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REVIEW

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# Sequencing and assembling bear genomes: the bare necessities

Courtney Willey and Ron Korstanje\*

## Abstract

Unique genetic adaptations are present in bears of every species across the world. From (nearly) shutting down important organs during hibernation to preventing harm from lifestyles that could easily cause metabolic diseases in humans, bears may hold the answer to various human ailments. However, only a few of these unique traits are currently being investigated at the molecular level, partly because of the lack of necessary tools. One of these tools is well-annotated genome assemblies from the different, extant bear species. These reference genomes are needed to allow us to identify differences in genetic variants, isoforms, gene expression, and genomic features such as transposons and identify those that are associated with biomedical-relevant traits. In this review we assess the current state of the genome assemblies of the eight different bear species, discuss current gaps, and the future benefits these reference genomes may have in informing human biomedical applications, while at the same time improving bear conservation efforts.

**Keywords:** Ursidae, Bear, Genome, Gene expression, Sequence

## The role of reference genomes for model and non-model organisms

A reference genome is a digital nucleic acid sequence database that is a representative example of a species and can be assembled from DNA sequences of various individuals. They can be used as a template to allow faster and cheaper assembly of the genomes of individuals from that same species or as a guide for gene expression studies. Reference genomes for model organisms have been important for the field of biomedicine by allowing for interspecies comparisons and linking specific genetic events to disease phenotypes [1–4]. Reference genomes also serve a role in understanding the biological significance of model organisms such as the mouse (*Mus musculus*) [5], the fruit fly (*Drosophila melanogaster*) [6], and the zebrafish (*Danio rerio*) [1]. Although, common model organisms such as these are standard in the biomedical

field, it does not mean that other organisms do not have biomedical relevance.

The growing number of reference genomes from non-model organisms has revolutionized a myriad of scientific fields with applications in biomedicine and conservation. Various organisms have unique adaptations that may inform the development of novel treatments for disease in humans [7, 8]. For example, the reference genomes of African and Asian elephants (*Loxodonta africana* and *Elephas maximus indicus*, respectively) have revealed differential inflammatory responses for disease defense and provided important evolutionary insights that may be translated into human patients with infections or cancer [9]. The Antarctic Weddell seal's (*Leptonychotes weddellii*) reference genome revealed evolutionarily favored genes that affect the cardiovascular system, regulation of hypoxia signaling and lipid synthesis, and transport mechanisms [10]. These findings hold biomedical potential for humans who would likely develop cardiovascular disease, from a similar high-lipid diet, lifestyle, and risk factors.

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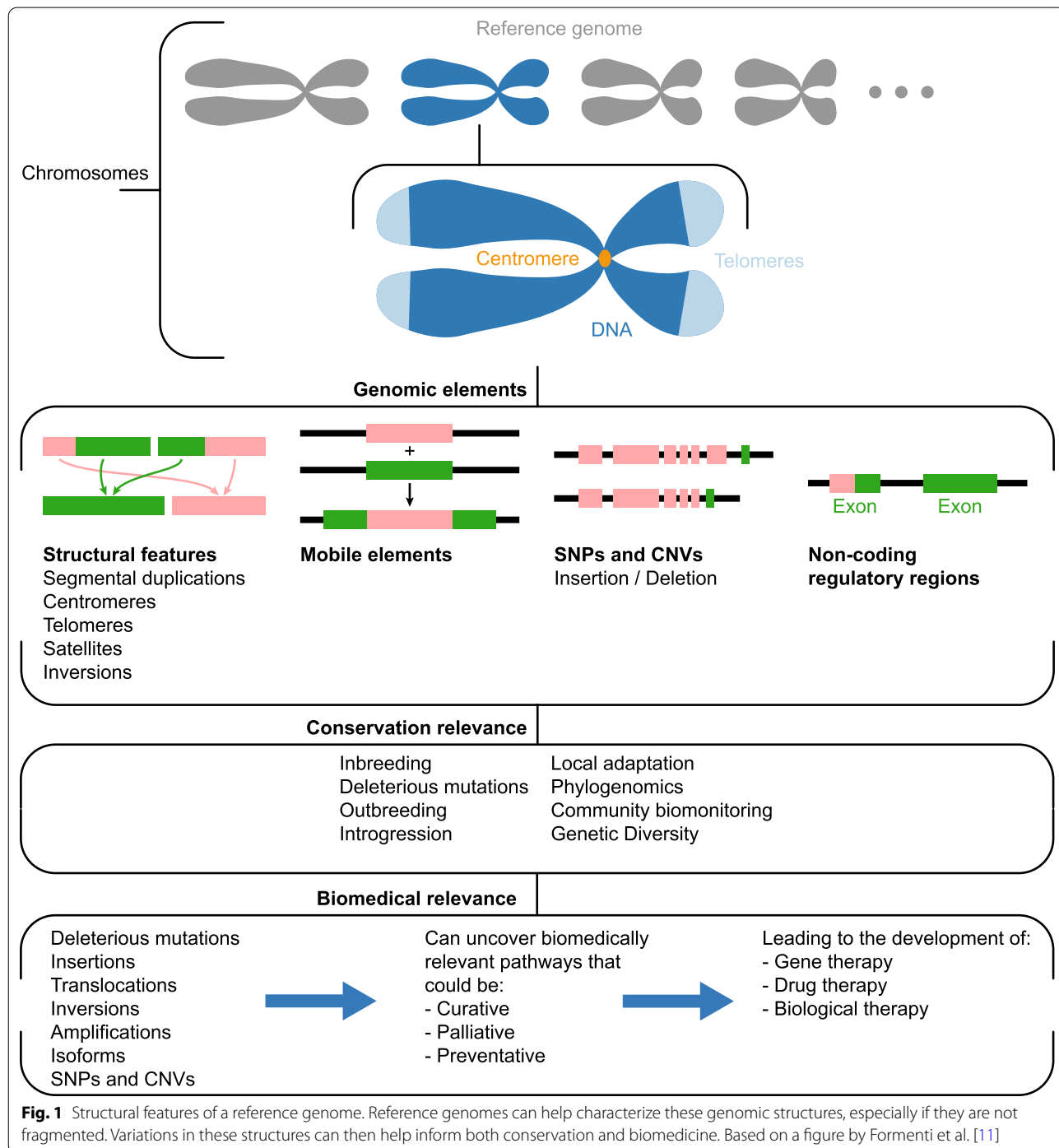


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### Applications in conservation

Mammalian genomes are sequenced for different reasons, yet efforts are typically focused upon conservation as reference genomes can be used to uncover valuable information about genomic diversity (inbreeding, deleterious mutations, outbreeding, introgression, local adaptation) that aid in conservation management strategies

(phylogenomics and community biomonitoring) (Fig. 1) [11, 12]. For example, modern day reference genomes for the Grauer’s gorilla (*Gorilla beringei graueri*) and the small mountain gorilla (*Gorilla beringei beringei*) compared to whole genomes from historical museum specimens revealed different genetic responses to population decline [13]. Another example, the Tasmanian



**Fig. 1** Structural features of a reference genome. Reference genomes can help characterize these genomic structures, especially if they are not fragmented. Variations in these structures can then help inform both conservation and biomedicine. Based on a figure by Formenti et al. [11]

devil (*Sarcophilus harrisi*), is threatened by a deadly transmissible cancer called devil facial tumor disease (DFTD) and its genome has revealed adaptive genetic variation at loci associated with DFTD as well as rapid evolution in response to DFTD [14]. As for bears, the Andean bear (*Tremarctos ornatus*), also known as the spectacled bear, Asiatic black bear (*Ursus thibetanus*), giant panda (*Ailuropoda melanoleuca*), polar bear (*Ursus maritimus*), sloth bear (*Melursus ursinus*), and sun bear (*Helarctos malanus*) are currently listed by the International Union for Conservation of Nature (IUCN) as vulnerable [15].

### Why sequence the bear genome?

Like many other species, bears have unique traits that are biomedically relevant. These traits were developed in response to the environment, diet, and hibernation status. Extant bears exhibit enormous variability regarding their environment, diet, and hibernation status, offering many traits to explore (Table 1 and Fig. 2). To make significant inroads into understanding these unique traits and their underlying molecular mechanisms, there is a need for high-quality, well-annotated reference genomes of the different bear species.

Different environments create unique challenges that bears have adapted to for survival. For example, the Asiatic black bear (*Ursus thibetanus*) and the Andean bear (*Tremarctos ornatus*), evolved to endure hypoxic conditions at high elevation [16–18], while polar bears (*Ursus maritimus*) endure hypoxic conditions when diving under-water for prey [19]. Understanding the genomic

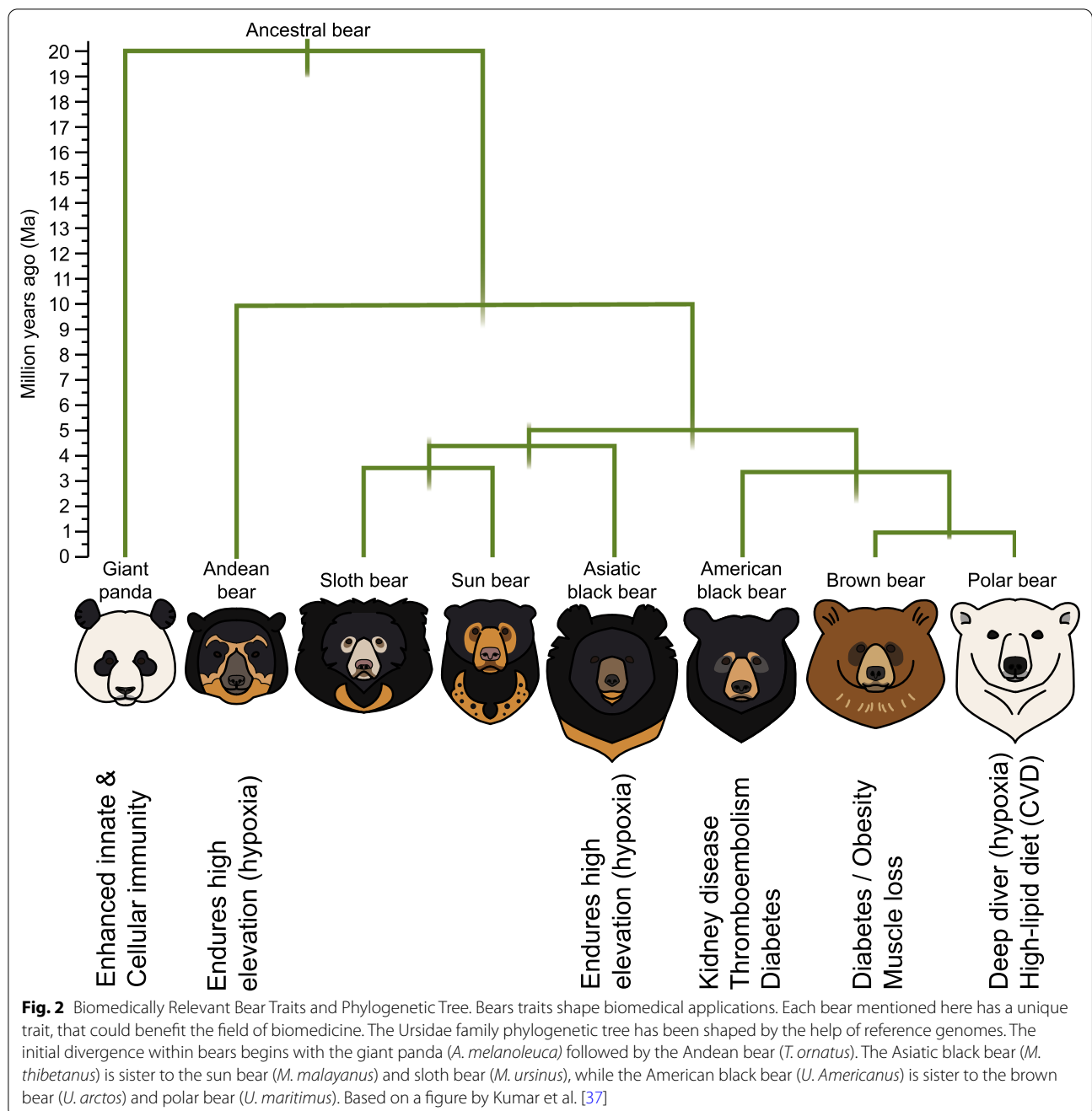
mechanisms behind these traits could inform the treatment of hypoxic conditions such as asthma, lung disease, or anemia.

Bears have also developed unique dietary adaptations, that may provide insights into our own diets and how it affects our health. Most bear species are omnivorous, except for the carnivorous polar bear and the herbivorous giant panda (*Ailuropoda melanoleuca*). The polar bear can protect its heart and vascular system from high low-density lipoprotein (LDL) levels, in response to their hyper-lipid diet of marine mammals [19, 20]. This suggests the polar bear’s diet may reveal useful information for human health, due to their unique ability to protect their heart and vascular system from the consequences of a high-fat diet.

The environment also determines whether or not some bear species hibernate, and determines how their metabolic system works, making hibernating bears (Asiatic black bear, American black bear (*Ursus americanus*), and brown bear (*Ursus arctos*)) of interest for studying metabolic diseases and “burden of lifestyle” diseases in humans (coronary heart disease, cancer, congestive heart disease, chronic kidney disease, obesity, type-2 diabetes, and non-alcoholic fatty liver disease) [7] as they first increase their metabolism to prepare for hibernation and subsequently lower it during hibernation [21–25]. Non-hibernating bears (sun bear (*Helarctos malayanus*), sloth bear (*Melursus ursinus*), giant panda, and polar bear) also offer unique opportunities by providing genetic information related to a non-sedentary lifestyle.

**Table 1** Important features and traits for each species

| Bear                | Environment   | Diet        | Hibernator   | Unique Traits  | Human relevance                                      | References  |
|---------------------|---|-------------|--------------|--|--|-------------|
| Giant panda         | Broadleaf & coniferous, temperate forests                   | Herbivorous | No           | Enhanced innate & cellular immunity  | Autoimmune diseases                                  | [27]        |
| Brown bear          | Variety of habitats (from deserts, to mountains, to tundra) | Omnivorous  | Yes          | Protects vital metabolic functions during hibernation                              | Diabetes, obesity, muscle loss                       | [23–25, 29] |
| Asiatic black bear  | High-elevation forested hills & mountains                   | Omnivorous  | Yes          | Endures hypoxic conditions & protects vital metabolic functions During Hibernation | Asthma, lung disease, anemia                         | [17, 30]    |
| Andean bear         | High-elevation forested hills & mountains                   | Omnivorous  | No           | Endures hypoxic conditions   | Asthma, lung disease, anemia                         | [18]        |
| Polar bear          | Arctic  | Carnivorous | Females only | Endures hypoxic conditions & a high-fat diet                                       | Cardiovascular disease, asthma, lung disease, anemia | [19, 20]    |
| American black bear | Coniferous & deciduous forests & open alpine habitat        | Omnivorous  | Yes          | Protects vital metabolic functions during hibernation                              | Kidney disease, venous thromboembolism, diabetes     | [21, 22]    |
| Sun bear            | Tropical rain forests                                       | Omnivorous  | No           | N/A  | N/A  | N/A         |
| Sloth bear          | Wet & dry tropical forests                                  | Omnivorous  | No           | N/A  | N/A  | N/A         |



**Reference genomes have revealed biomedical relevance**

**Giant panda**

The giant panda reference genome has provided insight to their unique innate and cellular immunity. RNAseq was used to obtain transcriptomic information for the giant panda’s heart, liver, lung, and kidneys and was compared to previous transcriptome information for the blood and spleen [26]. Expression profiles associated with

immunity revealed that breeding male giant pandas displayed enhanced innate immunity and cellular immunity with lower humoral immunity compared to non-breeding males, and identified 45 immune-related genes with altered expression (mostly up-regulated) [27]. In addition, the giant panda genome seems to have maintained the genetic requirements for being purely carnivorous, but a mutation in *TIR1*, that encodes a protein involved in sensing savory flavors might be (in part) why the panda

prefers bamboo. It has also been found that bamboo is very rich in protein and low in carbohydrates meaning the nutritional content of bamboo is similar to meat [28]. However, the panda lacks genes needed for bamboo digestion, suggesting a large role of its microbiome [28].

#### **Polar bear**

The polar bear is a marine Arctic dweller capable of swimming underwater and staying submerged for several minutes, a highly demanding lifestyle that holds biomedical potential for humans [19]. Such a high-energy lifestyle relies on selection in genes related to the production of nitric oxide (*NOS3*, *CPS1*, *TLR4*, *CAV3*, and *ENG*), a vasodilator, playing the role of an energetic gatekeeper. [19]. Though genomic analyses have not identified any enriched pathways linked specifically to hypoxia tolerance or hypoxia response signaling, there were changes in gene expression related to blood pressure [19]. In order to make sure the heart and brain are protected from apnea-induced hypoxemia during deep dives, a cardiovascular adjustment occurs in which peripheral arterial beds are more constricted [7]. This supporting evidence means polar bears have excellent cardiovascular control necessary for diving response, despite having a hyper-lipid marine mammal diet that would put humans at high risk for cardiovascular disease [19].

#### **Brown bear**

The genomes of hibernating bears such as the brown bear provide key information related to metabolic function. During hibernation (about 6 months out of the year), both brown bears and black bears lower their blood flow and heart rate to as low as 10 beats per minute to protect their bodies from physical inactivity [24, 29]. Humans cannot do this and therefore suffer from the consequences of physical inactivity, often an increased risk of developing a “burden-of-lifestyle disease such as venous thromboembolism (VTE) [29]. Comparing physical inactivity and platelet function in humans and brown bears has revealed that three weeks of bed rest had no effect on human platelet aggregation levels, but in hibernating brown bears, platelet aggregation was halved compared to summer [29]. This is believed to be a protective measure to avoid the formation of thrombi during periods of physical inactivity when circulation is decreased [29]. Interestingly, in late summer and fall, brown bears also gain up to 30% in body mass compared to in the spring and preserve insulin sensitivity (a feat humans cannot achieve) [24].

#### **American black bear**

Like the brown bear, the American black bear has evolved features in the kidney that allow them to endure

low renal function during hibernation and recover it soon after hibernation [21]. In 2019, a set of 169 differentially expressed genes that may be involved in the American black bear’s unique hibernation response were identified [21]. Specifically, the upregulation of three cytokine suppression genes were found after hibernation (*SOCS2*, *CISH*, and *SERPINC1*), while there was a lack of increased cytokine expression (*IL6*, *CCL2*, *CCL6*) and damage markers (*LCN2* and *HAVCR1*) normally found in low functioning or recovering kidneys in other species [21].

#### **Asiatic black bear**

Humans would typically suffer severe pulmonary hypertension when exposed to hypoxic conditions in high elevations yet, the Asiatic black bear is able to endure these conditions without any serious repercussions [17]. The Asiatic black bear lives predominantly in forested hills and mountains at elevations over 9,900ft in the summer and descend lower in the winter to prepare for the cold [30].

#### **Andean bear (spectacled bear)**

Like the Asiatic black bear, the Andean bear is adapted to high elevations. However, data is lacking on the Andean bear due to poaching and other threats which have limited studies concerning genetics and led to a focus on conservation methods [18].

#### **Current gaps and future benefits**

Currently, there is a lack of high-quality reference genomes for bears and some species are completely missing a reference genome (Table 2), creating gaps that are affecting the quality of research that can be accomplished. Some of the current limitations of Ursidae biomedical applications include the possibility of false positives that can occur during genome-wide analysis, as well as the lack of experimental validation, and how specific mechanisms can be turned into biomedical practices. These limitations provide roadblocks to achieving biomedical applications, however, these limitations may be remedied if more high-quality reference genomes are obtained. As more high-quality reference genomes are obtained and the number of reference genomes for a species increases, the possibility of false positives is reduced, and the lack of experimental validation is solved through comparison of genomes.

A good measure of the quality of a genome is scaffold-level contiguity [18]. Genome assemblies using a combination of techniques such as short read, long read, and proximity ligation data produce better quality assemblies (giant panda, NCBI Accession #PRJNA588422) than ones that purely rely upon one method such as short read

**Table 2** Summary of genome assemblies

| Species             | Sequencing technology                                     | Size (Gbp) | N50 (bp)    | # Scaffolds | Chr (2n) | NCBI Acc. # | References |
|---------------------|---|------------|-------------|-------------|----------|-------------|------------|
| Giant panda         | Illumina; 10X Genomics; Flow-sorted chromosome sequencing | 2.4        | 129,200,000 | 73,513      | 42       | PRJNA588422 | [36]       |
| Brown bear          | PacBio; Illumina  | 2.5        | 70,100,000  | 901         | 74       | PRJNA807323 | [23]       |
| Asiatic black bear  | Illumina NovaSeq  | 2.4        | 26,800,000  | 24,967      | 74       | PRJNA573607 | [17]       |
| Andean bear         | Illumina; Oxford Nanopore                                 | 2.2        | 21,100,000  | 12,402      | 52       | PRJNA472085 | [18]       |
| Polar bear          | Illumina HiSeq; Oxford Nanopore                           | 2.3        | 72,000,000  | 3899        | 74       | PRJNA669153 |            |
| American black bear | PacBio  | 2.4        | 13,900,000  | 2212        | 74       | PRJNA319796 | [21]       |
| Sun bear            | N/A   | N/A        | N/A         | N/A         | 74       | N/A         |            |
| Sloth bear          | N/A   | N/A        | N/A         | N/A         | 74       | N/A         |            |

(American black bear, NCBI Accession #PRJNA31976) [18]. Also, fragmented, or incomplete genomes cannot be used to accurately characterize structural features of a genome [11]. Structural features of a genome include the building blocks of chromosomes (centromeres, telomeres, satellites, and structural variations such as rearrangements and segmented duplications) (Fig. 1). Generating complete, highly contiguous, correctly annotated genomes for all Ursidae using long-read sequences will allow us to identify differences in genetic variants, isoforms, gene expression, and genomic features like transposons (see Glossary). These differences may lead to altered gene function and subsequent protein production, allowing for the identification of novel genes for biomedical research and conservation. Therefore, focusing on obtaining high-quality reference genomes, will improve the tools needed to identify genomic changes between species, and better inform biomedicine and conservation efforts. However, the possibility of false positives and the lack of experimental validation remains unless a larger number of high-quality reference genomes are produced for each species to allow for comparative and forward genomics.

Obtaining multiple high-quality genomes of Ursidae members, will improve current gaps in reference genome quality and annotations, resulting in clearer evolutionary history and allowing for higher quality gene expression studies, comparative genomics, and forward genomics to better inform conservation and human biomedicine, reducing the instance of false-positives and allowing for the discovery of experimental validation methods [2–4, 31]. Comparative genomics is a field of research in which complete genome sequences are compared between different species, while forward genomics is an approach to determine the genetic underpinnings responsible for a certain phenotype. Comparative and forward genomics highlight the need for high-quality reference genomes for all mammals to achieve a deeper understanding of which genetic variants lead to certain phenotypes,

especially disease phenotypes, and how we can predict these changes [2–4, 31]. Both, comparative and forward genomics also utilize multiple reference genomes to track when certain variants arose within a species, which can help designate evolutionary significance that dictates conservation priorities. Being able to pinpoint specific variants and genes related to disease phenotypes can help identify therapeutic targets for drug design in both humans and mammals (see Fig. 2) [2, 4]. As more high-quality genomes are produced and can be compared, false positives will be more readily identified allowing for some biological mechanisms to have a more obvious role.

Genome assembly and annotation can also be improved with the help of software like Progressive Cactus, an extension for Cactus, that allows for multiple large vertebrate genomes to be aligned while maintaining high quality [32]. Aligning sequences helps to identify similar regions of DNA for easy comparison of genome sequences between multiple large vertebrates, making Progressive Cactus a great addition to the field of comparative genomics. Aligning and analyzing extinct and extant genomes may even help explain discordances in evolutionary history and answer how evolution impacted the flow of genetic information on extant Ursidae members (see Fig. 2) [33, 34]. This also proves useful for identifying the genetic history of evolutionarily conserved traits that could hold biomedical importance.

A next step in resolving genomes, after obtaining complete high-quality reference genomes, is assigning contigs and scaffolds to individual chromosomes (see Glossary). Most bear species have 36 autosomes and two sex chromosomes, except for the giant panda (20 autosomes and two sex chromosomes) and the Andean bear (25 autosomes and two sex chromosomes). Chromosomal assignment will be useful for population genetic studies, as it allows selection of genetic markers that we know will be unlinked, and it can provide more insight into the evolution of bear species by studying chromosomal rearrangements. Assigning contigs and scaffolds to the sex

chromosomes can be achieved through male/female sequence comparison and sequence comparison with other mammalian species. Once high-quality genome assemblies have been obtained for all eight Ursidae species and have been assigned to different chromosomes, the next step would be to move onto obtaining the same information for all Ursidae subspecies. This would then provide a deeper genomic insight to the relationships between bears and how their unique traits came to be, further reducing gaps and limitations.

Currently available reference genomes for Ursidae show promise in uncovering future biomedical application in humans (Table 1 and Fig. 2). Understanding the biological mechanism that is responsible for enhanced innate immunity and cellular immunity in giant pandas may provide new methods of treatment for our own innate and cellular immunity [27]. Further studies related to the biology behind the polar bear's cardiovascular system and high-energy lifestyle could uncover biomedically relevant information useful for treating humans with cardiovascular diseases [19, 20]. Because brown bears and American black bears are evolutionarily adapted to periodic obesity and long periods of physical inactivity, their genomes may hold keys to prevention and treatment strategies for metabolic and "burden-of-lifestyle" diseases in humans such as CKD and VTE [21–25, 29]. In regards to the Asiatic black bear and Andean bear, a genomic study in humans adapted to the high elevation in Tibet (11,995ft), revealed three novel genes *EPAS1*, *EGLN1*, and *PPARA* that are strongly associated with lower hemoglobin concentration, increased lactate production, and decreased fatty acid oxidation [35]. It would be interesting to see if these same genes play a role in the Asiatic black bear and Andean bear or whether other genes allow for their adaptation to high elevation. This can help inform biomedical treatment of hypoxia related disease in humans (asthma, lung disease, and anemia) [17, 18, 30]. Uncovering these biomedical mechanisms is currently underway, and with future improvement to reference genome technology and the number of genomes obtained there is promise for biomedical applications in humans.

## Conclusions

Genomic resources such as reference genomes are important for uncovering the unique traits bears have due to variable environments, hibernation, and diets that may have important biomedical applications for humans. So far, reference genomes for the giant panda, polar bear, brown bear, American black bear, Asiatic black bear, and the Andean bear (Table 2) have provided evidence that their unique traits may be useful for the prevention and treatment of many diseases, mostly those of the

metabolic system. Based on the potential of what we have seen so far, generating high-quality reference genomes for all bears is beneficial for the conservation of bears vulnerable for endangerment, advancement of human biomedicine, and overcoming the current limitations hindering biomedical applications in humans.

## Abbreviations

LDL: Low-density lipoprotein; NCBI: National Center for Biotechnology Information; Gbp: Billion base pairs; bp: Base pairs; VTE: Venous thromboembolism; CKD: Chronic kidney disease; DFTD: Devil facial tumor disease.

## Glossary

|            |   |
|------------|---|
| N50        | The N50 value is calculated by first ordering every contig/scaffold by length from longest to shortest. Next, starting from the longest contig/scaffold, the lengths of each contig are summed, until this running sum equals one-half of the total length of all contigs/scaffolds in the assembly. This is used to measure the completeness of a genome |
| Scaffold   | A series of non-contiguous DNA sequences linked together  |
| Transposon | Also known as a transposable element, is a DNA sequence that can change position within a genome, potentially creating or reversing mutations that alter genetic identity and genome size   |

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## Author contributions

CW did the literature search and wrote the manuscript. RK edited the manuscript. Both authors read and approved the final manuscript.

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## Availability of data and materials

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## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## References

- Chernyavskaya Y, Zhang X, Liu J, Blackburn J. Long-read sequencing of the zebrafish genome reorganizes genomic architecture. *BMC Genomics*. 2022;23:1–3.
- L. Goodman, Advancing Comparative Genomics for Human Health: Fauna Bio Collaborates on study to compare 240 mammal genomes, 2020.
- Hiller M, Schaar BT, Indjeian VB, Kingsley DM, Hagey LR, Bejerano G. A "forward genomics" approach links genotype to phenotype using independent phenotypic losses among related species. *Cell Rep*. 2012;2:817–23.



4. Lindblad-Toh K, Garber M, Zuk O, Lin MF, Parker BJ, Washietl S, Kheradpour P, Ernst J, Jordan G, Mauceli E, Ward LD, Lowe CB, Holloway AK, Clamp M, Gnerre S, Alföldi J, Beal K, Chang J, Clawson H, Cuff J, Di Palma F, Fitzgerald S, Ficek P, Guttman M, Hubisz MJ, Jaffe DB, Jungreis I, Kent WJ, Kostka D, Lara M, Martins AL, Massingham T, Moltke I, Raney BJ, Rasmussen MD, Robinson J, Stark A, Vilella AJ, Wen J, Xie X, Zody MC, Worley KC, Kovar CL, Muzny DM, Gibbs RA, Warren WC, Mardis ER, Weinstock GM, Wilson RK, Birney E, Margulies EH, Herrero J, Green ED, Haussler D, Siepel A, Goldman N, Pollard KS, Pedersen JS, Lander ES, Kellis M. A high-resolution map of human evolutionary constraint using 29 mammals. *Nature*. 2011;478:476–82.
5. Blake JA, Baldarelli R, Kadin JA, Richardson JE, Smith L, Cynthia CJ, Bult AV, Anagnostopoulos JS, Beal SM, Bello O, Blodgett NE, Butler J, Campbell KR, Christie LE, Corbani ME, Dolan HJ, Drabkin M, Flores SL, Giannatto A, Guerra P, Hale DP, Hill J, Judd M, Law M, Mcandrews D, Miers C, Mitchell H, Motenko L, Ni H, Onda J. Mouse genome database (MGD): knowledgebase for mouse–human comparative biology. *Nucleic Acids Res*. 2021;49:D981–7.
6. Solares EA, Chakraborty M, Miller DE, Kalsow S, Hall K, Perera AG, Emerson JJ, Hawley RS. Rapid low-cost assembly of the *Drosophila melanogaster* reference genome using low-coverage, long-read sequencing. *G3 Genes Genomes Genet*. 2018;8:3143–54.
7. Stenvinkel P, Painer J, Johnson RJ, Natterson-Horowitz B. Biomimetics–nature’s roadmap to insights and solutions for burden of lifestyle diseases. *J Intern Med*. 2020;287:238–51.
8. Heck M, Neely BA. Proteomics in non-model organisms: a new analytical frontier. *J Proteome Res*. 2020;19:3595–606.
9. Tollis M, Ferris E, Campbell MS, Harris VK, Rupp SM, Harrison TM, Kiso WK, Schmitt DL, Garner MM, Aktipis CA, Maley CC, Boddy AM, Yandell M, Gregg C, Schiffman JD, Abegglen LM. Elephant genomes reveal accelerated evolution in mechanisms underlying disease defenses. *Mol Biol Evol*. 2021;38:3606–20.
10. Noh HJ, Turner-Maier J, Schulberg SA, Fitzgerald ML, Johnson J, Allen KN, Huckstadt LA, Batten AJ, Alföldi J, Costa DP, Karlsson EK, Zapal WM, Buys ES, Lindblad-Toh K, Hindle AG. The Antarctic Weddell seal genome reveals evidence of selection on cardiovascular phenotype and lipid handling. *Commun Biol*. 2022;5:140.
11. Formenti G, Theissinger K, Fernandes C, Bista I, Bombarely A, Bleidorn C, Ciofi C, Crottini A, Godoy JA, Högglund J, Malukiewicz J, Mouton A, Oomen RA, Paez S, Palsboll PJ, Pampoulie C, Ruiz-Lopez MJ, Svardal H, Theofanopoulos C, de Vries J, Waldvogel AM, Zhang G, Mazzoni CJ, Jarvis ED, Balint M, C. European Reference Genome Atlas. The era of reference genomes in conservation genomics. *Trends Ecol Evol*. 2022;37:197–202.
12. Hohenlohe PA, Funk WC, Rajora OP. Population genomics for wildlife conservation and management. *Mol Ecol*. 2021;30:62–82.
13. van der Valk T, Diez-Del-Molino D, Marques-Bonet T, Guschanski K, Dalen L. Historical genomes reveal the genomic consequences of recent population decline in Eastern Gorillas. *Curr Biol*. 2019;29:165–170.e6.
14. Hohenlohe PA, Mccallum HI, Jones ME, Lawrance MF, Hamede RK, Storer A. Conserving adaptive potential: lessons from Tasmanian devils and their transmissible cancer. *Conserv Genet*. 2019;20:81–7.
15. International Union for Conservation of Nature (IUCN), The IUCN Red List of Threatened Species, 2021–3.
16. Werhahn G, Senn H, Ghazali M, Karmacharya D, Sherchan AM, Joshi J, Kusi N, López-Bao JV, Rosen T, Kachel S, Sillero-Zubiri C, Macdonald DW. The unique genetic adaptation of the Himalayan wolf to high-altitudes and consequences for conservation. *Glob Ecol Conserv*. 2018;16:e00455.
17. Zhu C, Xu W, Li J, Liu C, Hu M, Yuan Y, Yuan K, Zhang Y, Song X, Han J, Cui X. Draft genome assembly for the Tibetan black bear (*Ursus thibetanus thibetanus*). *Front Genet*. 2020;11:231.
18. Saremi NF, Oppenheimer J, Vollmers C, O’Connell B, Milne SA, Byrne A, Yu L, Ryder OA, Green RE, Shapiro B. An annotated draft genome for the Andean bear, *Tremarctos ornatus*. *J Hered*. 2021;112:377–84.
19. Hindle AG. Diving deep: understanding the genetic components of hypoxia tolerance in marine mammals. *J Appl Physiol*. 1985;128(2020):1439–46.
20. Liu S, Lorenzen D, Eline M, Fumagalli B, Li K, Harris Z, Xiong L, Zhou SK, Thorfinn M, Somel C, Babbitt G, Wray J, Li W, He Z, Wang W, Fu X, Xiang CM, Claire A, Doherty JO, Mary OM, James WB, Erik L, Dalén R, Dietz L, Orlando C, Sonne G, Zhang R, Nielsen EW, Wang J. Population genomics reveal recent speciation and rapid evolutionary adaptation in polar bears. *Cell*. 2014;157:785–94.
21. Srivastava A, Kumar Sarsani V, Fiddes I, Sheehan SM, Seger RL, Barter ME, Neptune-Bear S, Lindqvist C, Korstanje R. Genome assembly and gene expression in the American black bear provides new insights into the renal response to hibernation. *DNA Res*. 2019;26:37–44.
22. Fazzalari A, Basadonna G, Kucukural A, Tanriverdi K, Koupenova M, Pozzi N, Kakuturu J, Friedrich AU, Korstanje R, Fowler N, Belant JL, Beyer DE Jr, Brooks MB, Dickson EW, Blackwood M, Mueller C, Palesty JA, Freedman JE, Cahan MA. A translational model for venous thromboembolism: micro-RNA expression in hibernating black bears. *J Surg Res*. 2021;257:203–12.
23. Taylor GA, Kirk H, Coombe L, Jackman SD, Chu J, Tse K, Cheng D, Chuah E, Pandoh P, Carlsen R, Zhao Y, Mungall AJ, Moore R, Birol I, Franke M, Marra MA, Dutton C, Jones SJM. The genome of the North American brown bear or grizzly: *Ursus arctos ssp horribilis*. *Genes (Basel)*. 2018;9:598.
24. Fröbert O, Fröbert AM, Kindberg J, Arnemo JM, Overgaard MT. The brown bear as a translational model for sedentary lifestyle-related diseases. *J Intern Med*. 2020;287:263–70.
25. Jansen HT, Trojahn S, Saxton MW, Quackenbush CR, Evans Hutzenbiler BD, Nelson OL, Cornejo OE, Robbins CT, Kelley JL. Hibernation induces widespread transcriptional remodeling in metabolic tissues of the grizzly bear. *Commun Biol*. 2019;2:336.
26. Li F, Wang C, Xu Z, Li M, Deng L, Wei M, Zhang H, Wu K, Ning R, Li D, Yang M, Zhang M, Ni Q, Zeng B, Li D, Li Y. Transcriptome profiling across five tissues of giant panda. *Biomed Res Int*. 2020;2020:1–13.
27. Shen H, Li C, He M, Huang Y, Wang J, Wang M, Yue B, Zhang X. Immune profiles of male giant panda (*Ailuropoda melanoleuca*) during the breeding season. *BMC Genom*. 2021;22:1–7.
28. Nie Y, Wei F, Zhou W, Hu Y, Senior AM, Wu Q, Yan L, Raubenheimer D. Giant pandas are macronutritional carnivores. *Curr Biol*. 2019;29:1677–1682.e2.
29. Arinell K, Blanc S, Welinder KG, Stoen OG, Evans AL, Fröbert O. Physical inactivity and platelet function in humans and brown bears: a comparative study. *Platelets*. 2018;29:87–90.
30. International Association For Bear Research and Management, Asiatic Black Bear, n.d.
31. Zoonomia C. A comparative genomics multitool for scientific discovery and conservation. *Nature*. 2020;587:240–5.
32. Armstrong J, Hickey G, Diekhans M, Fiddes IT, Novak AM, Deran A, Fang Q, Xie D, Feng S, Stiller J, Genereux D, Johnson J, Marinescu VD, Alföldi J, Harris RS, Lindblad-Toh K, Haussler D, Karlsson E, Jarvis ED, Zhang G, Paten B. Progressive Cactus is a multiple-genome aligner for the thousand-genome era. *Nature*. 2020;587:246–51.
33. Krause J, Unger T, Nocon A, Malaspina AS, Kolokotronis SO, Stiller M, Soibelzon L, Spriggs H, Dear PH, Briggs AW, Bray SC, O’Brien SJ, Rabeder G, Matheus P, Cooper A, Slatkin M, Paabo S, Hofreiter M. Mitochondrial genomes reveal an explosive radiation of extinct and extant bears near the Miocene-Pliocene boundary. *BMC Evol Biol*. 2008;8:220.
34. Gretzinger J, Molak M, Reiter E, Pfrengle S, Urban C, Neukamm J, Blant M, Conard NJ, Cupillard C, Dimitrijevic V, Drucker DG, Hofman-Kaminska E, Kowalczyk R, Krajcarz MT, Krajcarz M, Munzel SC, Peresani M, Romandini M, Rufi I, Soler J, Terlato G, Krause J, Bocherens H, Schuenemann VJ. Large-scale mitogenomic analysis of the phylogeography of the Late Pleistocene cave bear. *Sci Rep*. 2019;9:10700.
35. O’Brien KA, Simonson TS, Murray AJ. Metabolic adaptation to high altitude. *Curr Opin Endocr Metab Res*. 2020;11:33–41.
36. Fan H, Wu Q, Wei F, Yang F, Ng BL, Hu Y. Chromosome-level genome assembly for giant panda provides novel insights into Carnivora chromosome evolution. *Genome Biol*. 2019;20:267.
37. Kumar V, Lammers F, Bidon T, Pfenninger M, Kolter L, Nilsson MA, Janke A. The evolutionary history of bears is characterized by gene flow across species. *Sci Rep*. 2017;7:46487.

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