeding, could be representative of the beginning of the demographic collapse of this hominin phenotype.

The causes of the extinction of the Neandertal populations in western Eurasia by 40,000 BP is a topic of intense debate in human evolution. Some interpretations attribute this extinction to competition with early anatomically modern humans (AMHs), which would present differences expressed for instance through more efficient exploitation of dietary resources, possibly related to differential cognitive, behavioral and cultural abilities, that could rest on life-history and ontogenetic differences. However, other interpretations have recognized recent findings that support Neandertal dietary flexibility and multiple subsistence strategies, increasing evidence of symbolic behavior and complex technologies, and lack of fundamental differences in the overall pace of dental and skeletal growth and maturation in comparison with AMHs, all of which complicate a scenario of AMHs simply outcompeting Neandertals. Environmental change also has been considered as a potential important factor.
in the Neandertal demise, whether acting independently, or in combination with other previously-mentioned differences between the two hominins16-18. In the context of competition, the very fact of interbreeding within what has been called a hominin metapopulation19, would suggest a complex interaction between Neandertal, AMHs populations and Denisovans that has yet to be defined in detail20. For instance, demographic and eco-cultural modeling have included competition models, based on cultural and demographic differences21,22, and selectively-neutral models, based on migration dynamics and local dispersal and replacement alone (in absence of culturally-driven selection or environmental factors)23, with both resulting in the replacement of Neandertals by AMHs. Other models conclude that hunting-prey decline or climatic variations alone was not sufficient to cause the disappearance of Neandertals24. In all cases, most researchers agree that, “whatever the extent to which the eventual replacement of late archaic human morphology involved admixture, absorption, and/or population displacement, the process was ultimately a demographic one25.

In this regard, it has been suggested that the archaeological evidence supports substantial demographic differences at the Neandertal-to-AMH transition, with up to a tenfold increase in population density for early AMHs compared with Neandertals26, that could have been a critical factor in the Neandertal demise. Although others have recommended caution when making inferences about population size from the archaeological record27, it is not unreasonable to suggest that demographic differences in population size and density, and in group size, could have been an important factor in the disappearance of Neandertals28. In addition, the general demographic structure of Pleistocene Homo, with small effective population sizes (see below), a hunter-gatherer existence and population dispersal into separate small kindred groups, would have favored substantial levels of intragroup, and potentially intrafamily, mating29,30. Important contributions to Neandertal paleodemography in this direction come from genetic studies, where high levels of inbreeding, or mating among relatives, and a general decrease in heterozygosity have been observed. Specifically, Neandertals from the Altai, Vindija, Mezmaiskaya and El Sidrón sites present low levels of heterozygosity and small estimated effective population sizes averaging around 3000 individuals, both characteristics considered typical of archaic hominins, indicating that they lived in small and isolated populations31. Studies of genetic homozygosity indicate that Neandertals had a long history of high but variable levels of inbreeding. The most extreme values are found in the Altaï Neandertal, with long stretches of homozygosity that indicate recent inbreeding consistent with parental relatedness between two half-siblings33. In contrast, Vindija Neandertal homozygosity is comparable to modern human groups like the Karitiana and Pima, suggesting that consanguinity was not ubiquitous among all Neandertal populations34. At El Sidrón, a Neandertal sample (SD1253) had a larger cumulative length of homozygous genomic stretches of 10–100 Kb than samples from Vindija, Altaï, Denisoa, great apes and modern humans35, indicating a long history of inbreeding. In addition, the mitochondrial DNA (mtDNA) analysis of twelve El Sidrón individuals revealed low mtDNA genetic diversity and close kin relationships within the group36.

Within this context, it is reasonable to expect that a scenario of small, isolated groups of Pleistocene Homo with potentially high levels of intragroup mating would be also phenotypically expressed in the skeleton. For instance, recent analyses of bony labyrinth morphology in the Aroeira 3 cranium suggest a degree of demographic isolation in geographically and chronologically close hominins around the origin of the Neandertal clade36, as well as previously suggested37 and recently shown38, there is a high incidence of developmental abnormalities and anomalies in Pleistocene Homo, several of them very rare or with unknown etiology. In past and present modern human populations, dental and skeletal anomalies and low-frequency anatomical variants have been associated with geographical isolation and/or endogamy39. Given the nuclear and mtDNA genetic evidence that indicates that the 13 individuals from El Sidrón constitute a closely related kin group40, El Sidrón is the ideal Pleistocene sample to test for skeletal evidence of inbreeding. Previous morphological analyses of the El Sidrón Neandertals have reported congenital clefts of the first cervical vertebra41 and the retention of a deciduous mandibular canine in two individuals42, but a systematic analysis of the entire sample has not yet been done. Here we present the results of the complete morphological analysis of the 1674 identified skeletal specimens from a total of 2556 remains recovered from El Sidrón.

Results
We define anomalies as bone variants, both pathological and non-pathological, deviating from normal structure43-45 (Supplementary Information SI1). Our objective, rather than to obtain a differential diagnosis, was to state that the anomalies were congenital, a term understood as a condition that is present at birth and genetically driven, after discarding alternative explanations such as traumatic and infectious conditions, environmental stress and taphonomic processes as the cause of the observed anomalies (Supplementary Information SI1).

Maxilla and Mandible. The El Sidrón Adult 2 (A2) preserves several morphological features of interest in its maxilla and mandible (Fig. 1A). As described previously46, this individual, as well as El Sidrón Adolescent 3, retains a left mandibular deciduous canine. A metric comparison of the internal nasal fossa breadth of El Sidrón A2 (22.47 mm) with other Neandertals (mean 34.13 mm)47 and with modern humans (overall mean 32.87 mm, Arctic population mean 30.3 mm)48, places this maxilla at the smallest extreme of the observed range of variation (Supplementary Information SI2, Supplementary Fig. S1). The maxilla also has a right-side deviation of the anterior nasal crest along its entire length, and asymmetry to the dental arcade, although interpretation of both of these anomalies is hampered by taphonomic alteration of the bone (Supplementary Fig. S1). Our interpretation is that, besides the retained deciduous canine, the narrowing of the internal nasal fossa would be consistent with a congenital condition. A narrowing of the internal nasal fossa is present in several conditions, from congenital nasal pyriform aperture stenosis49-51, a condition potentially related to other anomalies and occurring in modern humans in approximately 1 in 25,000 births52, to more complex conditions affecting the middle third of the face, such as Goldenhar53, Aper54 and Binder55 syndromes. Since no other clear anomalies were observed in this anatomical region, complex conditions similar to the latter ones are not likely.
Vertebrae and Ribs. Several El Sidrón individuals preserve evidence of sagittal clefts of the cervical vertebrae. A first cervical vertebra (C1 or atlas) fragment (SD-636) shows evidence of a congenital anterior sagittal cleft (Fig. 1B, Supplementary Information SI3, Supplementary Fig. S2), similar to another C1 fragment (SD-1094) recently described as having another congenital anterior sagittal cleft. In addition, an almost complete atlas from El Sidrón (SD-1643) preserves a congenital posterior sagittal cleft and there are two C1 hemi-arches (SD-2045 and SD-1725) from the juvenile skeleton El Sidrón J1 interpreted as a congenital posterior sagittal cleft. In modern humans, the posterior synchondrosis is fused by six years of age in 95% of individuals and the remaining 5% correspond to cases of congenital posterior sagittal clefts. Thus the lack of fusion of the posterior synchondrosis PS in El Sidrón J1 is best interpreted as a congenital posterior sagittal cleft of the C1. In total, four out of five atlas specimens with observable anterior or posterior sagittal arches and four out of 13 identified Neandertal individuals at El Sidrón present congenital clefts of the atlas. The frequency of atlas congenital clefts in modern humans ranges from 0.087% to 0.1% for the anterior cleft, and from 0.73% to 3.84% for the posterior cleft. These clefts have been associated with several different congenital conditions, including Down’s syndrome, Chiari malformation, Klippel-Feil, Goldenhar syndrome, Conradi syndrome, and Loeys-Dietz syndrome, where a higher frequency of anterior (24%) than posterior (16%) C1 clefts have been observed. It is important to stress, however, that in modern humans these clefts are usually asymptomatic and often only identified in routine examinations.
A second cervical vertebra (C2 or axis) (SD-1601) preserves several morphological features consistent with congenital alterations. First, the right transverse process has not developed and there is bilateral asymmetry in the size of the transverse foramina (Fig. 1C, Supplementary Information SI4, Supplementary Fig. S3). The vertical/horizontal and transverse/longitudinal diameters of the right transverse foramen at its lateral and inferior borders fall at the smallest extreme of the modern human range of variation, while the diameters for the left foramen fall well within this interval (Supplementary Information SI4, Supplementary Tables S1, S2). Second, the right half of the tip of the spinous process has also not developed and there is bilateral asymmetry in the thickness of the laminae (Fig. 1C, Supplementary Fig. S3). The value of the thickness of the right lamina falls at the smallest extreme of modern human variation, while the thickness of the left lamina falls well within this interval (Supplementary Information SI4, Supplementary Tables S1, S2). Thus, the preserved morphology makes clear the bilateral asymmetry of this axis with an underdevelopment of its right side, possibly affecting the course of the left vertebral artery (Supplementary Information SI4). Additionally, this specimen has the shortest odontoid height and a short ventral height for its superior transverse diameter within the available Neandertal sample (Supplementary Information SI4, Supplementary Figs S3, S4). This metric assessment would be consistent with a partial hypoplasia of the dens (Supplementary Information SI4). In modern humans, hypoplasia or even aplasia of the dens of the axis is mostly an isolated, asymptomatic defect and a possible autosomal dominant trait, but it can be associated with C1-C2 instability and neurological symptoms, and it might occur in diverse genetic disorders (Supplementary Information SI4). But since metric data fall well within the 95% prediction interval from the linear regression for the small Neandertal sample (Supplementary Fig. S4), and due to the lack of a metric reference associated with this condition in the medical literature, the presence of a hypoplastic dens remains without support.

Finally, an articulated thoracolumbar spine (SD-437) shows cranial displacement of the thoracic transitional vertebra and a sagittal cleft of the arch of the last rib-bearing vertebra with lack of development of the spinous process (Fig. 1D, Supplementary Information SI5, Supplementary Fig. S5). While cranial displacement of the thoracic transitional vertebra is common in modern humans (23%) (Supplementary Information SI4), clefting of the neural thoracic arch is rare, with few reported dry-bone cases. A right rib (SD-292) is identified as either a 12th rudimentary or hypoplastic rib or a 13th lumbar rib resulting from a caudal border shifting of the thoracic–lumbar border (Fig. 1E, Supplementary Information SI6, Supplementary Fig. S6). Rib and vertebral anomalies may be isolated, asymptomatic findings, or may occur in association with different syndromes (Supplementary Information SI6, Supplementary Fig. S6). Rib and vertebral anomalies may be isolated, asymptomatic findings, or may occur in association with different syndromes.
with other Neandertals (including El Sidrón specimens), the metatarsals also show reduced proximal articular facets for the cuneiforms and cuboid (Supplementary Figs S9, S12, Supplementary Table S5).

The described features would be less consistent with an antemortem trauma or a past episode of infection, where again signs of fracture healing, bone formation secondary to trauma, or a more disorganized and irregular reduction of the plantar border of the articular facets would be expected. The unusual shape of tarsals, the reduced articular area from the calcaneo-cuboid joint to the tarso-metatarsal joints (with continuous, well-defined and rounded plantar borders delimitating the reduced facets, that lack additional bone formation or abrupt interruptions), and the increased plantar cortical thickness of the lateral tarsals, are consistent with a congenital anomaly of the foot affecting the plantar soft tissue structures (Supplementary Information S19) and a change of the normal load pattern of the left leg in this Neandertal. Finally, a cuboid-navicular non-osseous coalition was also observed (Fig. 1, Supplementary Information S10, Supplementary Fig. S13).

Discussion

The osteological findings presented here, together with the genetic evidence for Neandertals and specifically for El Sidrón reviewed above, constitute strong evidence for the presence of inbreeding and low biological variability in this Neandertal group. There are at least 16 congenital anomalies distributed throughout the skeleton in this Neandertal group. There are at least 16 congenital anomalies distributed throughout the skeleton in this group of 13 Neandertals, with at least four individuals affected by the same anomaly (Figs 1 and 2). We offer a comparison with modern human frequencies of similar conditions (Table 1) as the only available comparative data, but support the caution raised by Trinkaus in his recent, detailed review of Pleistocene hominin anomalies regarding direct comparisons between incidences in recent human and Pleistocene samples.

The health and survival consequences of inbreeding and consanguinity have been studied in humans and in conservation biology of endangered animal species. In humans, it has been observed that among first cousin offspring, there is an excess of 3.5% in overall prereproductive infant mortality, with a 1.7–2.8% higher prevalence of congenital anomalies, mostly attributable to autosomal recessive disorders, several of which have been reported from communities with high consanguinity rates. It is interesting to note that other impacts

Figure 2. Summary of the 17 congenital anomalies observed within the El Sidrón Neandertal family group. The number of observations for each condition is shown in the blue circles, together with a schematic representation of the condition. At least four Neandertal individuals present a cleft in the arch of the first cervical vertebra.
of high levels of inbreeding and consanguinity could be mediated by, for instance, an increased susceptibility to infectious diseases, with parental consanguinity as a known risk factor for primary immunodeficiencies. No negative associations with reproductive parameters (miscarriages and fertility) have been documented, and the associations with complex diseases and quantitative traits are inconsistent. Mild skeletal anomalies or variants have been observed in geographically isolated and/or endogamic human populations. For instance, in Canadian Inuit skeletons a higher frequency and intensity of several spine defects were observed in the smaller and more genetically isolated of the two compared populations. In a recent study on the impact on patterns of deleterious variation of an extreme and prolonged population bottleneck in Greenlandic Inuit, an increase up to 6% in the genetic load (reduction in mean fitness in a population caused by deleterious mutations relative to a mutation-free population) was observed across all models of dominance.

In a broader biological comparative context, studies on different endangered species that have suffered recent drastic population declines and range fragmentation – similar to conditions potentially experienced by Neandertals – have shown very low genetic diversity and high levels of recent, and in some cases long-term, inbreeding that can result in a reduction in population fitness, or inbreeding depression. For example, the Florida panther, Scandinavian wolf, and Iberian lynx show a range of conditions including heart defects, cryptorchidism and low semen quality. The Florida panther and Scandinavian wolf also show mild dental and skeletal (mostly vertebral) anomalies that have no direct effect on fitness but are indicative of high levels of inbreeding. Mountain gorilla genetic analyses indicate a population decline over tens of millennia, recent close inbreeding and increased homozygosity, suggesting that an increased burden of deleterious mutation and low genetic diversity (including at the major histocompatibility locus, of central importance to the immune system), could have compromised the resilience of the mountain gorillas to environmental change and pathogen evolution. In addition, genetic analysis of the extinct woolly mammoth reveal low heterozygosity and signs of inbreeding, including several detrimental mutations in one of the last surviving mammoths. Additionally, Late Pleistocene mammoths show a high incidence of cervical ribs, a potential signal of inbreeding and/or harsh environmental conditions.

In relation to the Neandertal long-term history of small and isolated populations, where the purging of deleterious alleles is predicted to be less efficient, some studies have observed a larger fraction of putative deleterious alleles in Neandertals than in present-day-humans. Specifically, genes associated to autosomal recessive traits have derived homozygous genotypes with likely deleterious effects, which could be suggestive of an enrichment in recessive disorders. But when both homozygous and heterozygous alleles in genes associated to autosomal recessive traits are considered, there is no clear difference between Neandertals and modern humans, and the authors conclude that the health significance of the estimated relatively (homozygous) higher genetic load in Neandertals is unclear, with no strong evidence for recessive disorders to have played a significant role in Neandertal extinction. Other authors have suggested that Neandertals suffered a high load of weakly deleterious mutations, with estimations resulting in at least 40% lower fitness than modern humans on average. With regard to the Altai Neandertal, it has been estimated that her overall genomic health was worse than 97% of present-day humans, mainly due to high risk for immune-related diseases, cancers, gastrointestinal and liver diseases, metabolic-related disorders, morphological and muscular diseases, and also neurological diseases. However, these estimates of Neandertal health should not be overinterpreted since the genetic risk scores employed in the study are not deterministic and the Altai Neandertal presents greater consanguinity than that of all other Neandertal samples. Furthermore, within the context of the interbreeding between Neandertals and early AMHs, the interpretation of the genomic landscape of introgression and the functional significance of Neandertal genetic material is complex and would include selection against Neandertal variants but also adaptive introgression, including potentially adaptive ones related to the immune system. In this regard, and in the context of the above-mentioned impact of inbreeding and consanguinity on the susceptibility to infectious diseases, it has been suggested that the transfer of pathogens between hominin populations in the Upper Paleolithic could have had negative consequences for Neandertals if these were more susceptible to some novel pathogens brought by early AMHs. But although differential pathogen resistance might have played a role in

| Anomaly                                      | Modern humans | El Sidrón |
|----------------------------------------------|---------------|-----------|
| Retained deciduous mandibular canine         | 0.001–1.8%    | 15.38%    |
| Nasal stenosis                               | 0.00004%      | 7.69%     |
| C1 anterior cleft                            | 0.087–0.1%    | 15.38%    |
| C1 posterior cleft                           | 0.73–3.84%    | 15.38%    |
| C2 bilateral asymmetry                       | —             | 7.69%     |
| T12 posterior cleft                          | —             | 7.69%     |
| Thoracic hypoplastic rib/Lumbar rib          | —             | 7.69%     |
| Scaphoid os centrale                         | 0.48–3.13%    | 23.07%    |
| Scaphoid bipartition                         | 0.13–0.60%    | 7.69%     |
| Triparte patella                             | 0.05–1.7%     | 7.69%     |
| Cuboid navicular non-osseous coalition       | 0.2%          | 7.69%     |
| Foot congenital anomaly                      | —             | 7.69%     |

Table 1. Congenital anomalies observed within the El Sidrón family group, with frequency in modern humans and El Sidrón (percentage of individuals affected).
the demographic collapse of the Neandertals, an explicit test of this hypothesis looking for an overall decrease in
diversity at immune system loci in Neandertals failed to fully support it110. Similar skeletal findings as those presented here for the Neandertals from El Sidrón are observed in some rare
syndromes in modern humans, as summarized above. In several of these syndromes, the patient presents con-
genital anomalies in different parts of the skeleton. At El Sidrón, the maxilla, mandible, spine at different levels
(C1, C2, T12), ribs, scaphoids, patella and foot are affected (Fig. 2). At least four Neandertals present congenital
clefts of C1, and/or scaphoid anomalies, and it would be reasonable to expect that more than one of the congen-
ital conditions described above could belong to the same individual (for instance the left patella and the left foot
could be associated), lending some support to the presence of a syndrome. Further genetic evidence indicates a
decrease of Neandertal ancestry with time in AMHs who lived between 45,000 and 7,000 years ago111, supporting
the idea that Neandertal variants were progressively purged out. If the findings presented here are indeed related
to recessive disorders or syndromes, and this scenario was not infrequent for at least late Neandertals, then this
would be compatible with an initial reduction of Neandertal ancestry over time after interbreeding with early
AMHs. However, although the morphological anomalies observed in the maxilla, patella and foot could have
been clinically relevant, in modern humans several of the described conditions correspond to asymptomatic,
iccidental findings in routine medical examinations, and a diagnosis of a complex disease based on isolated
skeletal elements is not possible. Thus, the possibility that the anomalies found at El Sidrón may reflect an under-
lying genetic syndrome remains speculative. Even in cases of consanguinity, when assessing the impact of mating
between close relatives on any aspect of health, “a clear causal relationship needs to be established, rather than
reliance on speculation driven solely by the presence of a close kin union in the family pedigree”29. Thus, whether
the findings presented here constitute just a strong skeletal signal of inbreeding and low biological variability, or
could be also considered as indicative of recessive disorders remains controversial.

An alternative or compatible scenario to the interpretation of the described conditions as congenital, genetic
and indicative of inbreeding would be the presence of adverse environmental conditions impacting early preg-
nancy and the growth period. Previous research has shown that Neandertals present nonspecific indicators of
stress, such as enamel hypoplasias, at a frequency within the ranges of variation shown by prehistoric samples of
modern human foragers112. Specific evidence from El Sidrón113 indicates that the inspection of all teeth resulted in
da ll dental individuals presenting enamel hypoplasia (incisors 59%, canines 50%, premolars 58%, and molars 32%),
although with varying degrees of intensity and within the frequencies observed in modern human historical sam-
ple s for the incisors and canines114,115. Furthermore, previous analysis of the El Sidrón J1 juvenile skeleton in-
dicated that the dental and skeletal growth and maturation values were similar to those of diverse modern human
juvenile populations116, while the size and shape studies of the adult postcranial remains from El Sidrón show that
these Neandertals fall well within the range of variation documented for this Paleolithic humans116–119. Together,
these analyses offer limited support for unusually harsh environmental conditions impacting the prenatal and/or
postnatal growth period as an explanation of the described anomalies in the Neandertals from El Sidrón. This
is consistent with ‘Trinkaus’ recent assessment of developmental anomalies and abnormalities in the Pleistocene
hominin fossil record, in which he concludes that stress during development could only account for a few of the
observed abnormalities120.

Current examples of animal species with a long-term history of low population size and depleted genetic
diversity may indicate a resilience to develop strategies to mitigate the effect of inbreeding7,8,9. Therefore, caution
has been advised when drawing conclusions about the reasons for Neandertal extinction98, since Neandertals
could have evolved diverse genetic and biocultural compensations to cope with a large deleterious genetic load110.
The persistence of Neandertals for tens of thousands of years, with increasing evidence for diverse subsistence
strategies6,7, symbolic behavior and complex technologies8–13 and healthcare120 (several of these examples coming
from El Sidrón), demonstrates the resilience of these Paleolithic hominins.

The Adult 2 Neandertal from El Sidrón exemplifies this resilience. This individual had a congenital narrowing
of the nasal fossa and a retained deciduous mandibular canine with a subsequent dentigerous cyst secondary to
dental trauma to that tooth. Previous analysis of the dental striation orientation39 suggest that this individual
coped with their dental pathology by alternating left-right hand use and avoiding chewing on the pathological
side of the mouth121. Adult 2 also presented the highest incidence of chipping in the dentition, and was the only
coped with their dental pathology by alternating left-right hand use and avoiding chewing on the pathological
dental trauma to that tooth. Previous analysis of the dental striation orientation99 suggest that this individual

strains are already suggested by the genetic results of these individuals have been interpreted as already suggest-
that this Neandertal individual could have had a specialized behavior. Furthermore, previous
studies have found evidence that this individual probably self-medicated the infected cyst120. Considering
the El Sidrón Neandertal group as a whole, and the findings presented here from the perspective of the bioarchae-
ology of care in Neandertals120, any interpretation of these findings as related to a genetic syndrome or recessive
disorder could point to another example of healthcare and resilience in this hominin group.

A scenario of small effective population sizes, a hunter-gatherer existence and population dispersal into sep-
arate small hominid groups, with probable intragroup mating, would have also affected early AMHs. Even con-
sidering the interbreeding episodes with early AMHs, and therefore somehow the permanence of Neandertals,
how early AMHs managed to support growing and geographically-expanding populations in the same environ-
ment while the Neandertal phenotype disappeared, remains a central question. The genetic analysis of a 45,000
years old modern human male from Siberia indicates lack of recent inbreeding among his ancestors122, and the
genomes analyzed from the Sunghir site, dated 34,000 years ago, indicate that they were not closely related (third
degree or closer)124. Beyond the osteological and paleopathological analysis of the skeletons from Sunghir that
could point to inbreeding122, the genetic results of these individuals have been interpreted as already suggest-
ing by 34,000 years ago the presence of the modern human hunter-gatherer social structure “with low levels of
within-band relatedness, complex family residence patterns, relatively high individual mobility, and multilevel
social networks”124. Currently, the available osteological evidence indicates absence of differences of younger
versus adult mortality pattern between Neandertals and early AMHs125, in agreement with biological models.
that would indicate similar demographic features between both126, and this would suggest that the demographic advantage of early AMHs would have been the result of increased fertility and/or reduced immature mortality25. Fertility and immature mortality would be related to the social structure of Paleolithic hominins, and the study of the impact of a reduced population dispersed in small an isolated groups on that social structure, as well as the study of the reproductive biology of hominins remains an important challenge for the future127.

The disappearance of the Neandertals and expansion of modern humans was most probably the result of a process involving several factors, one of them being the low population density of Neandertals. An analysis of the climatic niches of both Neandertals and early AMHs126 indicates that from 48 to 40 ka, the potential niche of Neandertals reduced significantly in size and spatial continuity (connection between optimal habitat patches), while optimal patches of early AMHs remained much better connected. Neandertal habitat reduction and fragmentation suggest that the Neandertal population was sharply decreasing in size and becoming more isolated126, a conclusion that is generally supported by paleogenetic data. The analysis of the genomes of Neandertals (Vindija33.19 and Altai), Denisovans and modern humans by Pairwise Sequential Markovian Coalescent (PSMC) method, indicates that after a reduction of population size that occurred sometime before 1.0 million years ago, the population ancestral to present-days humans increased in size, whereas the demographic history for both Neandertals and the Denisovan shared a recent history of very low effective population sizes129,132. Recent estimations suggest that in five low-coverage Neandertal genomes who lived around 39,000 to 47,000 years ago (Les Cottés, Goyet Q56-1, Mezmaiskaya 2, Vindija 87, Spy 94a)130, the levels of heterozygosity lie below those estimated from the high-coverage Vindija and Altai Neandertals, from around 50,000 years ago or at least predating 44,000 years (Vindija)131. The possibility of particularly low heterozygosity in these late Neandertals could reflect a small number of individuals near the end of its presence in Europe132. At 49,000 years ago, and in the context of a high incidence of cranial anomalies in Pleistocene Homo16, the Neandertal family group from El Sidrón, with genetic and skeletal evidence of inbreeding, could be representative of the beginning of the demographic collapse of this hominin phenotype.

Material and Methods
The bones were inspected using a binocular lens, a Environmental Scanning Electron Microscope (ESEM Femi-Quanta 200), and were micro-CT scanned with a Nikon XT H 160 at 155-114 kv and 48–85 µA, 1800 projections, reconstructed as 16-bit tiff stacks, voxel size interval from 0.027 to 0.079 mm. The data were loaded into AMIRA 5.4® (Thermo Fisher Scientific) for generating the virtual reconstructions. Photographs were obtained from different views and, when possible, with comparative Neandertal (El Sidrón) and modern human cases. Descriptions of specific procedures followed for the morphological analyses for each skeletal element are presented in the Supplementary Material.

Data Availability
All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Author Contributions
L.R. and A.R. designed the study. L.R., T.K., A.E., A.G.-T., R.H., Y.Q. and A.R. performed fossil anatomical identification and discussed the results. C.L.-F. and M.R. provided paleogenetic and archeological background information. L.R., T.K. and A.R. wrote the manuscript.

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