



## 20th anniversary of the history of genetic research on cave lions: A short review

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### ABSTRACT

The *Panthera* genus originated in Africa and subsequently spread to Eurasia, North America and South America. Species within this genus occupy dominant positions in ecological and food chains, but due to climatic fluctuations, changing ecosystems and various other ecological factors, several *Panthera* species have become extinct. The cave lion (*Panthera spelaea* Goldfuss) is one of the iconic species of Pleistocene megafauna, and its genetic research began around twenty years ago. Despite the information available so far, a number of issues regarding taxonomy, microevolutionary processes in populations, and the causes of extinction at the boundary between the Pleistocene and Holocene for this top predator remain unclear. This review aims to systematize the available data on cave lion genetics and develop new directions for studying this animal, as well as considering the genetic prospects for lion survival in the Holocene period.

### 1. Introduction

The cave lion (*Panthera spelaea*), a close relative of the modern lion (*P. leo*), was the top predator in the ecosystems of the Holarctic during the Pleistocene. This species was widely distributed in an area ranging from Alaska and northwestern Canada to western Europe. Surprisingly, this species went extinct simultaneously throughout its entire range at 14,500 – 12,000 years ago (Barnett et al., 2009; Boeskorov et al., 2012).

Despite the significant number of cave lion fossils found at various locations in the distribution range of this species, not many complete skeletons have been discovered, which has led to discussions about the taxonomic position of this animal. Firstly, the significant morphological similarity between the skulls of cave lions and modern tigers (*P. tigris*) led to the assumption that they are closely related (Groiss, 1996). Moreover, Nikolai K. Vereshchagin, a classic of Russian paleozoology, named this species "tigrolev" (tiger-lion) (Vereshchagin, 1971). At the same time, it is currently considered that the cave lion is either a subspecies of the modern lion (*P. leo*), or together with the extinct American lion (*P. atrox*) are an independent species (Sotnikova and Nikol'skiy, 2006; Barnett et al., 2016). Based on the taxonomic difficulties in species

determining of cave lion, the widespread introduction of molecular genetic methods into paleobiological research has significant potential to solve problems with the systematics of the *Panthera* genus. The variety of paleontological material from the cave lion's distribution range, including bones, teeth, skin fragments, and even mummified carcasses, determines the possibility of both systematic, phylogenetic and population genetic studies.

### 2. The first studies and individual DNA markers

For the first time, the results of the analysis of ancient DNA extracted from cave lion specimens were published twenty years ago (Burger et al., 2004). The researchers used a complex DNA primer system and were able to amplify and then sequence a fragment of the *cytochrome b*, *cytB* (1051 bp) mitochondrial gene from two cave lion bones discovered in Germany and Austria, which were dated at 47 Kya and 32 Kya (thousand years ago), respectively (Burger et al., 2004). Analysis of the *cytB* nucleotide sequences of extinct cave lions and other modern species of the genus *Panthera* confirms for the first time that modern lions are the closest relatives to the cave lion, despite significant differences in

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nucleotide sequences. Using a molecular clock-based approach, it was found that cave lions shared a common ancestor with modern lions about 600 Kya BP, not before the Cromerian Interglacial III or IV. (Burger et al., 2004).

A more detailed analysis of the variability of mitochondrial DNA in 52 lion samples was carried out five years later. The analysis included samples of modern lions from Africa and India as well as cave lion and American lion samples. For the first time using mitochondrial genome data, genetic continuity was shown between the population of cave lions in Western Europe and Beringia (Barnett et al., 2009). Phylogenetic analysis based on the sequence of the *ATP synthase 8 (ATP8)* gene and *hypervariable region 1 (HVR1)* of mitochondrial DNA makes it possible to separate modern lions from extinct cave lions in Eurasia and American lions. The phylogenetic tree suggests that the cave lion is a sister group to the American lion, and it is assumed that American lions originated from cave lions (Barnett et al., 2009), which is consistent with paleontological data (Turner, 1997; Christiansen and Harris, 2009).

In addition, it was concluded that the American lion finally separated from the cave lion lineage around 337 Kya BP. The analysis of the nucleotide variability of the mitochondrial genome of cave lions showed a significant decrease of its genetic diversity during the interglacial period between 46 and 48 Kya BP. In particular, after this time, there was a decrease in diversity of haplogroups among studied specimens, probably related to the species passing through a genetic bottleneck. The authors suggest that the extinction of cave lions after the last glacial maximum was caused by environmental changes, human hunting activities, and other factors involved in the extinction of Pleistocene megafauna. (Barnett et al., 2009). The demonstrated decrease in genetic diversity coincides with the dating of the fossils of cave lion discovered in Eurasia and Beringia during the Late Pleistocene (Stuart and Lister, 2011).

Significant differences in the sequence of mitochondrial genomes between cave lion and modern tiger (*P. tigris*) and jaguar (*P. onca*) suggests the absence of hybridization between these species (Barnett et al., 2009). This statement, apparently, requires additional research, given that the former distribution ranges of these species intersected in North and South America (the American lion and the jaguar) and in Central and Eastern Asia (the cave lion and the tiger) (Vereshchagin, 1971; Chimento and Agnolin, 2017). Moreover, interspecific hybridization of Felidae is a fairly common phenomenon that takes place both in nature and in zoos (Li et al., 2016). The genetic origin of the American lion also requires additional studies, involving markers of the nuclear genome, since its sister position to the cave lion remains controversial, especially among classical zoologists (Christiansen and Harris, 2009; King and Wallace, 2014).

Data on the variability of a fragment of the control region of mitochondrial DNA and the *ATP8* gene were studied in an expanded sample of cave lion specimens to previously published data (34 specimens) (Barnett et al., 2009) 14 more samples were added from different regions of Eurasia (Russia, Austria) with a range of dates from 15.5 up to >55 Kya BP (Ersmark et al., 2015).

The median-joining network was built on the basis of the nucleotide sequences of the control region and a fragment of the *ATP8* gene. Specimens of cave lion from Eurasia and Beringia can be divided into two groups. One group includes samples older than 37,000 years ago, and the other group includes both "older" and "younger" samples. From this, it can be concluded that one of the haplotypes has been completely eliminated from cave lion populations since 37,000 years ago (Ersmark et al., 2015).

Since most of the cave lion specimens were analyzed from the territory of Siberia (Russia), the analysis of nucleotide diversity ( $\pi$ ) was carried out from this territory and it was shown that, from 33 Kya up to 14 Kya, the genetic diversity of the local population of cave lion was significantly lower than during a similar time frame from 62 Kya to 48 Kya. In addition, Bayesian analysis suggests that the Beringian cave lion population experienced a genetic bottleneck around 48 kya, which

apparently led to the loss of one mitochondrial haplotype, but then this population recovered around 18 kya. This scenario is similar to what has been described for many mammal species of Pleistocene fauna (Ersmark et al., 2015). This scenario also corresponds to gap in the fossil record of cave lion in Siberia at 40–35 Kya BP (Stuart and Lister, 2011), and previously published data (Barnett et al., 2009).

In addition, paleogenomic methods were used to identify species of individual cave lion specimens. In particular, analysis of predator fur found on the banks of the Malyi Anyui River in Chukotka Peninsula (Russia), dating back 30,000 years ago, identified the animal as a *P. spelaea*. Comparative analysis of the *cytB* gene sequence and *ATP8* nucleotide sequence showed that it belonged to mitochondrial haplogroup I (Chernova et al., 2016), which was described in previous studies and was eliminated from the Beringian cave lion population 37,000 years earlier (Ersmark et al., 2015). Subsequently, fur specimen from this animal was used to reconstruct its mitochondrial genome (Barnett et al., 2016).

### 3. Mitogenomics of the cave lion

With the development of methods for extracting degraded DNA, sequencing of DNA and the development of new bioinformatics analysis methods, palaeobiological material is increasingly involved in analyzing complete mitochondrial and even nuclear genomes. This opens up new opportunities for clarifying the evolution and phylogeny of extinct or endangered species by collecting samples from which it is extremely difficult to obtain in nature (Chen and Nedoluzhko, 2023).

The first successful attempt, which ended with the publication of two mitogenomes of cave lions that lived on the territory of Beringia, was carried out on two animals whose remains were found in USA (the Quartz Creek site in Yukon) and in Russia (the Malyi Anyui River in Chukotka), and the latter date back to 30 thousand years ago (Barnett et al., 2016).

Using a comparative analysis of the complete mitochondrial genomes of modern species of the genus *Panthera* and the extinct *P. spelaea*, a species status for the extinct cave lion was proposed (Barnett et al., 2016), which coincides with the opinion of a number of paleontologists (Sotnikova and Nikolskiy, 2006). Moreover, sister relationship between *P. leo* and *P. spelea* has been confirmed. At the same time, using calibrated molecular clocks, it was estimated that these two species diverged 1.89 million years ago. (Barnett et al., 2016), such dates differing significantly from those obtained earlier (Burger et al., 2004).

A more extensive study involving 31 partial mitochondrial genome sequences (7929 bp) from cave lions at different points of their distribution (modern Russia, Canada, Germany, the Netherlands, Belgium and Austria) dating back to 13,500 years ago and older than 62,000 BP was also conducted (Stanton et al., 2020). Comparative analysis of these mitogenomic sequences revealed two deeply divergent and well-maintained monophyletic genetical lineages in cave lions. One of these lineages corresponds to the Beringian specimens, identified by Russian paleontologists as a distinct Beringia subspecies of cave lion, *Panthera spelaea vereshchagini*, in honor of Nikolai K. Vereshchagin, a paleozoologist mentioned earlier (Baryshnikov and Boeskorov, 2001), and the second one is Eurasian mitochondrial lineage (Stanton et al., 2020). In addition, a sample from the Beringia territory published earlier (Barnett et al., 2016), formed a separate clade.

Using the molecular clock approach, a new date for the divergence of cave lions and ancestors of *P. leo* was proposed. It was assumed that these species had a common ancestor 1.85 million years ago. It has also been argued that within the cave lion, at least two subspecies can be identified – the (1) Eurasian and (2) Beringian cave lions, which were originated much earlier than the subspecies of modern lions (Stanton et al., 2020).

Another scientific group reconstructed almost complete sequences of mitochondrial genomes of extinct cave and American lions; 24 and 15, respectively (Salis et al., 2022). These 39 mitochondrial sequences, as

well as two sequences from previous study (Barnett et al., 2016), were used for phylogenetic and phylogeographic studies of these extinct species of the genus *Panthera* in the Middle and Late Pleistocene. In general, the results obtained confirmed the sister origin of *P. spelaea* and *P. atrox*. At the same time, the study first recorded a specimen with the *P. atrox* haplotype north of Edmonton (Yukon Territory, ~64° N), which may serve as confirmation of the sympatry of *P. spelaea* and *P. atrox*. According to C<sup>14</sup> dating, the geological age of this specimen exceeded 50 Kya BP, at the same time, Bayesian analysis allowed to estimate its age as 67 Kya BP (Salis et al., 2022). In addition, in this study, the time of evolutionary split between *P. spelaea* and *P. atrox* was corrected (from 337 Kya to 165 Kya BP) as proposed earlier (Barnett et al., 2009). It is assumed that the dispersal of extinct cave lions and other predators (e.g., brown bears) from Eurasia to North America occurred in synchronously waves, and depended on fluctuations in the level of the World Ocean associated with glacial maximums (Salis et al., 2022).

In addition, another study based on a comparative analysis of mitochondrial genome markers from a significant number of *P. leo* individuals, as well as specimens generated in previous studies, suggested that the lineage of cave lions originated approximately 175 ± 8.5 thousand years ago, and later diverged into two species: *P. spelaea* 131 ± 3.5 and *P. atrox* 81 ± 8 thousand years ago (Broggini et al., 2024).

#### 4. Nuclear genomes of cave lion. The first, but not the last

Compared with mitochondrial DNA, the nuclear genome data provide significantly more information. Nuclear genome analysis allows to assess in detail the demographic history of extinct species, make assumptions about the possibility of ancient introgression, causes of species adaptation and extinction, directions of animal domestication, and etc (Barlow et al., 2021; Sharko et al., 2021; Dehasque et al., 2024; Librado et al., 2024).

Unfortunately, by now, quite little is known about the genomic diversity and demographic history of cave lions. Even though cave lions were top predators of mammoth fauna, only two genomic datasets of cave lion from Beringia (radiocarbon dated as approximately 30,000 years BP) are publicly available, belonging to the same subspecies – *P. spelaea vereshchagini* (de Manuel et al., 2020).

In a comparative genome-wide study, the coverage of two cave lions from Russia (Siberia) and northwestern America (Yukon) was 5.3X and 0.6X, respectively. At the same time, *P. leo*, was represented by 12 historical specimens collected between the 15th century and 1959, had a coverage ranging from 0.16X to 16.2X, while eight modern populations from Africa and India had coverage ranging from 4.73X to 27.26X. Phylogenetic reconstruction based on genomic data between individuals of the genus *Panthera* confirms earlier suggestions about the monophyly of cave lion and their evolutionary split from common ancestor with *P. leo*. Based on the same reconstruction modern lions which inhabited Africa and Asia can be divided into two main northern (includes Asian, West African, and North African populations) and southern (includes East African, South African, and Central African populations) *P. leo* lineages. These two lineages were diverged approximately 70,000 years ago. However, the subsequent gene flow between these populations has persisted and was disrupted due to the fragmentation of *P. leo* range of distribution and the extinction of populations in Asia and North Africa. The only remaining population in Gir Forest National Park, India, has demonstrated inbreed depression and an extremely low effective population size (de Manuel et al., 2020).

Given the disputes on time of divergence between *P. leo* and *P. spelea*, which existed for a long time (Burger et al., 2004; Barnett et al., 2016; Stanton et al., 2020; Broggini et al., 2024) nuclear genome data made it possible to clarify this issue. To solve this problem, three independent methods were used simultaneously based on: (1) Pairwise Sequential Markovian Coalescent (PSMC) model, (2) assessment of divergence of nuclear genome sequences based on purine-pyrimidine DNA mutations, and (3) number of heterozygous alleles in modern lion genomes

potentially derived from cave lions (about 15 %). The authors also used previously described generation parameters for five years, as well as mutation frequency of  $4.5 \times 10^{-9}$  per generation. All three methods indicated that the date of divergence for these two species was about 500 thousand years ago (de Manuel et al., 2020).

Another important point in this study was the use of *D-statistic* methods to estimate the likely gene flow between the cave lion and ancestor of modern lion, after the divergence of these two species. In this analysis, the authors combined all available genomic datasets from various populations of *P. leo* – 12 historical specimens that once inhabited Africa and the Middle East, six samples of modern lions from Africa and India, two genome datasets of the cave lion from Siberia and North America, and clouded leopard as an outgroup. The results showed that there was no or minimal gene flow between modern lion and the Siberian cave lion, while the Yukon cave lion from North America shared a significant number of alleles with the modern South African lion population, apparently due to low coverage of ancient genome of cave lion from North America (de Manuel et al., 2020).

In 2017–2018, fossilized cave lion cubs named "Boris" and "Sparta" were discovered on the shore of the Semyuelyakh River (Republic of Yakutia, Russia). These two new specimens were dated using the radiocarbon dating method (44,163 – 48,752 cal years BP). Preliminary genomic analysis was performed to determine the molecular identity of these two specimens, but genomic data has not yet been published. (Boeskorov et al., 2021).

#### 5. Conclusion

The cave lion is one of the iconic species of Pleistocene megafauna, and a significant number of its fossilized remains have been discovered in Eurasia and North America so far (Stuart and Lister, 2011; Boeskorov et al., 2012; Ersmark et al., 2015). At the same time, the genetic material accumulated is not comparable to that of another important element of Pleistocene fauna - the woolly mammoth (Diez-Del-Molino et al., 2023; Dehasque et al., 2024). These two species, being top-level consultants, largely shaped the environment and biocenosis until the Pleistocene-Holocene transition when both became extinct, quite simultaneously across their range, with a few exceptions (Vartanyan et al., 1993).

Despite the relative abundance of data on mitochondrial genome markers for cave lions, the dating of the divergence of this species using this marker varies significantly (Burger et al., 2004; Barnett et al., 2009, 2016; Broggini et al., 2024). Genetic clustering between individuals from different parts of its distribution is not entirely correct given the likely tendency to form prides (Boeskorov et al., 2021), as well as maternal inheritance of this marker. The date of evolutionary split between cave lions and their ancestors, and the modern lion, is still unclear, and requires additional reliable samples for C<sup>14</sup> dating and ancient DNA extraction and sequencing.

To date, only two nuclear genome datasets for cave lions are publicly available. Both are from the territory of Beringia and dated of around 30,000 years BP. Only one (from Siberia) has relatively deep coverage (de Manuel et al., 2020). Nevertheless, this genomic dataset is not enough to understand the demographic history of cave lions for a long time or the potential causes of their extinction alongside other Pleistocene species.

An important area is also genome-wide study of cave lion specimens that lived on the edge of this species distribution in Central and East Asia (Vasiliev et al., 2021; Aliyassova et al., 2022; Sherani et al., 2023), where there was a potential for introgressive hybridization between the ancestors of modern Asiatic lions and cave lions, the existing barriers to interspecific hybridization between these two species were violated at the time when the effective population size of cave lions sharply decreased 14.5 – 12 thousand years ago (Boeskorov et al., 2012).

Finally, the new paleogenomic data on the cave lion (as well as the American lion) are extremely important for subsequent studies of the

molecular evolution of modern and extinct members of the *Panthera* genus in the Holarctic region, as well as understanding the causes of mass extinctions and transient extinctions of Pleistocene megafauna.

### CRedit authorship contribution statement

**Artem Nedoluzhko:** Investigation, Supervision, Writing – original draft, Writing – review & editing. **Gennady Boeskorov:** Conceptualization, Investigation, Writing – review & editing. **Alexei Tikhonov:** Investigation, Supervision, Writing – review & editing. **Albert Protopopov:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests Artem Nedoluzhko reports financial support was provided by European University at Saint Petersburg. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Data availability

No data was used for the research described in the article.

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