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Wolf-Ekkehard Lönnig

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PART 2

The Panda's Thumb: Striking Imperfection Or Masterpiece of Engineering?

Continued from PART 1 – See please https://www.weloennig.de/PANDA.Part1.pdf
There: Some Key Points on a Long-Lasting Controversy as well as an Abstract
Consisting of the Core Points of the Contents and Introduction.
Note, please, also that some general points are now repeated here in the Footnote.[1]

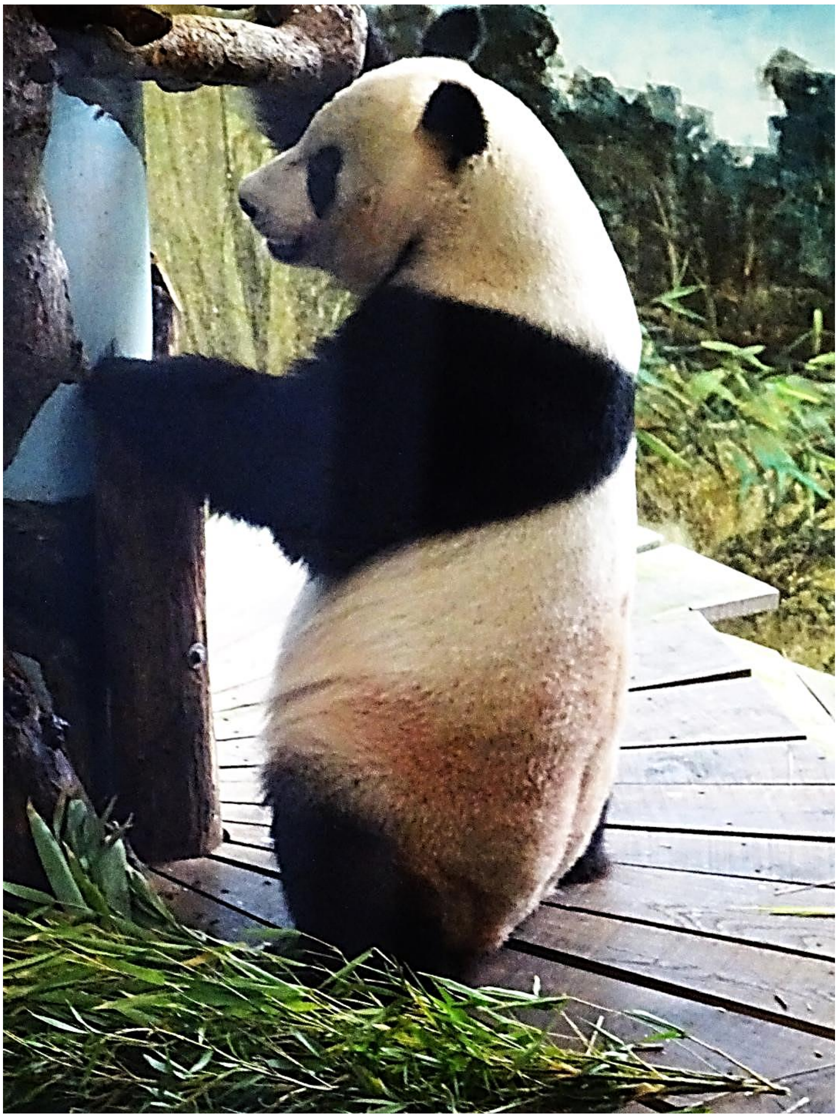

Photo W.-E. L.: Photographed through a thick pane of glass (Zoo Rhenen, The Netherlands 5 June 2024). The Panda bear may also stand up metaphorically for his ingeniously designed paws not only in my two articles. For "They are able to manipulate bamboo **with the dexterity of a Swiss watch maker** because they have an oversized radial sesamoid, a wrist bone, which functions as an opposable 'thumb' [in a "functional complex"]."[2]

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[1] **Emphasis:** As already mentioned for other articles of mine (for example: https://www.weloennig.de/Hippo.pdf): Note please that **virtually all highlighting/emphasis in the typeface by W.-E. L.** (except italics for ***genera*** and ***species*** names as well as adding a note when the cited authors themselves emphasized certain points). **Why so often**? Well, *since many people do not have the time to study a more extensive work in detail, these highlights can serve as* **keywords to get a first impression of what is being discussed** in the respective paragraphs.

Concerning the key points: ***Page numbers may change in a future update, so not presented here***.

Incidentally, citations do not imply consent of the authors quoted with my overall views nor *vice versa*. Moreover, I alone am responsible for any mistakes.

On some questions concerning absolute dating methods, see http://www.weloennig.de/HumanEvolution.pdf, p. 28.

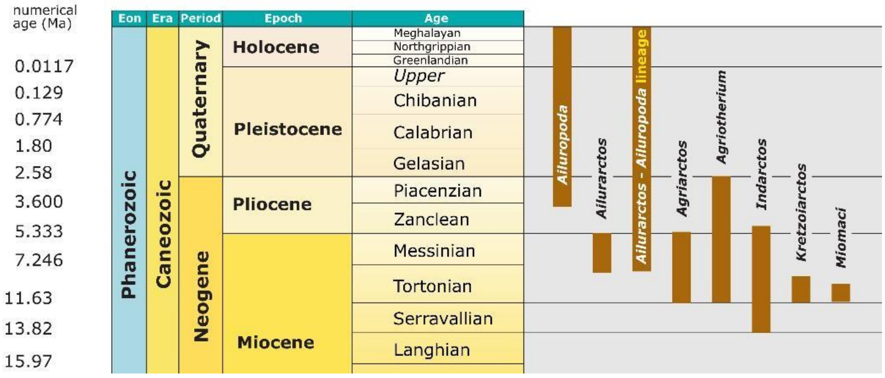
Also: a brief **note on the synonyms** that I'm using here like the "Double/Dual/Complementary Function" of the panda's thumb. Well, each of the synonyms has its own subtly different overtones so that the basic points discussed may be, I hope, better understood and can be easier memorized.

[2] Stephen Herrero: Book review of *The Giant Pandas of Wolong* (1985). George B. Schaller, Hu Jinchu, Pan Wenshi & Zhu Jing. Aniim Behav 34: 1274-1276.

Abstract (PART 2): Key Points of the Contents[3]

First, I would like to express my appreciation as a geneticist and biologist for the important work on the molecular investigations and many further topics of the panda's biology by a range of international researchers around the globe – especially the huge contributions of highly qualified Chinese scientists having the largest share in this significant work. – Now to the key points:

1. "**2.7 million** heterozygous SNPs in the panda diploid genome"
   "The estimated small indel rate was **1.2231024 and 0.7031024** on autosomes and sex chromosomes, respectively", also '**4,359 insertions and deletions** with a median length of **150 bp**, and **20** inversions'.
2. On the evolutionary method to detect "positively selected" genes.
3. Panda genes underlying its **unique *physiological*** traits.
4. The Panda's "closest living relatives (the bears) appear to be **more than 90 per cent herbivorous**".
5. What do we known about genes involved in the panda's **unique *morphological* traits**?
6. Dual Oxidase 2 Gene, ***DUOX2*** in mice and pandas: substitution of C with T, resulting in an Arginine to Termination codon in the 16th exon of the ***DUOX2*** gene" – what does it explain?
7. The "Optimal Panda Principle" considering the entire panda system.
8. "Full metabolic phenotype of giant pandas likely depends on yet-unknown genetic mechanisms affecting T4 to T3 conversion, or TSH levels".
9. Forward and reverse mutations in *Ailuropoda*?
10. In 850 000 000 000 *Ursus* bears the mutation in *DUOX2* could have happened on the nucleotide level (forward mutation): **8 500** times (10^{-8} x 850 000 000 000).
11. Mutations on the *DUOX2* gene level: **8 500 000** times (1 x 10^{-5} x 850 000 000 000).
12. Differences between *Ailurarctos* and *Ailuropoda* could be due to Mendelian recombination.
13. [Recall please the] Question whether the neo-Darwinian explanation of a ***1 thousandth of 1 mm longer hook in each generation*** would really constitute decisive selective advantages.
14. In 40 billion panda bears: Numbers of mutations: Now first the gene level for the *DUOX2* gene: Forward mutations: 40 000 000 000 x 1 x 10^{-5} = 400 000. Reverse mutations: 40 000 000 000 x 1 x 10^{-6} = 40 000. Nucleotide level: 400 and 40 respectively. "The apparently new mutations are not new; they are truly immemorial, as old as the mother species itself" (Nilsson).
15. What has happened to all these mutations – at least those affecting the phenotype?
16. **The Qinling Panda** [a classic example of a loss of function mutation].
17. **Constancy** (**Stasis**) of and in the Subfamily Ailuropodinae to which the pandas belong (Family Ursidae). Figure by Roland Slowik, Dietzenbach (Germany) for the present article (15 July 2024).



18. Options concerning the origin of pandas.
19. Some arguments for the theory of intelligent design.
20. Authors for intelligent design.
21. More points that could be discussed.

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[3] Recall please: As already mentioned for other articles of mine (for example: https://www.weloennig.de/Hippo.pdf): Note please that **virtually all highlighting/emphasis in the typeface by W.-E. L.** (except italics for ***genera*** and ***species*** names as well as adding a note when the cited authors themselves emphasized certain points). **Why so often**? Well, *since many people do not have the time to study a more extensive work in detail, these highlights can serve as* **keywords to get a first impression of what is being discussed** in the respective paragraphs.

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Photo: Manfred Werner/Tsui (2008): https://de.wikipedia.org/wiki/Gro%C3%9Fer_Panda
"Giant Panda (female adult and young bear of 10 months) at the Tiergarten Schönbrunn in Vienna"

To What Extent Are the Following DNA Sequences Involved in the Origin of Pandas?

In PART 1 have noted that Ruiqiang Li et al. (122 authors if a counted correctly) in their *Nature* paper (2010, p. 313)[4] there were "27 known panda mRNA genes in GenBank, one of which is the SRY sex determination gene located on chromosome Y, thus not present in the female panda" and also that the authors "were able to detect the remaining 26 genes in the assembled scaffolds with 99.3% total sequence aligned (Supplementary Table 4)."

They also reported (p. 314) that "there were **2,534 panda-specific genes**, which is nearly double the amount of dog-specific genes (**1,677**[5])."

Moreover, the authors had estimated (p. 313) that "**transposable elements** comprised approximately **36.2%** of the panda genome, which is similar to that of the dog genome (**36.1%**), and lower than the human genome (**46.1%**)."

Also (p. 313), they had "identified **3,095 duplicated fragments** with a total length 10.4Mb (0.43%) in the whole genome assembly" and additionally that they had "identified **5,485 segments** (.1 kb in length) with a total length of 13.9Mb."

P. 315: "We identified **2.7 million** heterozygous SNPs in the panda diploid genome."

P. 316: "In addition to SNPs, we identified **267,958 small indels** that ranged in size from 1 to 6 bp (Supplementary Table 19). The estimated small indel rate was **1.2231024 and 0.7031024** on autosomes and sex chromosomes, respectively—roughly one order of magnitude lower than that of the SNP rate."

P. 316: "There were **4,359 insertions and deletions** detected with a median length of **150 bp**, and **20** inversions (Supplementary Table 20)."[6]

On p. 315 the authors also stated (see the original paper for the larger context):

> "Using three different tests — one specific for the panda lineage, one specific for the dog lineage, and one combining evidence from all five species included in the alignment — we found **134, 94 and 182 positively selected genes (PSGs)**, respectively, using a conservative 5% false-discovery-rate criterion."

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[4] https://www.nature.com/articles/nature08696#Sec1

[5] This does **not**, however, mean that in comparison to the wolf the dog would display 1,677 **entirely new functional** genes or DNA sequences. At that time (2014), in fact, not even 1 such case was known (check: different today?) – almost all of the often strongly different phenotypes of the **dog breeds are the result of losses of genes/gene functions**. See details in https://www.weloennig.de/Hunderassen.Bilder.Word97.pdf [Addition 18 July 2024: Of utmost interest would be the number of **orphan genes** ("protein-coding open reading frames (ORFs) that occur only in one species or as taxonomically restricted genes (TRGs)" to be detected only in the pandas as compared to the other species of the Ursidae. For orphan genes in general see for example Richard S. Gunasekera et al. (2023): https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0291260 and https://communities.springernature.com/posts/the-evolutionary-mystery-of-orphan-genes.]

[6] For a discussion of these phenomena pro and contra natural selection, see please Part1: https://www.weloennig.de/PANDA.Part1.pdf: Last page but one:

How do Ruiqiang Li et al. know that these genes were ***positively selected***? They reference the paper by Nielssen et al. (2005)[7], which states (and this is the generally recognized method to do it):

> "The most common statistical technique for detecting positive selection takes advantage of the fact that mutations in coding regions of genes come in two classes: nonsynonymous mutations that change the resulting amino acid sequence of the protein and synonymous mutations, which do not change the encoded protein. ***An excess of nonsynonymous mutations over synonymous mutations, beyond what would be expected if the two types of mutations occur at the same rate, provides strong evidence for the past action of positive selection at the protein level***."[8]

So, in agreement with all the other evolutionary authors using this method, they ***simply interpret*** an excess of nonsynonymous differences as mutations due to the action of positive selection. So, what would happen if an ingenious genetic engineer had modified/changed all the sequences necessary for his overall goals?

Interestingly, Ruiqiang Li et al. have also suggested that "***loss-of-function might have an important role in functional evolution***" – a well-functioning and successful scientific approach that can be investigated without a *circulus vitiosus* (so without presupposing what has to be proved – see, for example Lönnig 1971, 1986/2001, 2015[9]; Behe several articles up to 2023[10]).

As mentioned above, in 2010 there were "27 known panda mRNA genes in the GenBank", so what have we learned during the last 14 years and what do we know now?

In brief: There has been an explosion-like extension in the description of DNA sequences and entire genes and proteins of the panda's genome[11] including finely differentiated corrections of formerly published data.[12] Yet, the answer to the question of the subheadline is still wide open, which leads us to the key topic, namely:

Panda Genes Underlying its Unique *Physiological* Traits

Apart from all the interesting DNA sequences mentioned above (millions of SNPs, small and large indels etc.), what we are especially interested in are, of course, genes involved in and underlying the panda's unique morphological and physiological traits.

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[7] Nielsen et al. (2005): A Scan for Positively Selected Genes in the Genomes of Humans and Chimpanzees. https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0030170

[8] See also https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2596312/ Sergey Kryazhimskiy and Joshua B. Plotkin (2008): The Population Genetics of dN/dS. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2596312/ "Evolutionary pressures on proteins are often quantified by the ratio of substitution rates at non-synonymous and synonymous sites. The dN/dS ratio was originally developed for application to distantly diverged sequences, the differences among which represent substitutions that have fixed along independent lineages. Nevertheless, the dN/dS measure is often applied to sequences sampled from a single population, the differences among which represent segregating polymorphisms. Here, we study the expected dN/dS ratio for samples drawn from a single population under selection, and we find that in this context, dN/dS is relatively insensitive to the selection coefficient. Moreover, the hallmark signature of positive selection over divergent lineages, dN/dS>1, is violated within a population. For population samples, the relationship between selection and dN/dS does not follow a monotonic function, and so it may be impossible to infer selection pressures from dN/dS. These results have significant implications for the interpretation of dN/dS measurements among population-genetic samples."
(2019) https://www.quora.com/Evolutionary-Biology-What-is-the-dN-dS-ratio
(2024) https://en.wikipedia.org/wiki/Ka/Ks_ratio on Limitations: "Although the Ka/Ks ratio is a good indicator of selective pressure at the sequence level, evolutionary change can often take place in the regulatory region of a gene which affects the level, timing or location of gene expression. Ka/Ks analysis will not detect such change. It will only calculate selective pressure within protein coding regions. In addition, selection that does not cause differences at an amino acid level—for instance, balancing selection—cannot be detected by these techniques." (Retrieved 17 June 2024)

[9] http://www.weloennig.de/Staatsexamensarbeit.pdf, https://www.weloennig.de/Artbegriff.html, https://onlinelibrary.wiley.com/doi/10.1002/9780470015902.a0026265 "…losses-of-function mutations are important in regressive evolution, the origin of ecotypes, cultivated plants and animal husbandry. Gene inactivations by TEs have been assumed and in part already detected to be of particular relevance for these areas of research."

[10] https://evolutionnews.org/author/mbehe/

[11] https://www.ensembl.org/Multi/Search/Results?q=%20Ailuropoda%20;site=ensembl;page=1 (19 June 2024) "**222299 results match *Ailuropoda***."
https://www.uniprot.org/uniprotkb?query=Ailuropoda (19 June 2024): *Ailuropoda*: "**54,234 results**"

[12] For example **Li et al 2022**: https://www.sciencedirect.com/science/article/pii/S0888754322002464: "We generated a 2.48-Gb chromosome-level genome (GPv1) of the giant panda named "Jing Jing" with a contig N50 of 28.56 Mb and scaffold N50 of 134.17 Mb, respectively. The total length of chromosomes (n = 21) was 2.39-Gb, accounting for 96.4% of the whole genome. **Compared with the previously published four genomes of the giant panda, our genome is characterized by the highest completeness and the correct sequence orientation**."
"Approximately **841.54 Mb of repetitive elements accounting for 33.61% of GPv1** were identified. Compared with other animals, **LTRs in the giant panda were the most abundant repeat elements, representing 26.98% of the genome**. De novo annotation identified **22,924 high-confidence protein-coding genes (PCGs), of which 92.3% were functionally annotated genes**. Chromosome names of GPv1 were defined by mapping data of individual flow-sorted chromosome to GPv1 and ASM200744v2 (Fig. 1C, Supplementary Figs. S1 and S2). The majority (95.6%) of the mammalian orthologous genes could be found in our genome (Table 1)."

To connect the last statement directly with a physiological characteristic right here: There has been a long discussion and many citations (82 so far up to 21 June 2024 in PubMed[13]) of the paper by Huabin Zhao, Jian-Rong Yang, Huailiang Xu, Jianzhi Zhang (2010) *Pseudogenization of the umami taste receptor gene Tas1r1 in the giant panda coincided with its dietary switch to bamboo*[14].

Their *Abstract* reads as follows (p. 2669):

> "**Although it belongs to the order Carnivora, the giant panda is a vegetarian with 99% of its diet being bamboo**. The draft genome sequence of the giant panda shows that its umami taste receptor gene *Tas1r1* is a pseudogene, prompting the proposal that the loss of the umami perception explains why the giant panda is herbivorous. To test this hypothesis, we sequenced all six exons of *Tas1r1* in another individual of the giant panda and five other carnivores. We found that the open reading frame (ORF) of *Tas1r1* is intact in all these carnivores except the giant panda. **The rate ratio (ω) of nonsynonymous to synonymous substitutions in *Tas1r1* is significantly higher for the giant panda lineage than for other carnivore lineages.**[15] Based on the ω change and the observed number of ORF-disrupting substitutions, we estimated that the functional constraint on the giant panda *Tas1r1* was relaxed ∼ 4.2 Ma, with its 95% confidence interval between 1.3 and 10 Ma. Our estimate matches the approximate date of the giant panda's dietary switch inferred from fossil records. It is probable that the giant panda's decreased reliance on meat resulted in the dispensability of the umami taste, leading to *Tas1r1* pseudogenization, which in turn reinforced its herbivorous life style because of the diminished attraction of returning to meat eating in the absence of *Tas1r1*. **Nonetheless, additional factors are likely involved because herbivores such as cow and horse still retain an intact *Tas1r1*.**"

Concerning their statement: "The rate ratio (ω) of nonsynonymous to synonymous substitutions in *Tas1r1* is significantly higher for the giant panda lineage **than for other carnivore lineages**." Well, – a reader may ask: have we not just read on the previous page the general rule to detect "the past action of positive selection", namely in the words of Nielssen et al. that "an excess of nonsynonymous mutations over synonymous mutations, beyond what would be expected if the two types of mutations occur at the same rate, provides strong evidence for the past action of positive selection at the protein level"? But mind the comparison: "…significantly higher for the giant panda lineage ***than for other carnivore lineages***".

As to the remark: "Nonetheless, additional factors are likely involved because herbivores such as cow and horse still retain an intact *Tas1r1*." So, despite "the observed number of ORF-disrupting substitutions" (including indels[16]), it will be wise not to prematurely conclude that the panda *Tas1r1* has no function at all. See examples by Casey Luskin's literature survey (2024) on 'junk DNA' and 'pseudogenes that are not pseudo any more'[17].

And last not least: "*Although it belongs to the order Carnivora*, the giant panda is a vegetarian with 99% of its diet being bamboo". I have come across many similar comments like "giant pandas are unusual in belonging to a *primarily carnivorous clade* and yet being extremely specialized herbivores that feed almost exclusively on highly fibrous bamboo" (Yonggang Nie et al. 2019)[18], "ancient ancestors of the panda were

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[13] https://pubmed.ncbi.nlm.nih.gov/?linkname=pubmed_pubmed_citedin&from_uid=20573776 (Retrieved 20 June 2024)

[14] https://pubmed.ncbi.nlm.nih.gov/20573776/ and full article here: https://academic.oup.com/mbe/article/27/12/2669/1071261

[15] Another introduction to Synonymous and Nonsynonymous Substitutions by Supratim Choudhuri (2014): https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/nonsynonymous-substitution ("The average rates of synonymous and nonsynonymous substitutions previously calculated were 4.7 substitutions/synonymous site **versus** 0.88 substitutions/nonsynonymous site per 10^9 (billion) years, respectively. This estimate was subsequently revised to ***3.51 substitutions/synonymous site versus 0.74 substitutions/nonsynonymous site*** per 10^9 (billion) years in rodents and humans, as stated earlier in this chapter.")

[16] Zhao et al., p. 2670: "We confirmed the previously reported 2-bp insertion in exon 3 and the 4-bp deletion in exon 6; these indels create multiple premature stop codons such that the resultant *Tas1r1* lacks any of its seven transmembrane domains and is nonfunctional." Now perhaps functional at another level? Some regulatory function? Yan-Zi Wen et al. (2012): "Published evidence has shown that pseudogenes are not only transcribed, but also post-transcriptionally modulate their cognate genes by three distinct mechanisms:(1) natural antisense RNA suppression;(2) RNA interference by producing siRNAs; and (3) acting as decoys of stabilizing or disabling/inhibiting factors (Fig. 1)." https://www.researchgate.net/publication/221759875_Pseudogenes_are_not_pseudo_any_more (full article).

[17] https://evolutionnews.org/2024/05/heres-a-far-from-exhaustive-yet-still-exhausting-list-of-papers-discovering-function-for-junk-dna/ Concerning the exact sequences (genes and amino acids) https://www.uniprot.org/uniprotkb?query=Ailuropoda+TAS1R1 https://www.uniprot.org/uniprotkb/A0A7N5KLM8/entry https://www.uniprot.org/uniprotkb/G1LSY8/entry (retrieved 22 June 2024)

[18] https://www.cell.com/current-biology/fulltext/S0960-9822(19)30395-1

actually carnivorous, ***just as you'd expect from a bear***" (Tom Hale 2019)[19], or "most notably, ***in contrast to all other bears***, the giant panda is herbivorous, with 99% of its diet being bamboo" and "multiple lines of evidence support that the giant panda descended from a carnivorous ancestor" (Huabin Zhao et al. 2010)[20].

> Same authors in same paper, p. 271: "It is possible that ancient giant pandas started to change their diet to bamboo **due to meat scarcity**. Their less reliance on meat may have rendered the umami taste less important, leading to the pseudogenization of *Tas1r1*. The gene loss may have in turn reduced the attraction of returning to meat eating because of the lack of the umami perception."[21]

Problem for all these statements appears to be the fact that – apart from the polar bear, which has no other option – ***all the other bear species are largely vegetarians***: **Up to 90% of their diet consists of plant material** (noted by many different qualified authors[22]):

> (On *Ursus arctos*, the brown bear) "Despite their reputation, most brown bears are not highly carnivorous, as **they derive up to 90% of their dietary food energy from vegetable matter**. Brown bears often feed on a variety of plant life, including berries, grasses, flowers, acorns (*Quercus* ssp.) and pine cones as well as mosses and fungi such as mushrooms. In total, **over 200 plant species have been identified in their foods**. Arguably the most herbivorous diets have come from the warmer temperate parts of Eurasia as more than 90% of the diet may be herbivorous."[23] "Brown bears are omnivores. They feed to **almost 80 percent**[24] on tree bark, leaves, roots, mushrooms, nuts, fruit and berries. Besides plant foods, they are not averse to meat (for example: small rodents, birds, frogs or snakes), fish and carrion.[25]
>
> (*Ursus arctos middendorffi*) "Though Kodiak bears are often touted as the world's largest land carnivore (meat eaters), they are really omnivores (using a variety of foods). **They actually spend more time eating grass, plants and berries than meat**. Fish are an important part of their diets, but few Kodiak bears expend the time or effort necessary to chase and kill mammals. They actually spend more time eating grass, plants and berries than meat." (Larry Van Daele Kodiak Area Wildlife Biologist)[26]
>
> (Black bear, *Ursus americanus*) "***What do bears eat most? Fruit, nuts, honey and other plant parts are favorites of bear***. They also eat Insects and sometimes fish, but most of their food comes from plants. Bears have an excellent sense of smell, and can easily find food using their noses."[27]
>
> (In general) "Bears spend most of their time perusing a patchwork of habitats throughout the year, feeding on vegetation, insects and other more reliable, though lower calorie food sources. Plant foods make up the majority of a bear's diet **– sometimes as much as 90 per cent**."[28]
>
> (*Ursus thibetanus*) "***Asiatic black bears are predominantly vegetarian***, mainly eating grasses, leaves, fruits, berries, nuts, seeds, roots and tubers. To a lesser extent, their diet includes invertebrates, small vertebrates like lizards or rodents, carrion, bee's nests and honey."[29] "Asiatic black bears are omnivorous, feeding on a wide range of plant and animal foods. ***They mostly feed on sedges, grasses, tubers, twig buds, conifer seeds, berries and other fleshy fruits, grains, and mast (i.e., acorns and other hard nuts)***. They also eat insects, especially colonial types such as ants. Because their foods vary greatly in abundance during the year, the bears have a highly seasonal diet."[30]
>
> (*Ursus malayanus/Helarctos malayanus*) "The diet of the Malayan sun bear varies widely and includes ***primarily fruits and vegetables***. They enjoy the young tips of palm trees as well as the sprouts. Their diet also includes honey, nectar from flowers, roots, berries and seeds. They also eat many insects like ants and termites. The Malayan sun bear has an extremely long tongue which he uses to extract food. In addition, they also eat some vertebrates like small mammals and birds."[31]

D. Dwight Davis had already put it in his renowned monograph about THE GIANT PANDA as follows: "*Ailuropoda* is a member of a group (the bear-raccoon line) of carnivores whose diet is more than 50 per cent herbivorous. ***Its closest living relatives (the bears) appear to be more than 90 per cent herbivorous***."[32]

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[19] https://www.iflscience.com/pandas-used-to-eat-meat-then-went-vegetarian-but-now-just-eat-bamboo-51411

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108379/ The quotation continues as follows: "For example, the distribution, structure, and morphology of the lingual papillae in the giant panda are more similar to those of carnivores than herbivores (Pastor et al. 2008). The giant panda also has powerful jaws and teeth that are capable of tearing meat (Bininda-Emonds 2004), a carnivore-like digestive system (Li et al. 2010), and all the genetic components of a digestive system that carnivores possess (Bininda-Emonds 2004; Li et al. 2010)."

[21] They continue: "An alternative scenario is that the giant panda lost *Tas1r1* prior to its change of diet, due to genetic drift in a small population. This scenario appears much less likely because, although the giant panda is endangered today, it may not have had a particularly small population in its evolutionary history. In fact, **the nucleotide diversity of the giant panda is about twice that of humans** and there is no apparent upsurge in the rate of gene loss in the giant panda compared that in other mammals (Li et al. 2010)." (See on the other side Stanley cited in http://www.weloennig.de/PANDA.Part1.pdf)

[22] Quoted either directly **or** referred to/cited in the articles or papers respectively.

[23] https://en.wikipedia.org/wiki/Dietary_biology_of_the_brown_bear (Retrieved 22 June 2024)

[24] Some varying percentages seem to depend on the different food resources.

[25] https://www.four-paws.org/campaigns-topics/topics/help-for-bears/brown-bear-food-feeding-behaviour (Date given on this page: 16.03.2022)

[26] Kodiak Bear Fact Sheet: https://www.adfg.alaska.gov/index.cfm?adfg=brownbear.trivia (Retrieved 22 June 2024)

[27] https://www.maine.gov/ifw/docs/Black%20Bears%20Food%20Chain.pdf (Retrieved 22 June 2024)

[28] https://www.bearsmart.com/about-bears/food-diet/ (Bear expert Kevin Van Tighem) (Retrieved 22 June 2024)

[29] https://www.four-paws.org/campaigns-topics/topics/help-for-bears/asiatic-black-bears

[30] https://www.encyclopedia.com/environment/encyclopedias-almanacs-transcripts-and-maps/asiatic-black-bear

[31] https://www.bearsinmind.org/Uploaded_files/Zelf/helarctos-malayanus-factsheet-eng.edc985.pdf Also: "Sun Bears love termites and ants, but have been known to consume more than 100 species of insects and more than 50 different kinds of plants. **Figs are a favorite Sun Bear treat**. The bears will also eat lizards, turtles and eggs. https://audubonnatureinstitute.org/malayan-sun-bear. And Sethy and Chauhan (2018): "Thus all these dietary compositions showed **that the frequency of occurrence of plant matter was more than the animal matter during all seasons**." (Note by W.-E- L.: Although the percentages of animal matter appear to be higher in sun bears than those of all the other bear species) https://nsojournals.onlinelibrary.wiley.com/doi/full/10.2981/wlb.00351. See perhaps as a kind of summary also: https://www.bioexplorer.net/what-do-bears-eat.html/#What_Do_Bears_Eat

[32] 1964, p. 27. See also Lönnig (2013/2014) https://www.weloennig.de/Hunderassen.Bilder.Word97.pdf pp. 211/212 ff. about the *Ursus arctos middendorfii* and probably **the largest bear** who ever lived: ***Ursus speleus*** (the cave bear) and the somewhat smaller *Ursus deningeri*.

Moreover, Qigao Jiangzuo and John J. Flynn have shown in 2020 that *The Earliest Ursine Bear Demonstrates the Origin of* ***Plant-Dominated*** *Omnivory in Carnivora*: *Aurorarctos tirawa* gen. et sp. nov. from the late Middle Miocene [15–12.5 Ma].

> "Here we propose that special dental characters of Ursinae (parallel buccal and lingual ridges) permit a sagittally oriented mastication associated with increasing emphasis on plant foods. This pattern can be traced back to a new early diverging bear of plant-dominated omnivorous diet, *Aurorarctos tirawa* gen. et sp. nov. from the late Middle Miocene of North America, which was supported as the earliest known ursine bear by phylogenetic analysis."[33]

Thus, all the arguments and discussions starting the origin and evolution of the panda (*Ailuropoda*) from essentially *carnivorous bears* or, more generally formulated, a *carnivorous ancestor*, appear to be doubtful.

> "It is possible that ancient giant pandas started to change their diet to bamboo due to meat scarcity." Since most bears live from plants material up to about 90% (and more) anyway and don't (or hardly) eat meat often for months (Kodiak bear almost only in the fall when the salmon[34] come) – I am not so convinced that meat scarcity could be involved into turning a bear like *Ursus thibetanus* into a panda like animal changing its diet to bamboo – a food source that is not entirely unproblematic in itself.
>
> "Their less reliance on meat may have rendered the umami taste less important, leading to the pseudogenization of *Tas1r1*." Yes, the function of genes that are not necessary anymore might get lost through random mutations. However, is *less* reliance already a sufficient reason to do this? (Problem of incipient phases of evolution.)
>
> "The gene loss may have in turn reduced the attraction of returning to meat eating because of the lack of the umami perception." Well, to respond with an important discovery by the authors themselves, to wit that "additional factors are likely involved because **herbivores such as cow and horse still retain an intact *Tas1r1*.**

I would like to add that such discussions on the *pros* and *cons* of evolutionary possibilities, which can hardly scientifically be tested, ***in no way affect the elaborate work of the excellent/outstanding/superb molecular biology investigations and important results published by the authors cited***.

To sum up the topic of genes involved in and underlying the panda's unique physiological traits I can hardly do better than cite Yisi Hu et al. (2024, pp. 78/79):

> "Comparative genomic analyses also found convergent evolution [in giant and red pandas] and in ***several positively selected genes involved in the digestion and utilization of bamboo nutrients***, including serine protease genes (*PRSS1*, *PRSS36*, and *CPB1*) and several genes related to fatty acid and vitamin utilization (*ADH1C*, *CYP3A5*, *CYP4F2*, and *GIF*). Recent comparative transcriptomics studies comparing both pandas and other non-herbivorous mammals identified convergent ***differentially expressed genes*** related to carbohydrate metabolism, lipid metabolism, and lysine degradation in the liver and pancreas of giant and red pandas. The differential expression of these genes may be governed by convergent differential DNA methylation in promoter regions (86). Similarly, convergent differentially expressed genes and differentially methylated promoters related to nutrient metabolism are also found in the stomach and small intestine of both pandas (87), together acting as adaptive responses to the high-carbohydrate, low-lipid and -lysine bamboo diet at the gene-expression and gene-regulation levels."

Concerning *positively selected genes*, see above please the comments on the evolutionary method applied.

What do We Known About Genes Involved in the Panda's Unique *Morphological* Traits?

The present answer appears to be: Not very much. On the involvement of genes in the development of the radial sesamoid of the red and giant pandas, Hu et al. mention the following points in their review (2024, p. 78):

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[33] Although packaged into a series of evolutionary presuppositions and assigned to a different subfamily (Ursinae/panda Ailuropodinae), the data point to plant-dominated omnivory in this so far **earliest known bear species** according to the geological time table: https://www.cell.com/iscience/pdf/S2589-0042(20)30420-X.pdf Note please some uncertainties in the history of "Systematics: Ever since the giant panda was first described to science, they have been a source of taxonomic confusion, having been **variously classified as a member of Procyonidae, Ursidae, Ailuridae, or even their own family Ailuropodidae**. Part of their similarities with the red panda is in particular the presence of a "thumb" and five fingers; the "thumb" – a modified sesamoid bone – that helps it to hold bamboo while eating. Recent genetic studies have shown that **ailuropodines are indeed members of the bear family** as they are not closely related to red pandas, which are placed in their own family Ailuridae." https://en.wikipedia.org/wiki/Ailuropodinae (Retrieved 25 June 2024). However, there can be hardly any doubt that the other bears of the family Ursidae are the closest living relatives of the panda.

[34] Similarly some grizzly populations when the Karibu calves are born in May/June.

> "Comparative genomics research found that this phenotypic convergence may be driven by genetic convergence of **two genes involved in limb development, *DYNC2H1* and *PCNT***, which are positively selected with convergent amino acid substitutions in both pandas but not in other mammals investigated."

And p. 80:

> "In the giant panda genome, **dual-oxidase 2 (*DUOX2*)**, a gene critical for thyroid hormone synthesis, contains a giant panda–unique single-nucleotide mutation that results in a premature stop and possibly a nonfunctional protein (100). Experiments using gene-edited mice confirmed that the same giant panda–unique point mutation could cause metabolic phenotypes in mice in body size, food intake, physical activity, organ size, serum thyroxine level, daily energy expenditure, and even gut microbiota, demonstrating that this mutation identified by genomic analysis may explain the profound adaptive changes in giant panda (Figure 4)."

Interesting/impressive/captivating as these investigations and results are, all the authors agree, of course, with Rudolf et al. (2021) that this single-nucleotide mutation will most certainly not be sufficient to transform a 'normal' bear into a panda.

Also, Rudolf et al. have stated (2021, p. 1 of PDF) that "homozygous mice were 27% smaller than heterozygous and wild-type ones, had 13% lower body mass-adjusted food intake, 55% decreased physical activity, lower mass of kidneys (11%) and brain (5%)[35], lower serum thyroxine (T4: 36%), decreased absolute (12%) and mass-adjusted (5%) daily energy expenditure, and altered gut microbiota. Supplementation with T4 reversed the effects of the mutation."[36]

Johnson et al. reported in their paper (2007) on *Congenital Hypothyroidism, Dwarfism, and Hearing Impairment Caused by a Missense Mutation in the Mouse Dual Oxidase 2 Gene, **Duox2*** the following:

> "We mapped the new spontaneous mouse mutation to chromosome 2 and identified it as a **T>G base pair change in exon 16 of *Duox2***. The mutation changes a highly conserved valine to glycine at amino acid position 674 (V674G) and was named "thyroid dyshormonogenesis" (symbol thyd) to signify a defect in thyroid hormone synthesis. ***Thyroid glands of mutant mice are goitrous and contain few normal follicles, and anterior pituitaries are dysplastic.*** **Serum T4 in homozygotes is about one-tenth the level of controls and is accompanied by a more than 100-fold increase in TSH**. The weight of adult mutant mice is *approximately half that of littermate controls*, and serum **IGF-I is reduced**. *The **cochleae of mutant mice exhibit abnormalities** characteristic of hypothyroidism, including a delayed formation of the inner sulcus and tunnel of Corti and an abnormally thickened tectorial membrane*. Hearing thresholds of adult mutant mice are on average 50–60 decibels (dB) above those of controls.[37]

So, I would say that these mice are really ill/debilitated/impaired/"kaputt" in clear contrast to *Ailuropoda* (*cf.* again all the stark defects in mice just mentioned above). These mice mutants could never survive and flourish in any natural environment in the wild.

Well, although in the investigations of Rudolf et al. the "supplementation with T4 reversed the effects of the mutation" in their mice, higher serum thyroxine in pandas most certainly/undeniably could ***not*** transform them into a new bear species like *Ursus thibetanus, U. arctos* or *U. malayanus*). Applying the "*Optimal Panda Principle*"[38] here, considering ***the entire panda system*** (including genes involved in their physiological and morphological traits – known and probably additional ones unknown/unidentified at present –, the **radial sesamoid**[39] synorganized into the panda's entire anatomy and behavior for grasping, walking and climbing, not forgetting the panda's significance for major ecological tasks etc. – and, as I put it in PART 1, 'exactly as a far-sighted ingenious genetic engineer would have considered and implemented it on all biological levels') will not be fully explained by the "panda-unique single-nucleotide mutation in the

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[35] *Cf.* also Sienkiewicz et al. (2019): https://www.frontiersin.org/journals/neuroanatomy/articles/10.3389/fnana.2019.00079/full (There further references).

[36] Agata M. Rudolf , Qi Wu, Li Li , Jun Wang, Yi Huang, Jacques Togo, Christopher Liechti, Min Li, Chaoqun Niu, Yonggang Nie, Fuwen Wei, and John R. Speakman (2021): A single nucleotide mutation in the dual-oxidase 2 (*DUOX2*) gene causes some of the panda's unique metabolic phenotypes. National Science Review 9: nwab125, 2021 https://academic.oup.com/nsr/article/9/2/nwab125/6321853 Advance access publication 15 July 2021.

[37] https://academic.oup.com/mend/article/21/7/1593/2738480?l **As for humans**, see https://www.genecards.org/cgi-bin/carddisp.pl?gene=DUOX2 (*cf.* Defects)

[38] Cf. PART 1 https://www.weloennig.de/PANDA.Part1.pdf (p. 24)

[39] Not mentioned in the paper of Rudolf et al. – By the way, would it not be, in fact, a category mistake to equate sick mice in a lab with healthy pandas in the wild?

DUOX2 gene, which is absent in other carnivores, mice and humans. In pandas the mutation involves **substitution of C with T** [7], resulting in **an *Arginine to Termination* codon in the 16th exon of the *DUOX2* gene”** (Rudolf et al. 2021, p. 2).[40]

Rudolf et al. also state (p. 5):

> “….in addition to the *DUOX2* mutation, the ***full metabolic phenotype of giant pandas likely depends on yet-unknown genetic mechanisms affecting T4 to T3 conversion, or TSH levels***. **Other possible mutations** affecting panda metabolic phenotype may include **genomic mitochondrial genes**. Two such mutations have been identified in pandas, one in **cytochrome c oxidase** (***COX***), a rate limiting enzyme of the electron transport chain, and another in ***ATP8*, encoding and affecting posttranslational modification of ATP synthase**. The effects caused by the *Duox2* mutation reported by Johnson *et al.* [also in mice] appear larger than those observed in our mice, including a 90% decrease in T4 levels, versus a 36% decrease in *Duox2*A625T/A625T mice.”

Moreover, applying an extended application of the *Law of Recurrent Variation*[41] here, let’s briefly turn to the question of forward and reverse/back mutations in *Ailuropoda*.

Forward and Reverse Mutations in *Ailuropoda*?

Reverse (or also called) back mutation:

> “The process that causes reversion. ***A change in a nucleotide pair in a mutant gene that restores the original sequence and hence the original phenotype***.”[42]
>
> “**A point mutation can be reversed by another point mutation, in which the *nucleotide is changed back to its original state*** (true reversion).”[43]
>
> “In most of the mutations we have considered so far, a wildtype (normal) gene is changed into a form that results in a mutant phenotype, an event called a forward mutation. ***Mutations are frequently reversible, and an event that restores the wildtype phenotype is called a reversion***. A reversion may result from a reverse mutation, **an exact reversal of the alteration in base sequence that occurred in the original forward mutation, restoring the wildtype DNA sequence**. A reversion may also result from the occurrence, ***at some other site in the genome, of a second mutation that in any of several ways compensates for the effect of the original mutation***. Reversion by the exact reversal mechanism is infrequent. The second-site mechanism is much more common, and a mutation of this kind is called a suppressor mutation.”[44]

Gene level: In the context of the equilibrium frequencies when mutation is reversible, the authors calculated with **1 x 10^{-5} for forward mutations and 1 x 10^{-6} for reverse mutations** (but a word of caution: the values can fluctuate strongly[45]).

Single nucleotide level: “The normal mutation rate is often stated as **$10^{−7}$ to $10^{−8}$ per nucleotide** per cell division.”[46]According to washington.edu/genetics/courses it is “**around $10^{−8}$ mutations per generation and site for DNA**” [47]

> “Mutations are rare events, yet the frequency at which they are introduced into genomes at each generation varies considerably across taxa, **from approximately $10^{−11}$ mutations per site per generation in unicellular eukaryotes up to approximately $10^{−7}$ mutations per site per generation in multicellular eukaryotes.**”[48]

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[40] The authors continue: “It is not yet known whether this premature stop codon results in no translation of the gene or whether a truncated version of the protein is produced that may have biological functions.” Recall please in this context C. Luskin’s literature survey of 2024 on junk DNA – see above.

[41] https://www.weloennig.de/Gesetz_Rekurrente_Variation.html https://www.weloennig.de/Loennig-Long-Version-of-Law-of-Recurrent-Variation.pdf https://www.weloennig.de/ShortVersionofMutationsLawof_2006.pdf

[42] https://www.genscript.com/biology-glossary/8679/back-mutation

[43] https://en.wikipedia.org/wiki/Mutation

[44] Daniel L. Hartl (Harvard University) and Elizabeth W. Jones (Carnegie Mellon University): Genetics: Principles and Analysis. Fourth Edition (1998). Jones and Bartlett Publishers, Sudbury, Mass. (Similarly in more recent editions.) See also S. M. Rosenberg (2013): Reverse Mutation. (“True reversions restore the wild-type gene sequence, whereas pseudoreversions restore the wild-type phenotype by a compensating gene sequence change. Pseudoreversions can occur in the same gene as the original forward mutation or in a different gene or sequence.”) https://www.researchgate.net/publication/323814907_Reverse_Mutation

[45] “**Back mutations 2.5 x 10^{-6} Forward 11.2 x 10^{-6}** If we consider a locus with two possible alleles (A and a)) then we can consider a forward (u) and backward mutation (v). Forward mutation is the mutation from wildtype allele to the detrimental allele. Backward mutations undo the forward mutation. Because there are many ways to destroy the function but fewer ways to undo that harm, backward mutations are normally more rare than forward mutations.” https://depts.washington.edu/genetics/courses/genet453/2001/summaries/summary-jan24.html
“Mutation frequencies for coding genes are typically on the order of 10^{-5} - 10^{-8} per cell per generation, meaning that one may expect a new (recurrent) mutation at a gene to appear every 10^5 - 10^8 individuals; this is too low to change gene (allele) frequencies significantly **unless one considers hundreds to thousands of generations**.” https://agrilife.org/gold/files/2012/08/Lecture-11.pdf https://agrilife.tamu.edu/ Paper: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1451187/ (in Bacteriophage φX174)

[46] https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/mutation-rate

[47] Again: https://depts.washington.edu/genetics/courses/genet453/2001/summaries/summary-jan24.html

[48] Lucie A. Bergeron et al. (2023): Evolution of the germline mutation rate across vertebrates. https://www.nature.com/articles/s41586-023-05752-y (“We show that the per-generation mutation rate varies among species by a factor of 40, with mutation rates being higher for males than for females in mammals and birds, but not in reptiles and fishes.”)

Considering "the earliest ursine bear" *Aurorarctos tirawa* from the Middle Miocene to be 15-12.5 Ma old (see above), and the present numbers of wild bears just in the US and EU as follows:

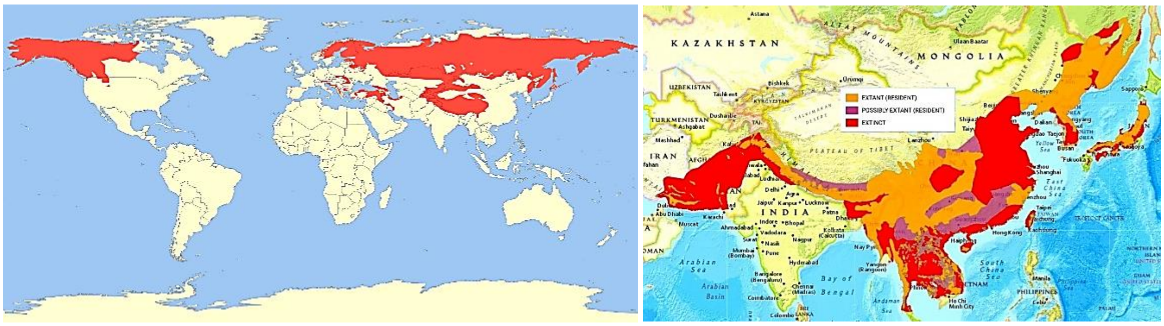
> "Wild bears population size across the US and the EU. The US has **340 000** wild bears (**300 000 Black bears, 33 000 Brown/Grizzly bears, 7 000 Polar bears**). The EU has **15 500 wild bears** (zero Black bears, **15 500 Brown/Grizzly bears**, zero Polar bears). 2008-2022 data USEU [OC].[49]

The IUCN presents of higher numbers of black bears in all of North America:

> "The International Union for Conservation of Nature and Natural Resources (IUCN) lists the black bear as a species of least concern [not endangered]. The species is widespread across North America, and population studies estimate **that some 850,000 to 900,000 black bears** currently live in North America.[50]

Numbers of brown bears (*Ursus arctos*):

> "Brown bears (*Ursus arctos*) were once native to Europe, much of Asia, the Atlas Mountains of Africa, and North America, but are now extirpated in some areas, and their populations have greatly decreased in other areas. There are approximately **200,000 brown bears left in the world**. **The largest population is in Russia, with 120,000 individuals**. The brown bear occupies the largest range of habitats of any *Ursus* species with recorded observations in every temperate northern forest and at elevations as high as 5,000 m."[51]



Left: Brown bear range map (11 December 2010): Additional data here: Wikipedia: https://commons.wikimedia.org/wiki/File:Ursus_arctos_range_map.svg
Right: https://en.wikipedia.org/wiki/Asian_black_bear#/media/File:Asian_black_bear_distribution.jpg

Asiatic black bear (*Ursus thibetanus*):

> "The International Union for Conservation of Nature and Natural Resources classifies the Asiatic black bear as a vulnerable species. The organization notes that, while few rigorous population studies have been conducted, rough estimates suggest that there are **likely fewer than 60,000 animals remaining worldwide**."[52]
>
> "Japan estimates 12,000 to 19,000 animals (as of 2011), Russia estimates 5,000 to 7,000 animals (as of 2006), India also (as of 2007), China even estimates the population at up to 28,000 Asiatic black bears (as of 2006). **Most countries report declining populations due to habitat loss and poaching**."[53]
>
> Pandas (*Ailuropoda*): "According to the last major panda census in 2014, there are at least **1,864 animals in the wild** (excluding dependent cubs under 1.5 years of age).[54]

So, for the time being, let's work with a probably underrepresented number of some 500 000 *Ursus* bears for the last 12 Ma years and a generation time of 7 years: Thus, a bit more than 1.7 million generations.

1 700 000 generations x 500 000 = 850 000 000 000 individual *Ursus* bears
Or in words: **eight hundred fifty billion** bears (in German: **850 Milliarden**)

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[49] https://www.reddit.com/r/dataisbeautiful/comments/zzuewu/wild_bears_population_size_across_the_us_and_the/?rdt=34504#%20:

[50] https://www.britannica.com/animal/black-bear

[51] https://en.wikipedia.org/wiki/Distribution_of_brown_bears (Retrieved 1 July 2024)

[52] https://www.britannica.com/animal/Asiatic-black-bear

[53] https://www.wwf.de/themen-projekte/artenlexikon/kragenbaer Original German text: "Japan gibt 12.000 bis 19.000 Tiere an (Stand 2011), Russland geht von 5.000 bis 7.000 Tieren aus (Stand 2006), Indien ebenfalls (Stand 2007), China schätzt die Population sogar auf bis zu 28.000 Asiatische Schwarzbären (Stand 2006). Die meisten Länder berichten von rückläufigen Populationen aufgrund von Lebensraumverlust und Wilderei."

[54] https://www.wwf.de/themen-projekte/artenlexikon/grosser-panda# "Der letzten großen Panda-Zählung im Jahr 2014 zufolge gibt es mindestens 1.864 Tiere in freier Wildbahn (ohne abhängige Jungtiere unter 1,5 Jahren)."

Now a few calculations according to some numbers presented above by different authors:

(a) Gene level: 1 x 10^{-5} for forward mutations and 1 x 10^{-6} for reverse mutations.
(b) Nucleotide level: around 10^{-8} mutations per generation and site for DNA.
Reverse mutations 10^{-9}.

We have already heard that "in the giant panda genome, dual-oxidase 2 (*DUOX2*), a gene critical for thyroid hormone synthesis, contains a giant panda–unique single-nucleotide mutation that results in a premature stop and possibly a nonfunctional protein" – non-functionality being an open question. And that there is a "panda-unique single-nucleotide mutation in the *DUOX2* gene, which is absent in other carnivores, mice and humans." Moreover: "In pandas the mutation involves **substitution of C with T** [7], resulting in **an *Arginine to Termination* codon in the 16th exon of the *DUOX2* gene**".

In 850 000 000 000 *Ursus* bears this mutation could have happened on the **nucleotide level** (forward mutation): **8 500 times** (10^{-8} x 850 000 000 000)

If reverse mutations occur about a power of ten less frequently (i.e. 10^{-9}) we arrive at a figure of **850 times** back to **C** (if **T** affected bears survived as populations).

On the gene level, the numbers are significantly higher:

Mutations on the ***DUOX2* gene level**: **8 500 000 times** (1 x 10^{-5} x 850 000 000 000)

Reverse mutations (again if such affected bears survived as populations):
850 000 times (1 x 10^{-6} x 850 000 000 000).

This raises the question: So, why do they occur in pandas only and not in other bear species?

Or, to extend the question, considering also mice and humans – not to speak of all the other species outfitted with the ***DUOX2* gene** – the number of such mutations on the nucleotide and gene levels ***runs into the billions***. So, why did they only survive in panda populations? (As far as we know, but perhaps an exceptionally few identical or similar mutations will be discovered in additional organisms with a slow metabolism – like sloths, anteaters, armadillos etc.).[55]

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[55] Some interesting points here: Bahareh Nazari, Vincent Jaquet, Karl-Heinz Krause (2023): NOX family NADPH oxidases in mammals: Evolutionary conservation and isoform-defining sequences ("A search of the ortholog database together with a separate inspection of the NCBI genome viewer showed that **DUOXA1 and DUOXA2 maturation factors were present in all mammals except for the *Ailuropoda melanoleuca*** (giant panda). In this species, the neighboring genes were present and there were no sequencing gaps, but still, there was no sign of the respective DUOXA1 and DUOXA2. In addition, a blast search of unnamed open reading frames in the corresponding chromosomal region did not result in the identification of these maturation factors. Based on this evidence, we considered the possibility that the DUOXA1 and DUOXA2 subunits were absent in the giant panda.
…**The absence of DUOXA1 and DUOXA2 in the giant panda is of great interest**. **Indeed, thyroid hormone levels are extremely low in this species compared to their mammalian norm**. DUOX2 is essential for thyroid hormone synthesis and this specific hypothyroidism has been attributed to the presence of a unique mutation in the DUOX2 gene of the giant panda [24,25]. As DUOXA2 is essential for DUOX2 function [26]-and cannot be complemented by DUOXA1, our findings bring a so far unexplored possibility for the low thyroid hormone levels found in the giant panda.

The reasons for the high conservation of DUOX2 remain enigmatic. With respect to the dehydrogenase domain, there are some indications that the catalytic activity of DUOX2 might not be limited to NADPH, but that it might also metabolize NAADPH [27], which obviously would put a restraint on the sequence flexibility. Within the highly conserved regions of DUOX2, there are also functionally important cysteines: Cysteines 568 and 582 form intermolecular disulfide bonds with cysteines 167 and 233 of DUOXA2, which play a significant role in DUOXA2 stability and function. Cysteine 1162 forms an intramolecular disulfide bond with cysteine 124 and is crucial for DUOX2 function [28].") https://www.sciencedirect.com/science/article/pii/S2213231723002525

Françoise Miot & Xavier De Deken (2023): DUOX1 and DUOX2, DUOXA1 and DUOXA2. (Chapter) ("**DUOX2 and to a lesser extent DUOXA2 genes are frequently mutated and non-functional variants are frequently associated with congenital hypothyroidism**, but with variable penetrance and hypothyroid phenotypes ranging from transient to permanent hypothyroidism and partial to total iodide organification defect. **DUOX1 and 2 are also expressed on epithelial surfaces of the airways, salivary gland ducts and DUOX2 along the gastrointestinal digestive tract**. Associated with lactoperoxidase, **they constitute an efficient host defense mechanism against bacterial and viral infections**. In the gut, DUOX2 is robustly induced to neutralize microbial proliferation and to maintain immune homeostasis. Deleterious variants of DUOX2 associated with congenital hypothyroidism could therefore increase the susceptibility to develop inflammatory bowel disease.") https://link.springer.com/chapter/10.1007/978-3-031-23752-2_14

Generally: "The *DUOX2* gene provides instructions for making an enzyme called dual oxidase 2. This enzyme is found in the thyroid gland, …. The enzyme is also found in salivary glands, the digestive tract, and airways in the throat and lungs. Dual oxidase 2 helps generate … hydrogen peroxide. In the thyroid, **hydrogen peroxide is required for one of the final steps in the production of thyroid hormones**. **Thyroid hormones play an important role in regulating growth, brain development, and the rate of chemical reactions in the body (metabolism)**." https://medlineplus.gov/genetics/gene/duox2/

So, why does "the substitution of C with T, resulting in an Arginine to Termination codon in the 16th exon of the *DUOX2* gene" occur in the pandas only and not also in any of the other bears (or in any other species – as far as we know)?

Although at present I cannot exclude here some originally irrelevant losses of functions[56] in the genome of *Ailuropoda*, considering the entire panda system (**see above and Part 1**) the termination codon in the 16th exon of the *DUOX2* gene is most probably not simply a pointless accident, a coincidence, a random event, but rather belongs to the integral part and parcel of the overall ingeniously designed sum total of the panda system, the panda arrangement or panda organization, on all its biological levels, summed up in the *Optimal Panda Principle*.

Snapshot from brief panda film by W.-E. L. through thick pane of glass (Zoo Rhenen, The Netherlands 5 June 2024)

Time and again the theory of intelligent design has been proven to be scientifically much more fertile than neo-Darwinism because it first looks carefully for biological functions thus avoiding a premature rush to the conclusion to any unproven biological non-functionalities[57] – as the latter has often been practiced by many evolutionists.

Hence, according to the *Optimal Panda Principle* the C with T substitution in the *DUOX2* gene has been fine-tuned from the outset/from the start/from the very beginning into and coordinated with the entire optimal panda system.

This hypothesis can either be falsified (no functions at all) or further corroborated (functions will be found).

Of course, more research is needed to answer such still open scientific questions.

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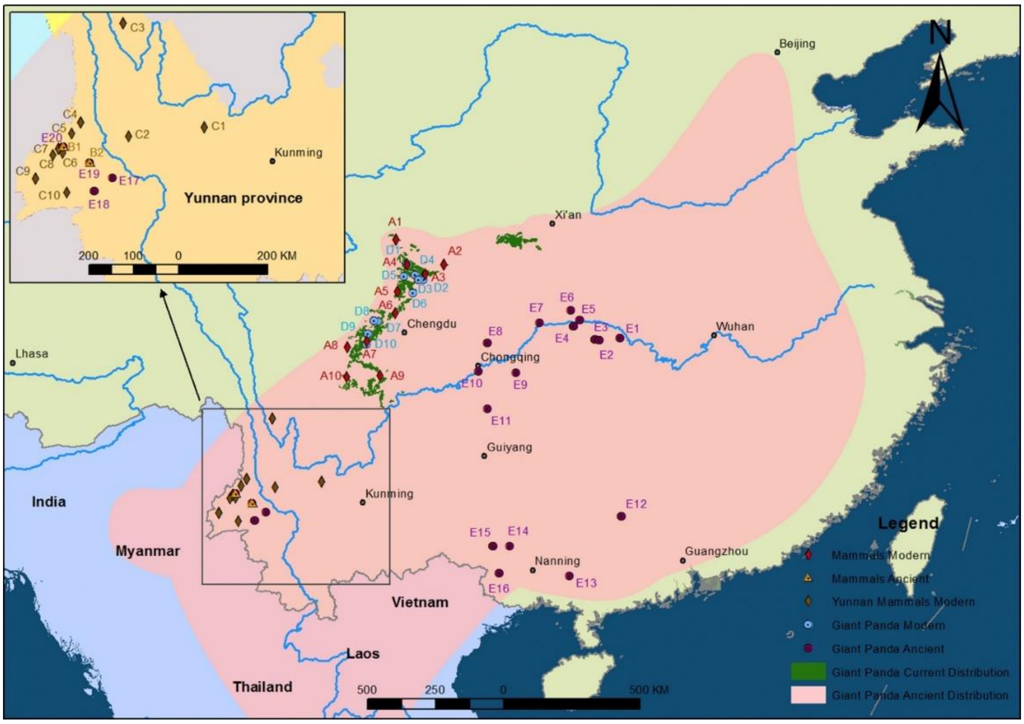
[56] See https://www.weloennig.de/Artbegriff.html especially on the topic of https://www.weloennig.de/AesV1.1.Dege.html (DEGENERATION IM ORGANISMENREICH). The points mentioned by Rudolf et al. (2021) that "pandas have smaller brains, kidneys and livers compared to other large mammals, which may also contribute to their low metabolic rates [7,8]. In addition, they have low levels of thyroid hormones thyroxine (T4) and triiodothyronine (T3), which average ~50% and~60%, respectively, of that expected for similar sized mammals [8]." Well, there us, of course, also an enormous variation of these parameters in similar sized mammals – in pandas all their special features could be understood to be necessary/combined/integrated parts of the entire *Optimal Panda Principle* considering not just isolated organs (like the radial sesamoid especially), but carefully ***all the different aspects of the panda's biology*** (see details in Part 1 https://www.weloennig.de/PANDA.Part1.pdf)

[57] See please again the footnote above with links to the topic of "junk DNA" ("Published evidence has shown that pseudogenes are not only transcribed, but also post-transcriptionally modulate their cognate genes by three distinct mechanisms: (1) natural antisense RNA suppression; (2) RNA interference by producing siRNAs; and (3) acting as decoys of stabilizing or disabling/inhibiting factors.") In this context I would like to remind the reader of the objection of the two PhD students also mentioned in PART 1 (again: https://www.weloennig.de/PANDA.Part1.pdf) See also: https://www.weloennig.de/Kidney1x.pdf

Now let's apply our probability calculations for forward and reverse mutations also on *Ailuropoda* itself. The time scale given for *Ailuropoda* fossils is 2.588 to 0.781Ma according to PBDB (see Table below), but for the panda *Ailurarctos* up to 8 Ma.

The panda's geographical present and former distribution has been discussed in detail by Han et al. (2019)[58] including the Late Miocene panda *Ailurarctos lufengensis*:



Above: Figure 1. by Han et al. 2021: "The Distribution of Ancient and Modern Giant Pandas and Sampling Sites in this Study: Ancient pandas (pink) occupied different habitats over southern, central, and northwestern China that extended as far north as Beijing and as far south as Myanmar, northern Vietnam, Laos, and Thailand. Modern pandas (green) only occupy forest habitats in Sichuan, Shaanxi, and Gansu provinces in China. Th combinations of numbers and letters were used to represent all selected sample locations for pandas and sympatric fauna. A1–AX, modern mammal samples; B1–BX, ancient mammal samples; C1–CX, modern Yunnan mammal samples; D1–DX, modern giant panda samples; E1–EX, ancient giant panda samples."

Below: "An artist reconstruction of *Ailurarctos* from Shuitangba. The grasping function of its false thumb (shown in the right individual) has reached to the level of modern pandas, whereas the radial sesamoid may have protruded slightly more than its modern counterpart during walking (seen in the left individual). Art by Mauricio Antón." https://commons.wikimedia.org/wiki/File:Ailurarctos_paleoart.webp

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[58] https://www.sciencedirect.com/science/article/pii/S0960982219300041#bib7

From a geneticist's point of view, the usually slight anatomical differences detected so far[59] between *Ailurarctos* and *Ailuropoda* could be due to Mendelian recombination and also be affected by classic modifications[60] within "the *Ailurarctos-Ailuropoda* lineage" (term by Wang et al. 2022). On the dental pattern, for example, the authors remark:

> "Within ursids, dental patterns in ailuropodines are some of the most elaborate, with numerous, highly distinct crown cuspules advantageous for crushing tough bamboo, i.e., durophagous mastication. These features are associated with a robust mandible28 and lateral movements of the temporomandibular joint29. It is evident that **the dental pattern of *Ailurarctos* has reached the level of complexity of modern *Ailuropoda***, as recognized by Qiu and Qi. In fact, **the degree of enamel crenulation on most M2s of *Ailurarctos* is even greater than in *Ailuropoda*.** If it is accepted that the robust cuspation in *Ailuropoda* is linked to a bamboo diet, dental specializations in *Ailurarctos* strongly suggest both an ancestral relationship to *Ailuropoda* as well as a diet including bamboo."

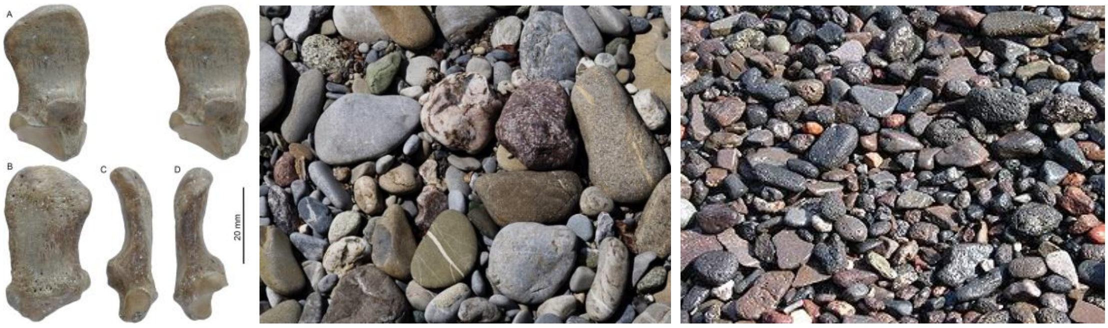
Considering this complexity of the dental pattern and taking into account the incomplete fossil record, I would hardly be surprised when further paleontological research also detected an *Ailurarctos*-like animal with a small hook at the end of its radial sesamoid.

Also, it would be most interesting to decipher the genetical basis of that slight hook in *Ailuropoda*.

Moreover, one may also recall in this context the question[61] whether the neo-Darwinian explanation of ***1 thousandth of 1 mm longer hook in each generation*** would really constitute decisive selective advantages for the survival of panda populations?[62]

One may also ask how it was possible for *Ailurarctos* to grasp and handle bamboo obviously so very successfully for many generations (as also the dental pattern suggests) without that hook at the end of the radial sesamoid? And if this worked so well for long periods of time, why was and additional hook necessary at all?

Incidentally, some of the fossils depicted by Wang et al. appear to me to look somewhat rounded – a bit like gravel and pebbles, whose outer edges have been rounded by water. My question: Could some slight modifications of such fossils have occurred during the last 7 Ma?[63]



Left: *Ailurarctos* left radial sesamoid fossil: *Ailurarctos* cf. *A. lufengensis*, ZT-2015–0056, left radial sesamoid, (**A**) left lateral (in stereo), (**B**)medial, (**C**) proximal, and (**D**) distal views. https://en.wikipedia.org/wiki/Ailurarctos
Middle: https://en.wikipedia.org/wiki/Gravel#/media/File:Gravel_on_a_beach_in_Thirasia,_Santorini,_Greece.jpg
Right: https://upload.wikimedia.org/wikipedia/commons/0/0a/Bodenacker_-_Aare_-_Kieselsteine.jpg

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[59] "…an enlarged radial sesamoid, as well as an isolated M2, a broken canine, and a partial humerus"
The authors also note that "The fact that there was no further elongation of the false thumb in the panda lineage after the late Miocene, suggests that an adequate grip for bamboo had been obtained, i.e., good enough for grasping a single stem or small bundle, and that further enlargement was inhibited by countervailing selection for weight-bearing and walking (Fig. 8). We caution, however, that **the fossil record is too incomplete** to allow a full understanding of this process and future discoveries will likely reveal unforeseen details."

[60] See in this context perhaps https://www.weloennig.de/KidneyEvolution.pdf (2023), https://www.weloennig.de/Hippo.pdf "modifications" (2023), https://www.weloennig.de/Artbegriff.html (especially https://www.weloennig.de/Artbegriff.html) (2001)

[61] https://www.weloennig.de/PANDA.Part1.pdf

[62] See also https://www.weloennig.de/OmnipotentImpotentNaturalSelection.pdf

[63] Jablonski et al. (2014): "Shuitangba [where the fossils were found] is an open-pit lignite mine located in the Zhaotong Basin of northeastern Yunnan (Fig. 1), one of many coal-bearing basins of the western South China fold belt (Wang et al., 1998). The fossil-bearing Neogene Zhaotong Formation of Shuitangba accumulated at a margin of a sub-basin within the Zhaotong Basin. Three superposed lignite beds typify the Zhaotong Formation (Dai and Chou, 2007), but at Shuitangba the youngest lignite is absent and **the 23-m section includes layers of water-lain silt, clay, gravel, and lignite** (Fig. 2). Vertebrate fossils occur only in fine, dark-colored clays intercalated between layers of lignite."
https://www.researchgate.net/publication/265606160_The_Site_of_Shuitangba_Yunnan_China_Preserves_A_Unique_Terminal_Miocene_Fauna#pf2
Consider please that generally "fossils have often somewhat been deformed … during and following the process of fossilization, among the factors are differences in soil structure (physicochemical environment) and moreover, earth movements in the millions of years here stipulated for these fossils (hurricanes, typhoons, and cyclones, fires, floods and earthquakes)." https://www.weloennig.de/Hippo.pdf

For the following calculations I am treating the two genera of the *Ailurarctos-Ailuropoda* lineage **as a single unit** applying the ***genetical species concept*** (considering Mendelian populations, modifications, gender, differences due to DNA variation *within* species and genera regarding the length of bones and further structures, the effects of fluctuating environmental factors on the phenotypes, as well as the closely related topics of biocoenosis[64], the ecosystem[65], and behavior[66] ***with the yardstick of the often enormous variation within extant species***):

Calculating with 7 Ma from the Miocene to the present, a generation time of 7 years, populations consisting of about say about 40 000 individuals (as an educated guess[67]) for most of the time, let's work now with 1 million generations:

(1) some 40 000 panda bears per generation
(2) for the last 7 Ma years and
(3) a generation time of 7 years

1 000 000 generations x 40 000 = 40 000 000 000 individual panda, or in words:
40 billion panda bears (in German: 40 Milliarden Pandabären) (a most pleasant idea).

Now first the **Gene level** for the *DUOX2* gene:
Forward mutations: (a) 1 x 10^{-5}
40 000 000 000 x 1 x 10^{-5} = 400 000
Reverse mutations: (b) 1 x 10^{-6}
40 000 000 000 x 1 x 10^{-6} = 40 000

Nucleotide level: around 10^{-8} mutations per generation and site for DNA
Forward mutations: (a) 1 x 10^{-8}
40 000 000 000 x 1 x 10^{-8} = 400
Reverse mutations (b)10^{-9}
40 000 000 000 x 1 x 10^{-9} = 40

So, one may ask what happened to all these mutations – at least those affecting the phenotype – considering not only the *DUOX2* gene but the entire panda genome? The answer was already given by Nobel Laureate Muller and is still all the more valid today:

> Hermann J. Muller, founder of mutation genetics and winner of the "Nobel Prize in Physiology or Medicine" in 1946, summed up the broad range of aspects and implications of mutation research in his Nobel Lecture on "The Production of Mutations". … One key point on mutations in general certainly was his inference that due to the fact that "***the great majority of the changes should be harmful in their effects, just as any alterations made blindly in a complicated apparatus are usually detrimental to its proper functioning, many of the larger changes should even be totally incompatible with the functioning of the whole, or, as we say, lethal***". Hence, concerning medical aspects he later emphasized that "it becomes an obligation for radiologists - though one far too little observed as yet in most countries – to insist that the simple precautions are taken which are necessary for shielding the gonads, whenever people are exposed to such radiation, either in industry or in medical practice"[68]

Another excellent geneticist compared almost all mutants affecting the phenotype to a certain degree to the brief existence of soap bubbles:

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[64] The "community of biologically integrated and interdependent plants and animals" https://www.collinsdictionary.com/de/worterbuch/englisch/biocenosis

[65] "All the living things in an area and the way they affect each other and the environment" https://dictionary.cambridge.org/dictionary/english/ecosystem#google_vignette
"A biological system composed of all the organisms found in a particular physical environment, interacting with it and with each other. Also in extended use: a complex system resembling this." https://www.oed.com/dictionary/ecosystem_n?tl=true

[66] "…a meta-analysis of scientific literature states that "behavior is the internally coordinated responses (actions or inactions) of whole living organisms (individuals or groups) to internal or external stimuli" … A broader definition of behavior, applicable to plants and other organisms, is similar to the concept of phenotypic plasticity. It describes behavior as a response to an event or environment change during the course of the lifetime of an individual, differing from other physiological or biochemical changes that occur more rapidly, and excluding changes that are a result of development (ontogeny).[4][5] …Behaviour can be regarded as any action of an organism that changes its relationship to its environment. Behavior provides outputs from the organism to the environment." https://en.wikipedia.org/wiki/Behavior (retrieved 7 July 2024)

[67] Taking into account the former large geographical distribution of the pandas and its drastically reduced area in recent times (see Han et al. 2021) this number may also be too low/underrepresented and the real number could have been much higher.

[68] https://www.weloennig.de/Loennig-Long-Version-of-Law-of-Recurrent-Variation.pdf

> “If you let the greatest experimenter of all, namely nature, speak, you also get a clear and irrefutable answer to the question of the significance of mutants for the formation of species and for evolution. ***They disappear under the competitive conditions of natural selection, like soap bubbles bursting in the wind. Just as these can only live a short and fragile life when there is no wind, mutants can only have a visible life course under the nurturing care of culture***. This seems to be the real and complete secret of mutability.”[69]

However, as for pandas there appears to be an important exception to this rule: The brown-and-white Qinling panda (subspecies *Ailuropoda melanoleuca qinlingensis*) as compared to the panda bears of *Ailuropoda melanoleuca* we have studied so far. The Qinling panda is a **classic example of a loss of function mutation**[70], which may have occurred around 400 000 times in the history of pandas, for:

> “…the mutability is just as old as the gene, because an instability can hardly appear suddenly. The apparently new mutations are not new; they are truly immemorial, as old as the mother species itself; they have appeared many times in the history of the species but have disappeared again.”[71]

But why has the loss of function mutation in the ***Bace2*** gene survived in the Qinling panda? Answer so far: “This subspecies is restricted to the Qinling Mountains, at elevations of 1,300–3,000 metres (4,300–9,800 ft). *Its coloration is possibly a consequence of inbreeding*: as the population is closed off from genetic variation and this might have led to the preservation of the mutation responsible.”[72]

Left: The Qinling panda https://commons.wikimedia.org/wiki/File:Qinling_panda.jpg [presently about 200-300 of these pandas in the wild]
Right: https://commons.wikimedia.org/wiki/File:Atlanta_Zoo_Panda.jpg

In their abstract Dengfeng Guan et al. say about this captivating discovery (2024)[73]:

> “**Brown-and-white giant pandas** (hereafter brown pandas) are distinct coat color mutants found **exclusively in the Qinling Mountains, Shaanxi, China**. However, its genetic mechanism has remained unclear since their discovery in 1985. Here, we identified the genetic basis for this coat color variation using a combination of field ecological data, population genomic data, and a CRISPR–Cas9 knockout mouse model. We de novo assembled a long-read-based giant panda genome and resequenced the genomes of 35 giant pandas, **including two brown pandas and two family trios associated with a brown panda**. **We identified a homozygous 25-bp deletion in the first exon of *Bace2*, a gene encoding amyloid precursor protein cleaving enzyme, as the most likely genetic basis for brown-and-white coat color**. This deletion was further validated using PCR and Sanger sequencing of another 192 black giant pandas and CRISPR-Cas9 edited knockout mice. Our investigation revealed that this mutation reduced the number and size of melanosomes of the hairs in knockout mice and possibly in the brown panda, further leading to the hypopigmentation. These findings provide unique insights into the genetic basis of coat color variation in wild animals.”

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[69] Heribert Nilsson (1953, pp. 174/175, similarly p. 1158): Synthetische Artbildung. 1303 pp. Original German Text stating the general rule as follows: „Wenn man den unbedingt größten Experimentator, nämlich die Natur, sprechen lässt, erhält man auch eine klare und unwiderlegbare Antwort auf die Frage nach der Bedeutung der Mutanten für die Artbildung und für die Evolution. Sie verschwinden unter den Konkurrenzverhältnissen der Naturselektion, wie Seifenblasen im Winde zerplatzen. Wie diese nur bei Windstille ein kurzes und fragiles Leben fristen können, so kann auch den Mutanten nur unter der erhaltenden Pflege der Kultur ein sichtbarer Lebenslauf zuteil werden. Das scheint das wirkliche und ganze Geheimnis der Mutabilität zu sein.“ More on the present situation see the links on the Law of Recurrent Variation above.

[70] See again: https://www.weloennig.de/Staatsexamensarbeit.pdf, https://www.weloennig.de/Artbegriff.html, https://onlinelibrary.wiley.com/doi/10.1002/9780470015902.a0026265 “…losses-of-function mutations are important in regressive evolution, the origin of ecotypes, cultivated plants and animal husbandry. Gene inactivations by TEs have been assumed and in part already detected to be of particular relevance for these areas of research.” And especially https://evolutionnews.org/author/mbehe/ https://evolutionnews.org/2019/03/lessons-from-polar-bear-studies/ https://evolutionnews.org/2010/12/the_first_rule_of_adaptive_evo/

[71] Geneticist H. Nilsson p. 1151. Emphasis in the typeface by Nilsson.

[72] https://en.wikipedia.org/wiki/Qinling_panda (retrieved 9 July 2024). For coat color mutants in dogs *cf.* https://www.weloennig.de/Hunderassen.Bilder.Word97.pdf pp.76ff.

[73] Dengfeng Guan, Shuyan Sun, Lingyun Song, , and Fuwen Wei (2024): Taking a color photo: A homozygous 25-bp deletion in Bace2 may cause brown-and-white coat color in giant pandas. https://www.pnas.org/doi/10.1073/pnas.2317430121 https://en.wikipedia.org/wiki/Qinling_panda (retrieved 8 July 2024): “It differs from the more familiar nominate subspecies by its smaller skull and dark brown and light brown (rather than black and white) fur, and its smaller overall size.”

Constancy (Stasis) *of* and *in* the Subfamily Ailuropodinae to Which the Pandas Belong (Family Ursidae)

According to the Paleobiology Database (PBDB) 4 July 2024:

"Age range: Maximum range based **only on fossils**: base of the Serravallian to the top of the Late/Upper Pleistocene or 13.82000 to 0.01170 Ma Minimum age of oldest fossil (stem group age): 12.5 Ma" [74]

Collections (101 total)

Time interval	Ma	Country or state	Original ID and collection number
Miocene	23.03 - 5.333	USA (Nevada)	Agriotherium sp. (18841)
Barstovian	16.3 - 12.5	USA (Oregon)	Indarctos oregonensis (210633)
Barstovian - Clarendonian	16.3 - 9.4	USA (Nebraska)	Indarctos sp. (230906)
Serravallian	13.82 - 11.62	Moldova (Chișinău)	Indarctos vireti (210536)
Tortonian	11.62 - 7.246	China (Yunnan)	Indarctos sp., Indarctos sinensis (11798)
Tortonian	11.62 - 7.246	USA (Florida)	Agriotherium schneideri (18505)
Tortonian	11.62 - 7.246	Germany (Bavaria)	Kretzoiarctos beatrix (206345)
Tortonian - Zanclean	11.62 - 3.6	Ethiopia	Agriotherium sp. (22139)
Vallesian	11.608 - 8.7	Spain (Zaragoza)	Kretzoiarctos beatrix (35876)
Late/Upper Miocene	11.608 - 5.333	Turkey (Usak)	Indarctos sp. (34462)
Late/Upper Miocene	11.608 - 5.333	Algeria	Indarctos arctoides (34642)
Late/Upper Miocene	11.608 - 5.333	Turkey	Indarctos arctoides (56563)
Late/Upper Miocene	11.608 - 5.333	Bulgaria	Agriarctos nikolovi (231920)
Late/Upper Miocene	11.608 - 5.333	China (Gansu)	Agriotherium inexpetans (34694)
Late/Upper Miocene - Zanclean	11.608 - 3.6	Uganda	Agriotherium aecuatorialis (230937)
MN 9	11.1 - 9.7	Hungary (Borsod-Abaúj-Zemplén)	Miomaci pannonicum (75481)
Hemphillian	10.3 - 4.9	USA (Oregon)	Indarctos oregonensis (18935 18936 19015)
Hemphillian	10.3 - 4.9	USA (Nevada)	Indarctos nevadensis (19101) Indarctos sp. (18974 19057)
Hemphillian	10.3 - 4.9	USA (Florida)	Indarctos sp. (18581 18601)
Hemphillian	10.3 - 4.9	USA (Nebraska)	Agriotherium sp. (18439) Indarctos oregonensis (18086)
Hemphillian	10.3 - 4.9	Mexico (Guanajuato)	Agriotherium schneideri (18718)
Hemphillian	10.3 - 4.9	USA (Texas)	Agriotherium coffeyorum (18097) Indarctos sp. (18072 18198)
Hemphillian	10.3 - 4.9	USA (Kansas)	Agriotherium schneideri (210284) Agriotherium sp. (18140 18241)
Hemphillian	10.3 - 4.9	Mexico (Jalisco)	Agriotherium schneideri (18745 189788 189790)
Hemphillian	10.3 - 4.9	USA (California)	Agriotherium sp. (19446) Indarctos sp. (19448)
Hemphillian	10.3 - 4.9	Mexico (Hidalgo)	Agriotherium schneideri (212307) Agriotherium sp. (18746)
Hemphillian	10.3 - 4.9	USA (Oklahoma)	Agriotherium sp. (18304)
Hemphillian	10.3 - 4.9	USA (Arizona)	Agriotherium sp. (19272) Indarctos sp. (18933)
Late/Upper Hemphillian	10.3 - 4.9	Mexico (Guanajuato)	Agriotherium schneideri (18713 18737 18740)
Late/Upper Hemphillian	10.3 - 4.9	Mexico (Chihuahua)	Agriotherium schneideri (18734 18755)
Late/Upper Hemphillian	10.3 - 4.9	USA (California)	Agriotherium sp. (19306 19604) Hyaenarctos gregoryi (19445)
Late/Upper Hemphillian	10.3 - 4.9	USA (Texas)	Agriotherium sp. (18036)

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[74] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=104008&is_real_user=1

MN 10	9.7 - 8.7	Turkey (Thrace)	Indarctos arctoides (67661)
Turolian	8.7 - 5.333	Spain (Valencia)	Agriotherium roblesi (40758)
Turolian	8.7 - 5.333	Kazakhstan	Indarctos sp. (34436)
Turolian	8.7 - 5.333	China (Gansu)	Indarctos atticus (42676)
Turolian	8.7 - 5.333	China (Yunnan)	Indarctos sp. (44222 44223 44224) Indarctos sp., Indarctos sinensis (44220)
Messinian	7.246 - 5.333	Libya	Agriotherium sp. (102370) Indarctos sp. (102369)
Messinian	7.246 - 5.333	Greece	Indarctos atticus (95691)
Messinian - Piacenzian	7.246 - 2.588	South Africa (Cape)	Agriotherium africanum (59167)
Early/Lower Pliocene	5.333 - 3.6	Bulgaria (Yambol)	Agriotherium sivalensis (184410)
Zanclean	5.333 - 3.6	South Africa	Agriotherium africanum (22221 22222)
Zanclean	5.333 - 3.6	Ethiopia	Agriotherium sp. (22160)
Zanclean	5.333 - 3.6	Libya	Agriotherium sp., Indarctos sp. (102372)
Ruscinian	5.333 - 3.2	China (Shanxi)	Agriotherium sp. (42273)
Blancan	4.9 - 1.8	USA (Idaho)	Agriotherium schneideri (93106)
Blancan	4.9 - 1.8	Mexico (Hidalgo)	Agriotherium schneideri (20079)
MN 15	4.2 - 3.2	Poland	Agriotherium intermedium (33396)
MN 15 - MN 16	4.2 - 2.588	Ukraine	Agriotherium sp. (50943)
Late/Upper Pliocene	3.6 - 2.588	China (Guangxi)	Ailuropoda microta (73636)
Late/Upper Pliocene	3.6 - 2.588	South Africa (Langebaanweg)	Agriotherium africanum (21713)
Late/Upper Pliocene	3.6 - 2.588	Greece (Grevena)	Agriotherium sp. (185859)
Early/Lower Pleistocene	2.588 - 0.781	China (Anhui)	Ailuropoda microta (68380)
Early/Lower Pleistocene	2.588 - 0.781	China (Guangxi)	Ailuropoda microta (230325)
Early/Lower Pleistocene	2.588 - 0.781	China (Hunan)	Ailuropoda melanoleuca (36819)
Early/Lower Pleistocene	2.588 - 0.781	China (Guangxi Zhuang Autonomous Region)	Ailuropoda wulingshanensis (214689)
Early/Lower Pleistocene - Middle Pleistocene	2.588 - 0.129	China (Sichuan)	Aeluropus fovealis (226365)
Pleistocene	2.588 - 0.0117	Myanmar (Mandalay)	Aelureidopus baconi (168038)
Pleistocene	2.588 - 0.0117	China (Jiangxi)	Ailuropoda sp. (35923)
Middle Pleistocene	0.774 - 0.129	China (Guangdong)	Ailuropoda melanoleuca (120834) Ailuropoda sp. (40341)
Middle Pleistocene	0.774 - 0.129	Vietnam (Lang Son)	Ailuropoda melanoleuca (92781)
Middle Pleistocene	0.774 - 0.129	China (Guangxi)	Ailuropoda melanoleuca (38649)
Middle Pleistocene	0.774 - 0.129	China (Guizhou)	Ailuropoda melanoleuca (51100)
Middle Pleistocene	0.774 - 0.129	China (Hubei)	Ailuropoda wulingshanensis (234753)
Middle Pleistocene	0.774 - 0.129	Vietnam	Ailuropoda melanoleuca (108001)
Middle Pleistocene - Late/Upper Pleistocene	0.774 - 0.0117	China (Guangdong)	Ailuropoda melanoleuca (13293)

So far the data of the fossil record including the age determinations according to the present time scale of the geological record[75] of the genera *Aelureidopus*, *Aeluropus*, *Agriarctos*, *Agriotherium*, *Ailuropoda*, *Indarctos*, *Kretzoiarctos*, *Miomaci*. **To be added** to this Table are the genera *Ailurarctos* (Late Miocene: ca. 8 Ma[76]) and *Huracan* ("10.30000 to 1.80000 Ma")[77].

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[75] https://stratigraphy.org/ICSchart/ChronostratChart2021-05.pdf and https://stratigraphy.org/ICSchart/ChronostratChart2023-09.pdf (I have also checked the time scales back to 1937: many astonishing differences (would have been interesting back to say 1900) – see Harland et al. 1990: A geologic time scale. Cambridge University Press. There especially Fig 1.5. Comparison of earlier time scales with GTS 89. And Fig. 1.6 shows the "Deviations from 1989 Time Scale". – Is presently interpreted as scientific progress.)

[76] https://paleobiodb.org/classic/basicTaxonInfo?taxon_no=txn:374801

[77] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=470226&is_real_user=1 ("…hypercarnivorous in dental features")

Constancy (Stasis) in:

Aelureidopus (Woodward 1915) Synonym for *Ailuropoda*:

“**Maximum range** based only on fossils: base of the Late/Upper Pliocene to the top of the Late/Upper Pleistocene or **3.60000 to 0.01170 Ma**. Minimum age of oldest fossil (stem group age): 2.588 Ma”[78]

Aeluropus (Milne-Edwards 1871) Again: Synonym for *Ailuropoda*

Ailuropoda: See above. Total: 21 collections each including a single occurrence.

Ailurarctos: “Late Miocene of China, some 8 million years ago.”[79]

Agriarctos: Collections: Only one.

“Age range: Late/Upper Miocene or **11.60800 to 5.33300 Ma**”[80]

Agriotherium: Collections: 30 total (each including a single occurrence).

“Age range: base of the Messinian to the top of the MN 15 or **7.24600 to 3.20000 Ma**”[81]

Indarctos: Collections: 30 total (including 32 occurrences).

“Age range: base of the Serravallian to the top of the Hemphillian or **13.82000 to 4.90000 Ma**”[82]

Kretzoiarctos: Collections: 2 total (each including a single occurrence).

“Age range: Vallesian or **11.60800 to 8.70000 Ma**”[83]

Miomaci: Collections: Only one.

“Age range: MN 9 or **11.10000 to 9.70000 Ma**”[84]

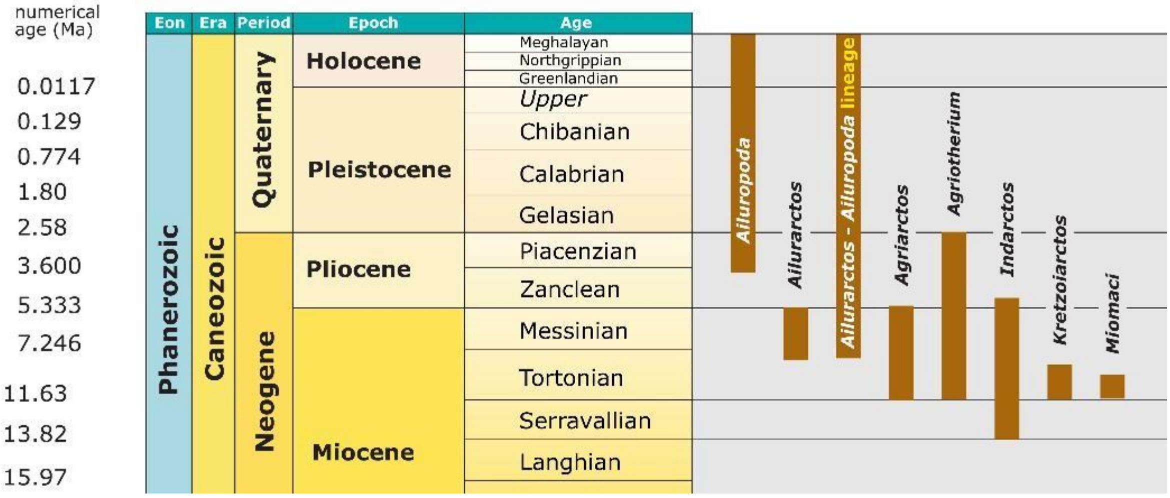

Figure by Roland Slowik, Dietzenbach (Germany) for the present article (15 July 2024)

Concerning the origin of these genera, I am going to mention the ensuing options, which I have discussed in depth in many articles and several books:

(1) ***Mendelian Recombination***: A topic that has largely been underrated especially by many paleontologists. See the potential of Mendelian recombination in *Der Genetische Artbgriff*: https://www.weloennig.de/AesIV3.html, fertile hybrids between different bear genera and between

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[78] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=41304&is_real_user=1

[79] https://en.wikipedia.org/wiki/Ailurarctos (There 4 literature references) (retrievd 10 July 2024)

[80] https://paleobiodb.org/classic/basicTaxonInfo?taxon_no=txn:104010

[81] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=41303&is_real_user=1 (Possibly earlier: https://zh.mindat.org/paleo_collection.php?col=18841 speaks of “**23.03** - 5.333 Ma (Miocene)” And Late/Upper Pliocene South Africa (Langebaanweg) and Greece (Grevena) “3.6 – **2.599**”.)

[82] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=41315&is_real_user=1

[83] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=374798&is_real_user=1

[84] https://paleobiodb.org/classic/checkTaxonInfo?taxon_no=105133&is_real_user=1

(All PBDB references retrieved 9 July 2024) genera of some other organisms https://www.weloennig.de/AesIV3.Fr.html. *Cf.* also just the skull size and form of several dog races in https://www.weloennig.de/Hunderassen.Bilder.Word97.pdf on pp. 40 and 41. However, *Ailuropoda* and further pandas like *Ailurarctos* displaying all their ***totally new*** and basically distinguishing characteristics (considering not only the ingeniously designed dual-functioning front paws for walking and grasping "with the dexterity of a Swiss watch maker" – key word: **radial sesamoid** –, but also the entire panda system summed up in the *Optimal Panda Principle* – most probably speaking for ID) – appear so suddenly in the fossil record that for the time being I tentatively tend to assume the potential of Mendelian recombination only within and possibly also between the panda genera *Ailurarctos* (granted that the fossil record is imperfect and they met each other) and *Ailuropoda* and within its species (*A. melanoleuca*, *A. microta*, *A. wulingshanensis*).[85] So Mendelian recombination (**often due to loss of function alleles**) can explain variation within giant pandas, but for their ultimate origin ID is necessary.

(2) Evolution by a ***steady input of new information***: "There must have been a steady input of new information which we have ascribed to the activity of Creative Intelligence" (Edmund Jack Ambrose, Professor of Cell Biology).[86] This proposal could be subsumed under the topic of *Theistic Evolution*.

(3) ***Preordained evolution/front-loaded evolution***: atheistic/naturalistic: For example, Professor of Biochemistry Christian Schwabe: *The Genomic Potential Hypothesis*[87]. And theistic: Denis Lamoureux, Professor of Science and Religion: *Evolutionary Creation*[88]. Also, the entire group of scientists working for *BioLogos* (founded by Francis Collins, "one of the top biologists in the world" *cf.* https://biologos.org/about-us). Cannot convincingly explain the panda's origin.

(4) ***Intelligent Design*** – just to remind my readers on the topic of intelligent design by a few brief excerpts from some of my previous articles:

> Now, if one is prepared to break away from the prohibition of materialistic philosophy, one could, for example, accept the following reasoning – in part according to Austrian cell physiologist Siegfried Strugger (professor of botany at the University of Münster): "The cell is the most perfect cybernetic system on earth [usually consisting of thousands of spatiotemporally precisely matched gene functions, gene interactions, cascades and pathways in a steady-state network of ingeniously complex physiological processes characterized by specified as well as (often) irreducible complexity including an abundance of information at least to the gigabyte to terabyte range]. In comparison to the cell, all automation of human technology is only a primitive beginning of man in principle to arrive at a biotechnology."
>
> Well, if the first steps on the way/the path to the ingenious level of cybernetic complexities of the cell, i.e. the "primitive beginning" in Strugger's formulation, demands conscious action, imagination, perception, intelligence, wisdom, mental concepts, spirit and mind – all being already absolutely necessary for the basic start, – so how much more so does this have to apply to the origin of the thousand times more complex cybernetic systems of the life forms themselves – including all the specified and irreducibly complex structures inescapably necessary for the origin of man.[89]
>
> "The theory of intelligent design holds that certain features of the universe and of living things are best explained by an intelligent cause, not an undirected process such as natural selection" (Meyer); ID is usually recognized by "a purposeful arrangement of parts" (Behe), ***the pandas show brilliant, ingenious artwork***, **not the work** of an endless number of infinitesimally small coincidences haphazardly chained together by the "truly hideous process" of natural selection, being "rife with happenstance, contingency, incredible waste, death, pain and horror" etc.).
>
> So, I would apply this line of reasoning also to the origin of pandas – as well as this conclusion: **an absolutely ingenious artist was at work here, transcending all human abilities, ideas and power**.[90]
>
> Exactly/precisely/definitely when, where and how are questions which have to be further investigated.

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[85] The proposal to put Giant Pandas in an independent family may be interesting in this context: DONG Wei and ZHANG Juefei, Paleontologists from Institute of Vertebrate Paleontology and Paleoanthropology (IVPP), Chinese Academy of Sciences, published the following suggestion (2011): *Cranial Endocasts Supporting Giant Pandas Evolved As an Independent Family* https://english.cas.cn/newsroom/archive/research_archive/rp2011/201502/t20150217_143508.shtml. – D. D. Davis 1964, p 182: "*Ailuropoda* differs from the bears, and apparently from all other carnivores, in the distinctness of the two heads of the brachialis."

[86] https://www.weloennig.de/AesIV4.html (Cell biologist: Admund Jack Ambrose (1982): The Nature and Origin of the Biological World. Chichester; similarly 1990: The Mirror of Creation)

[87] Published by Landes Bioscience (Routledge). Georgetown, Texas (2001). – Best summed up in the atheistic https://rationalwiki.org/wiki/Christian_Schwabe as follows: "Schwabe rejects common descent and his hypothesis is that all species on earth have an independent but natural origin from chemical pools of nucleic acids." Species are constant/unchanging.
I once invited him to give a lecture at the Max Planck Institute for Pant Breeding Research (Cologne) – which he did.

[88] The Lutterworth Press. Cambridge UK (2009). *Cf.* discussion by Stephen C. Meyer (2021, pp. 279-298): Return of the God Hypothesis. HarperOne. New York.("God organized the big bang, so that the deck was stacked" – as cited by Meyer 2021, p. 282).

[89] https://www.weloennig.de/HumanEvolution.pdf

[90] https://www.weloennig.de/Hummingbirds.pdf

Checking Google and Amazon: See more on the theory of intelligent design in the articles and books by scientists like Douglas Axe, Günter Bechly, Michael J. Behe, David Berlinski, Tom Bethell, Stuart Burgess, William A. Dembski, Michael Denton, Marcos Eberlin, Phillip E. Johnson, David Klinghoffer, Matti Leisola, Wolf Ekkehard Lönnig, Casey Luskin, Stephen C. Meyer, J. P. Moreland et al. (eds.), Paul Nelson, Walter James ReMine, John C. Sanford, Siegfried Scherer, Granville Sewell, David W. Swift, James Tour, Jonathan Wells, and many, many others – *cf*. see the authors at https://evolutionnews.org/ as well as a large part of the scientists at https://www.discovery.org/m/securepdfs/2021/07/Scientific-Dissent-from-Darwinism-List-07152021.pdf (2021).

As for the topic of the *Panda's Thumb*, many more points could be discussed, for example *Bamboo Is Basically 'Fake Meat' for Giant Pandas*[91], [moreover the issue of *orphan genes*[92]] as well as applying Jakob von Uexküll's theories on the panda[93], and perhaps also the large topic of vitalism[94].

Concerning the basic question for the two articles *The Panda's Thumb: Striking Imperfection Or Masterpiece of Engineering?* I would like to point the reader's attention to a statement by professor Stuart Burgess (email 4 April 2024 to W.-E. L.[95]):

"Because evolution predicts bad design, they [the evolutionists] impose their view of bad design despite the evidence."

As emphasized above: The panda [being a masterpiece of engineering] also shows brilliant, ingenious artwork.

Pandas Lei Lei and Xiao Xiao
https://commons.wikimedia.org/wiki/File:Ailuropoda_melanoleuca_Lei_Lei_Xiao_Xiao_220610g.jpg
10 June 2022, Ueno Zoo, Tokio

Back to Internet Library

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[91] Jason Daley (2019): https://www.smithsonianmag.com/smart-news/bamboo-fake-meat-giant-pandas-180972101/ There literature references. https://www.sciencedirect.com/science/article/pii/S0960982219303951#

[92] See footnote above.

[93] http://www.zbi.ee/uexkull/publik.htm

[94] Daniel Witt (2024): https://evolutionnews.org/2024/05/is-vitalism-making-a-comeback/ From a theological/Biblical point of view *cf.* for instance Psalm 104: 29 – 31.

[95] Quoted with his permission 15 July 2024