Genome assembly of the tayra (*Eira barbara*, Mustelidae) and comparative genomic analysis reveal adaptive genetic variation in the subfamily Guloninae

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Abstract

Species of the mustelid subfamily Guloninae inhabit diverse habitats on multiple continents, and occupy a variety of ecological niches. They differ in feeding ecologies, reproductive strategies and morphological adaptations. To identify candidate loci associated with adaptations to their respective environments, we generated a *de novo* assembly of the tayra (*Eira barbara)*, the earliest diverging species in the subfamily, and compared this with the genomes available for the wolverine (*Gulo gulo*) and the sable (*Martes zibellina*). Our comparative genomic analyses included searching for signs of positive selection, examining changes in gene family sizes, as well as searching for species-specific structural variants (SVs). Among candidate loci that appear to be associated with phenotypic traits, we observed many genes related to diet, body condition and reproduction. For the tayra, which has an atypical gulonine reproductive strategy of aseasonal breeding, we observe species-specific changes in many pregnancy-related genes. For the wolverine, a circumpolar hypercarnivore that must cope with seasonal food scarcity, we observed many specific changes in genes associated with diet and body condition. Despite restricting some of our analyses to single-copy orthologs present in all three study species, we observed many candidate loci that may be linked to species traits related to environment-specific challenges in their respective habitats.

Introduction

The Mustelidae are the most ecologically and taxonomically diverse family within the mammalian order Carnivora, representing a remarkable example of adaptive radiation among mammals that is rich with recent speciation events (Koepfli et al. 2008; Liu et al. 2020). Closely related mustelid species often inhabit vastly different ecosystems, where they experience diverse environmental challenges and are thus exposed to different evolutionary pressures. This is particularly pronounced in the mustelid subfamily Guloninae, within which species occupy a variety of ecological niches, ranging from scansorial omnivores in the neotropics to terrestrial hypercarnivores in circumpolar regions. Members of the Guloninae display a range of behavioural and physiological adaptations associated with environment-specific resource availability, and consequently differ markedly in feeding ecology, reproductive strategy and morphology (Zhou et al. 2011; Heldstab et al. 2018). Here, we focus on tayra, wolverine and sable (Figure 1), for which genomic resources are now available.

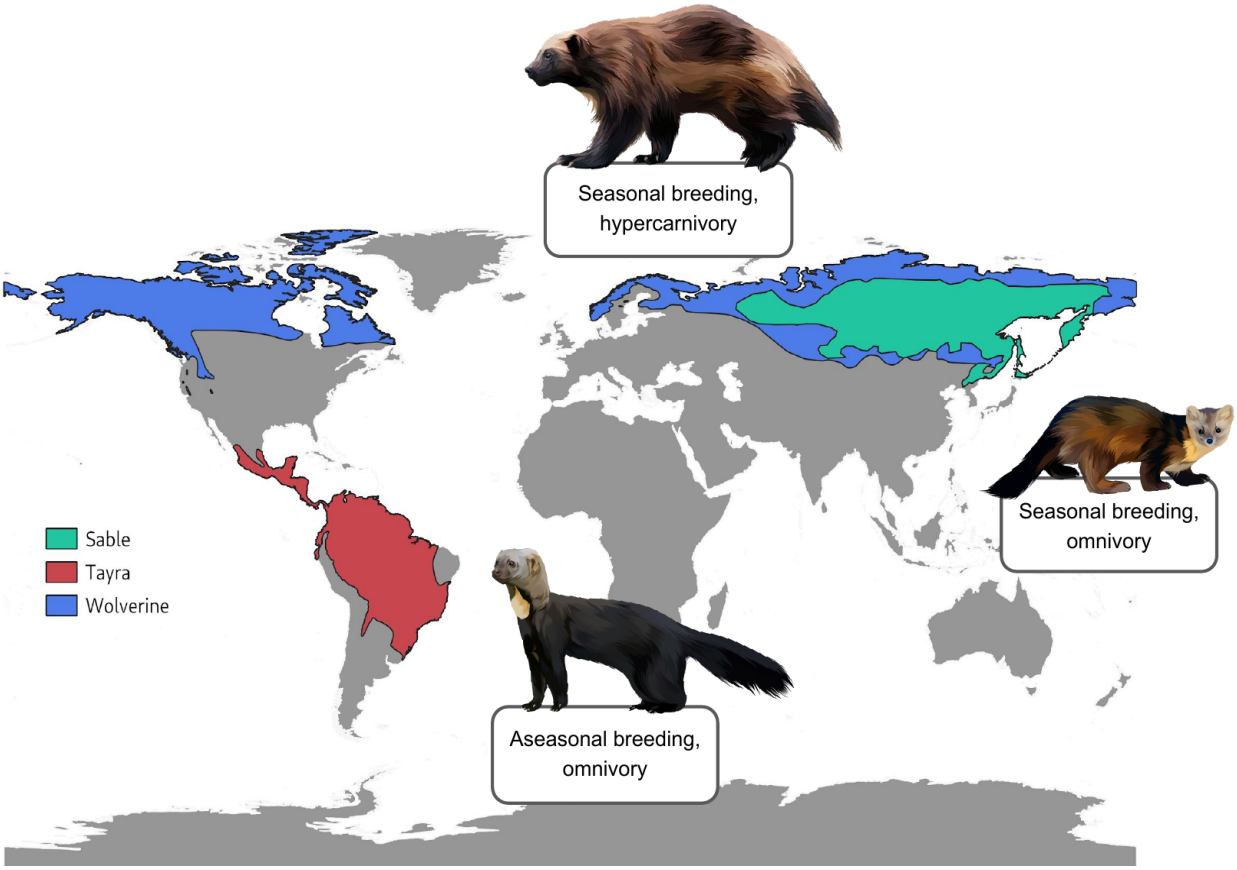

Figure 1. Distribution and species-specific traits of the tayra (*Eira barbara*), wolverine (*Gulo gulo*), and sable (*Martes zibellina*). Vector graphics of species are created based on royalty-free images (source: Shutterstock).

The tayra (*Eira barbara)* is a predominantly diurnal, solitary species that inhabits tropical and subtropical forests of Central and South America, ranging from Mexico to northern Argentina (Wilson and Mittermeier 2009). It is a scansorial, opportunistic omnivore, feeding on fruits, small mammals, birds, reptiles, invertebrates and carrion. Caching of unripe fruit for later consumption has been observed (Soley and Alvarado-Díaz 2011). Unlike other gulonine species, which are characterized by seasonal breeding and embryonic diapause, the tayra is an aseasonal polyestrous breeder and does not exhibit delayed implantation (Proulx and Aubry 2017), which may be due to the less prominent seasonality and fluctuation in food availability in neotropical habitats (Heldstab et al. 2018).

The largest terrestrial mustelid, the wolverine (*Gulo gulo)*, is a circumpolar species, inhabiting alpine and boreal zones across North America and Eurasia (Ekblom et al. 2018). The wolverine is an opportunistic predator and facultative scavenger, either

feeding on carrion or actively hunting medium to large-sized mammals, such as roe deer, wild sheep and occasionally moose (Pasitschniak-Arts and Larivière 1995). Morphological and behavioural adaptations such as dense fur, plantigrade locomotion facilitating movement through deep snow, and food caching, enable wolverines to survive in cold habitats with limited food resources (Copeland and Kucera 1997). In addition, wolverines occupy large home ranges, display territoriality, seasonal breeding and delayed implantation, traits indicating an adaptive response necessary for survival in scarce resource environments (Inman et al. 2012).

The sable (*Martes zibellina)* is distributed in the taiga and deciduous forests of north central and north eastern Eurasia. The sable is solitary and omnivorous, relying on hearing and olfaction to locate prey, even under a snow cover during winter months (Monakhov 2011; Liu et al. 2020). Unlike wolverines, seasonal changes do not cause dramatic fluctuations in resource availability for sables as they are able to exploit a wider variety of food sources, and are adapted to tolerate short-term food scarcity (Mustonen et al. 2006). Their diet consists of small mammals, birds, nuts and berries, and in some instances food caching during the winter period has been reported (Monakhov 2011). Similar to wolverines and many other species of mustelids, sables have a well-defined reproductive season and exhibit delayed blastocyst implantation (Proulx and Aubry 2017).

To date, only a few studies have investigated adaptive variation in mustelids using comparative genomics (Abduriyim et al. 2019; Beichman et al. 2019; Liu et al. 2020; Miranda et al. 2021). Here, we generated a highly contiguous genome assembly of the tayra, an early diverging gulonine (Koepfli et al. 2008; Law et al. 2018), and compared it to previously published genomes of the wolverine and sable to identify the genetic basis underlying the adaptations to the diverse environments inhabited by these species.

In addition to identifying genes under positive selection, we investigated gene family evolution and structural variants (SVs), as these types of variants represent a significant source of intra- and interspecific genomic differentiation, affecting more nucleotides than single-nucleotide polymorphisms (SNPs) (1000 Genomes Project Consortium et al. 2015; Catanach et al. 2019). Gene copy number variation and large SVs can be associated with an adaptive response to new ecological circumstances (e.g. diet in brown and polar bears (Rinker et al. 2019), and are thus an important source of genomic novelty to consider when studying adaptive divergence among species (Hecker et al. 2019). Interpretation of our results focuses on candidate loci linked to species-specific traits related to environment-specific challenges associated with resource availability in the respective habitats in each of the three species.

Results

Genome Assembly

Using the 10x Genomics Chromium linked-read technology (Weisenfeld et al. 2017), we generated the first highly contiguous reference genome assembly for *Eira barbara* from genomic DNA obtained from a captive male tayra. The linked-read technology leverages long-range genomic information while maintaining the advantages of short-read sequencing on Illumina platforms (Armstrong et al. 2019). The extracted genomic DNA had an average molecule size of 50.75 kb and was sequenced at ~76-fold coverage (SI Table S1). The final assembly showed a total length of ~2.44 Gb (excluding scaffolds shorter than 5 kb), with a contig N50 size of 290 kb and a scaffold N50 size of 42.1 Mb. Whole genome alignment between tayra and domestic ferret assemblies shows identity in 95% of all positions (SI Figure S1). The tayra assembly has higher contiguity than the Illumina-only based assemblies of both wolverine and sable, but it is more fragmented than the chromosome-length domestic ferret (*Mustela putorius furo)* assembly we used as reference genome (Table 1, SI Figure S2A). The haploid genome size of ~2.4 Gb is contained in 162 scaffolds (>100 kb) with 40 scaffolds having lengths above 50 Mb (SI Figure S2A).

The tayra assembly has high gene completeness as assessed with BUSCO v4.1.2 using 9226 conserved mammalian orthologs (Simão et al. 2015). In total, 8540 (92.5%) complete Benchmarking Universal Single-Copy Orthologs (BUSCOs) were identified, encompassing 8492 (92.0%) of complete and single-copy, and 48 (0.5%) complete and duplicated orthologs. Additionally, 104 (1.1%) orthologs were fragmented and 582 (6.4%) were missing. As measured by this metric, the presented tayra genome has higher gene completeness than the published genomes of wolverine, sable or domestic ferret (SI Figure S2B).

Table 1. Comparison of genome assembly metrics among four mustelid species.

Species	Tayra (*Eira barbara*)	Domestic ferret (*M. putorius furo*)	Sable (*Martes zibellina*)	Wolverine (*Gulo gulo*)
Assembly Accession/ reference	JAHRIG000000000 (This study)	DNA Zoo (Dudchenko et al. 2018; Dudchenko et al. 2017; Peng et al. 2014)	GCA_012583365.1 (Liu et al. 2020)	GCA_900006375.2 (Ekblom et al. 2018)
Sequencing/ assembly approach	Illumina + 10xGenomics/ Supernova	Illumina/ ALLPATHS-LG + Hi-C scaffolding	Illumina/ SOAPdenovo2	Illumina/ SOAPdenovo
Raw coverage	75.6x	162x	114.5x	76x
Contig N50	289.9 kb	44.7 kb	41.7 kb	3.6 kb
Scaffold N50	42.0 Mb	145.3 Mb	5.2 Mb	0.2 Mb
Number of scaffolds	14,579	7,428	15,814	47,417
Total genome length	2.44 Gb	2.40 Gb	2.42 Gb	2.42 Gb

Repetitive elements

The ‘repeat landscape’ of the tayra assembly contains ~0.85 Gb of repetitive elements (SI Table S2). L1 type LINE elements are the most abundant, constituting 23% of the tayra genome. L1 elements also show signs of recent proliferation in comparison to DNA transposons and LTR retroelements (SI Figure S3). Endogenous retroviruses constitute 3.8% of the tayra genome and can be classified as Gammaretroviruses and Betaretroviruses.

The overall ‘repeat landscape’ of the tayra genome assembly is comparable to other carnivore genomes (C. Peng et al. 2018; G. Liu et al. 2020). It is similar to that of the sable genome, differing mostly in the number of L1 LINE elements, which have been recently proliferating and accumulating within the tayra genome more than in other Guloninae genomes. The diversity of endogenous retroviruses is similar to other mustelids. Although endogenous delta-retroviruses have been described from a broad

range of mammal genomes, including several smaller carnivores like mongoose (family Herpestidae) and the fossa (*Cryptoprocta ferox*) (Hron et al. 2019), no delta-retroviruses were found in the genome of tayra.

Demographic reconstruction

The reconstruction of historical demography from whole genome data for tayra and sable using the Pairwise Sequentially Markovian Coalescent model (PSMC; Li and Durbin 2011) showed similar effective population sizes (Ne) during the last one million years of the Pleistocene, but started to differ around twenty thousand years ago, when the Ne of the sable increased compared with that of the tayra (SI Figure S4). PSMC analysis for the wolverine genome was in agreement with a previous study (Ekblom et al. 2018), also displaying low Ne. Similarly, low Ne was previously observed in the African cheetah genome, also characterized by very low genetic diversity (Dobrynin et al. 2015).

Nucleotide diversity

The tayra, sable and wolverine assemblies were generated using different approaches and differ significantly in contiguity (Table 1). To address this issue, we generated pseudochromosome assemblies for each species using the chromosome-length assembly of the domestic ferret as reference. The domestic ferret has more chromosomes than the other species analyzed (2n=40 vs. 2n=38), and the same number (20) of pseudochromosomes (Lewin et al. 2019) were obtained after scaffolding in each case. For each assembly, we identified the X chromosome (labeled as *ps_chrX*) and arranged pseudoautosomes (labeled as *ps_aut1 - ps_aut19*) according to the length of the original scaffolds in the domestic ferret reference. This allowed us to verify the sex of the animals using a coverage-based approach (SI Figure S5), which confirmed morphological sexing for the tayra (male) and wolverine (female) individuals.

Surprisingly, we found a discrepancy between the results of our genome-based sexing for sable and the original results published with the sable genome (Liu et al. 2020). There, the sable individual is referred to as a male, our analysis suggests it is a female. Its *ps_chrX* had uniform full (relative) coverage (0.75x - 1.25x relative to median whole genome coverage, SI Figure S5B), similar to the wolverine individual (SI Figure S5C). In contrast, we observed a clearly visible pseudoautosomal region (PAR) in the male tayra individual (SI Figure S5A), which had full (relative) coverage, whereas the rest of

ps_chrX had half coverage. Additional verification using the SRY protein gene sequence as a Y-specific marker confirmed this result. The orthologous full-length CDS of SRY (Supplementary files 1 and 2) was detected only in the tayra assembly, while only partial hits with low similarity were observed in the two other assemblies. This provides evidence that the sable individual is not male but female, and also neither XXY (Klinefelter syndrome in humans; Wikström and Dunkel 2011) nor XX with translocation of the SRY locus to the X chromosome (de la Chapelle syndrome in humans; De la Chapelle et al. 1972).

We counted heterozygous SNPs in 1 Mbp stacking windows for all three species and scaled it to SNPs per kbp (Figure 2). Median values for tayra, sable and wolverine were 1.89, 1.44 and 0.28 SNPs per kbp, respectively, the latter being in agreement with previous findings (Ekblom et al. 2018). All scaffolds of $\geq$ 1 Mbp in pseudochromosome assemblies were taken into account. Exclusion of ps_chrX resulted in slight increases of medians to 1.93, 1.47 and 0.29, respectively (SI Table S3, SI Figure S6). The finding of similar patterns in the male tayra and the female sable and wolverine is explained by two different facts. First, in males most of the X chromosome is hemizygous, and heterozygous variants in this region arise from artefacts of alignment and variant calling. Second, in females the X chromosome is diploid, but diversity in the same region of X chromosome that is hemizygous in males, is lower than in autosomes (A) even if the X/A ratio in the population is taken into account (Kondo and Ueda 2013). The PAR demonstrates the opposite pattern, but it is too short to significantly affect mean and median values (Filatov and Gerrard 2003). Regardless of whether the ps_chrX was included or excluded, the genome-wide diversities among the three species were significantly different (p-values $<< 0.001$, Mann-Whitney test).

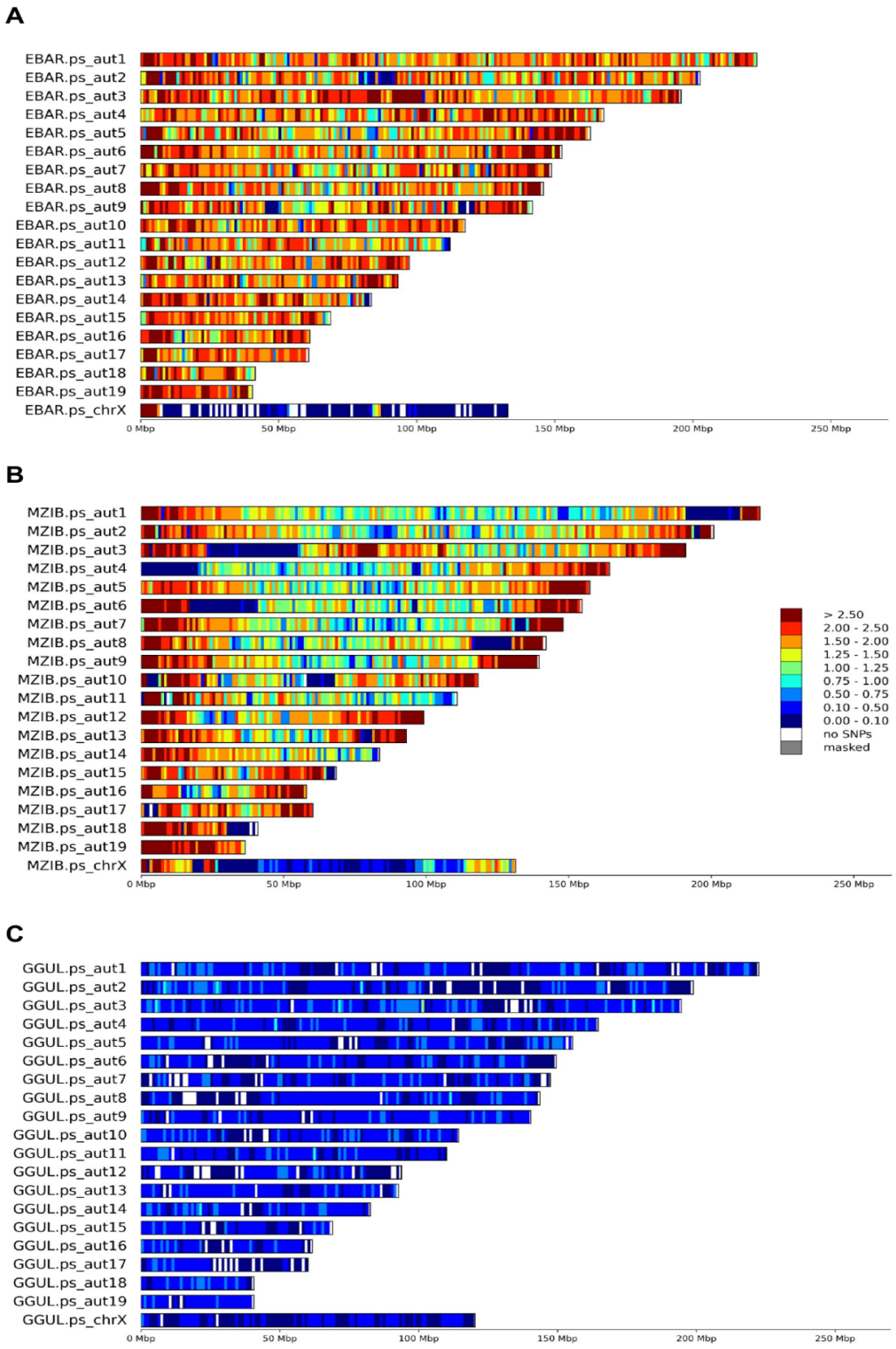

Figure 2. Heterozygosity density among pseudochromosomes for (A) tayra, (B) sable and (C) wolverine. Heterozygous SNPs were counted in stacking windows of 1 Mbp and scaled to SNPs per kbp. Tayra is a

male individual and thus heterozygous SNP density is underestimated (due to only one X chromosome), while sable and wolverine are females and therefore likely representative of true SNP density.

Phylogenomics and molecular dating

We reconstructed the phylogenetic relationships using single-copy orthologous genes from the BUSCO genome completeness analysis for assemblies of the following carnivoran species: domestic cat, domestic dog, walrus, northern elephant seal, domestic ferret, wolverine, sable, and tayra. Sequence alignment, cleaning and model adequacy assessment led to a phylogenomic data set with 2457 gene regions comprising over 3.2 million nucleotide sites. Phylogenomic analyses using concatenation and summary coalescent methods led to an identical resolution of the relationships among mustelid taxa. Within Guloninae, the wolverine and sable were placed as sisters, to the exclusion of the tayra (Figure 3). Branch supports were maximal across all branches using both approximate likelihood-ratio test (aLRT) and local posterior probabilities. Similarly, concordance factors (CF) for genes and sites (gCF, sCF) were high across branches and consistently more than twice as high as the values of the discordance factors (gDF, sDF). The lowest concordance factors were those in support of the resolution of *Gulo* and *Martes* as sisters (gCF = 64.52, sCF = 54.38). However, the discordance factors were less than half these values (gDF < 14, sCF < 24), suggesting substantial decisiveness across genes and sites for this resolution.

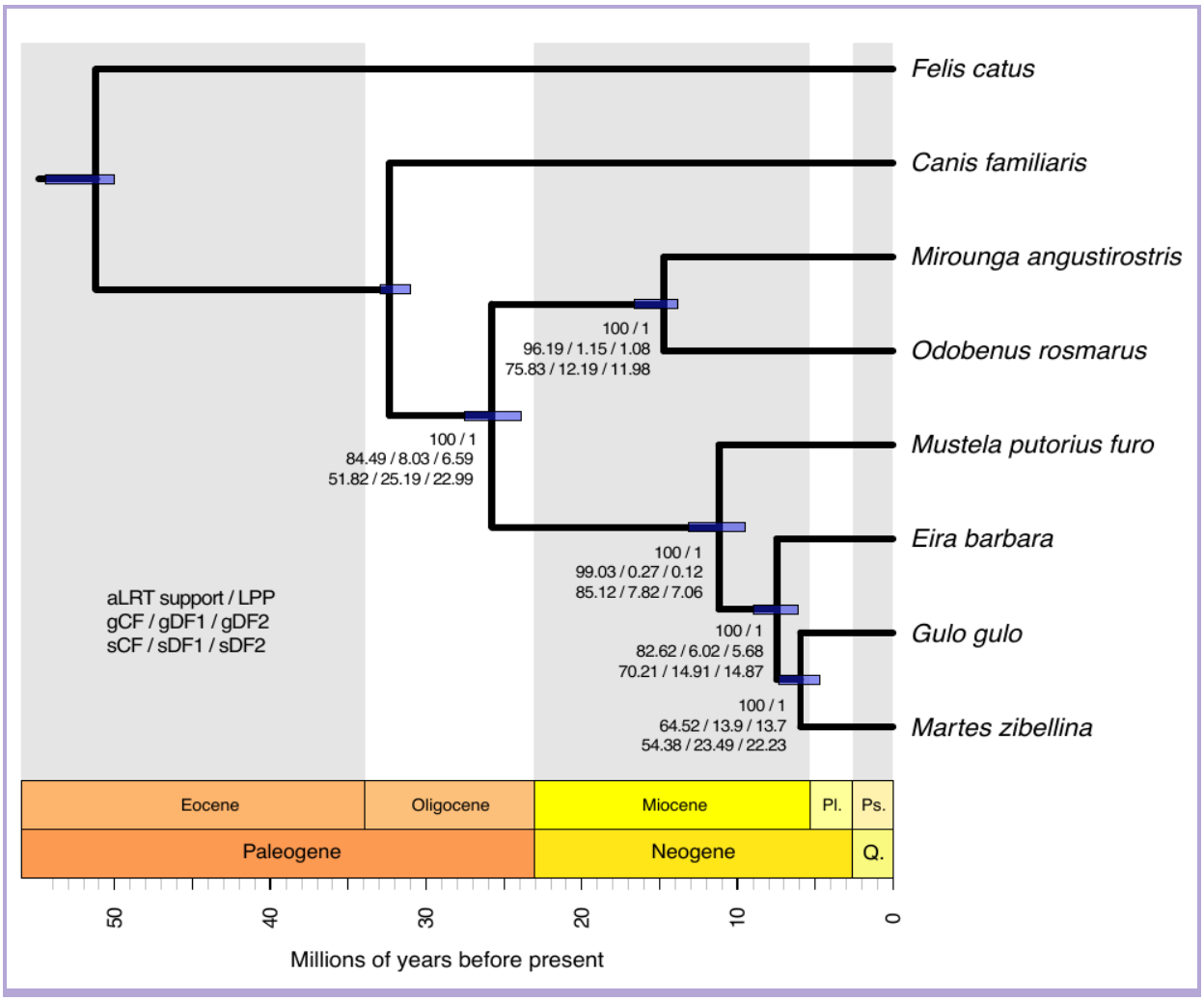

Figure 3. Phylogenetic tree and divergence times of Guloninae and five other carnivorans. The mean age of each node is shown, with 95% confidence intervals depicted as purple bars. The gene and site concordance (gCF, sCF) and discordance (gDF, sDF) factors are given, along with the branch support for both approximate likelihood-ratio test (aLRT) and local posterior probabilities (LPP).

Molecular dating was performed using 992 single-copy orthologous gene regions (comprising 0.53 million sites). Divergence time estimates across mustelids were largely in agreement with previous findings (Koepfli et al. 2008; Sato et al. 2012; Li et al. 2014; Law et al. 2018), placing the split between *Mustela* and Guloninae at 11.2 million years ago (Mya) (highest posterior density interval (HPDI) between 13.1 and 9.5 Mya), and the split between *Eira* and the *Gulo-Martes* group at 7.5 Mya (HPDI between 9 and 6.1 Mya). The split between *Gulo* and *Martes* was dated at 5.9 Mya (HPDI between 7.4 and 4.7 Mya).

Positive selection on single-copy orthologs

We searched for sites under positive selection in single-copy orthologs in the three Guloninae species and in the five carnivoran species (domestic dog, domestic cat, domestic ferret, walrus, northern elephant seal) also used for the phylogenomic inference, to identify candidate loci involved in adaptation of the tayra, sable and wolverine to their respective environments. The CODEML branch-site test for positive selection was run on 6003 single-copy orthologs present in all species, for three separate foreground branches: tayra, sable and wolverine. We found sites under positive selection (5 > dN/dS ratio > 1, Barnett et al. 2020) in 55 orthologs, which were highly significant (free-ratio > 2). Of these 55 positively selected genes (PSGs), 15 were observed in tayra, 22 in wolverine, and 18 in sable (Figure 4A-B; SI Table S3).

Among the 15 PSGs we detected in tayra, five are associated with reproduction (*NSMCE1*, *ETV2*, *SPATA25*, *MUC15*, and *PIH1D2*) with functions involving spermatogenesis, placenta and embryo development, and blood vessel morphogenesis (Shyu et al. 2007; Dong et al. 2014; Metzger et al. 2015; Singh et al. 2019; Gòdia et al. 2020). Among the remaining ten PSGs, *HSPB6* is involved in vasodilation and muscle contraction (Dreiza et al. 2010), *DERA* is associated with environmental stressors, including exposure to toxins (Salleron et al. 2014), and uricase (*UOX*) is a liver enzyme involved in purine catabolism and regulation of fructose metabolism (Johnson et al. 2020). Three PSGs (*IP6K3*, *MAGIX* and *FAM149B1*) are found to be associated with the nervous system, synapse formation and structural plasticity, as well as motor skills and coordination (Feng and Zhang 2009; Crocco et al. 2016; Shaheen et al. 2019). Three further PSGs (*DUSP19*, *TNLG2B*, and *LRRC4*) are related to the immune system (Ye and Ting 2008; Premzl 2016; Xie et al. 2020) and *HEMK1* regulates methylation processes (Ishizawa et al. 2008).

We detected 22 PSGs in wolverine, including six genes associated with energy production and conversion. Among them, *ATP6V0B, KMO,* and *SLC16A4* are primarily involved in insulin level regulation, and the metabolism of carbohydrates and fatty acids (Sun-Wada et al. 2001; Pierre et al. 2007; Avnet et al. 2020). Three PSGs (*OIP5*, *ZADH2* and *MTPAP*) are specifically associated with adipose tissue formation and intramuscular fat deposition (Xiao et al. 2006; Yu et al. 2013; Inoue et al. 2014). Additionally, we found three PSGs (*NBR1*, *TMEM38B*, *PPP1R18*) involved in selective autophagy as response to nutrient deprivation along with bone mass and density regulation, and resorption (Xu et al. 2015; Cabral et al. 2016; Matsubara et al. 2018). We also detected PSGs (*DAB1*, *OPA1* and *CTNS*) linked to cognition, brain

development and vision (Blume et al. 2017; Del Dotto et al. 2018; Browning et al. 2019). Several PSGs (*BNIPL*, *IL18BP*, *CRNN*) were associated with the immune system; (Im et al. 2002; Xie et al. 2004; Nelson et al. 2008) while three others (*ANAPC7*, *RNF212B*, *IZUMO3*) are involved in reproduction processes (Grayson and Civetta 2012; Reynolds et al. 2013; Wild et al. 2018) and *USB1* and *CLCN4* have a role in basal cell cycle processes (Picollo and Pusch 2005; Nomura et al. 2018). For the last two, *CEP95* and *FAM185A*, it was not possible to associate a specific phenotypic trait.

Among the 18 PSGs detected in the sable, three (*PRRT2*, *ATL2*, *SELENOI*) are associated with locomotion, and coordination (Rismanchi et al. 2008; Horibata et al. 2018; Valente et al. 2019), and *USP53* is associated with sensory perception and nervous system (Kazmierczak et al. 2015). Two PSGs, *VEGFC*, *RASA1*, are associated with blood vessel formation (Rauniyar et al. 2018; Chen et al. 2019), three (*TTC4*, *ZBP1*, *CD247*) with the immune system (Kuriakose and Kanneganti 2018; Shang et al. 2018; Ye et al. 2019) and three (IQUB, *UBQLNL*, *MEIKIN*) with reproduction (Shi et al. 2009; Bao et al. 2010; Kim et al. 2015). Several PSGs (*EEF2KMT*, *DEUP1*, *ECD, IQCK*) are associated with cell cycle processes (Bähler and Rhoads 2002; Kim et al. 2010; Zhao et al. 2013; Davydova et al. 2014), and *ZC2HC1C* and *CCDC17* could not be associated with a particular function or biological process.

Gene family expansions and contractions

Adaptive divergence between species may also be caused by changes in gene family sizes that occur during genome evolution and are due to gains (expansions) or losses (contractions) of genes or groups of genes (Olson 1999; Tigano et al. 2020). We analysed gene gains and losses while accounting for phylogenetic history by applying a probabilistic global birth and death rate model on gene sets containing 7838 orthologs present as either ‘single-copy’, ‘duplicated’ or ‘missing’ in at least one of the eight carnivoran species. Overall, the eight species analysed displayed more gene family contractions than expansions, with the wolverine having the highest contraction rate. This is most likely not a real biological finding but rather an artefact due to the fragmented genome assembly (SI Figure S7).

Tayra and sable had similar numbers of gene family expansions and contractions (SI Figure S7): 34 expansions and 169 contractions in tayra, and 33 expansions and 162 contractions in sable. The less contiguous wolverine genome contained 7 expansions and 649 contractions (SI Tables S4A, S4B). Due to the stochastic nature of gene losses

and the potential inflation of estimates resulting from different genome assembly contiguities, we here focus on gains of gene copies.

Expanded gene families in the tayra genome are associated with cell cycle, metabolism, nervous and immune system, and reproduction, among others (Figure 4C-D; SI Table S4B). Of the three reproduction-related genes, *SLC38A2* regulates supply of nutrients for fetal growth through the placenta and supports embryo development during the peri-implantation period of pregnancy (Coan et al. 2010; Forde et al. 2014). The second one, *HSD17B10*, is associated with regulation of pregnancy-sustaining steroid hormones (Martin Hill et al. 2010) while the *RBP2*, is involved in retinol binding and vitamin A metabolism necessary for oogenesis and embryogenesis (Brown et al. 2003) and also vision (D'Ambrosio et al. 2011). Three genes (*ATP6V1D*, *DBX2*, *SLC38A1*) are associated with cerebral cortex development, synapse formation, visual perception, and learning processes (Gu et al. 2001). *ANKRD13A* is also associated with vision (like *RBP2*), more specifically with lens fiber generation and vitamin A metabolism required for the formation of the photoreceptor rhodopsin (Avellino et al. 2013). The *MAPKAPK5* gene is part of signalling pathways regulating fear conditioning and memory (Gerits et al. 2007) and *N6AMT1* is involved in modulation of arsenic-induced toxicity (Zhang et al. 2015). The olfactory receptor gene *TAAR5*, specific for trimethylamine, a bacterial metabolite found in some animal odors, is involved in behavioral responses in mammals (Li et al. 2013; Liberles 2015) and was duplicated in both tayra and sable. We detected one putative triplication of *FKBP3*, a gene associated with immunoregulation, predominantly of T-cell proliferation (Kang et al. 2008). The PRR11 could not be associated with a particular function or biological process.

In the wolverine, two duplicated genes are related to the nervous system: *GFRA4* is implicated in motor neuron development (Masure et al. 2000) and *KCNS1* in regulating mechanical and thermal pain sensitivity (Tsantoulas et al. 2018). The *MTM1* gene is associated with positive regulation of skeletal muscle tissue growth (Hnia et al. 2011) and MON1B is implicated in immune response to viral infection (Guo et al. 2006).

In the sable, expansions involve gene families associated with the nervous system, here specifically with sensory perception and locomotion, with angiogenesis, hair follicle development, and the immune system. The *DUSP8* gene is involved in neuronal development, vision, olfaction, and spatial memory formation (Baumann et al. 2019; Martell et al. 1995). *FBXL3* is associated with regulation of the circadian clock (Siepka et al. 2007) and *TIMM10* with hearing (Paschen et al. 2000). Two genes, *CDC42* and *TCHHL1*, are implicated in hair-follicle development (Wu et al. 2006; Yamakoshi et al. 2013). Additionally, *CDC42*, a gene coding for a cell division control protein, is also

involved in angiogenesis and hematopoiesis, alongside TNFRSF12A and *LXN* (Wiley et al. 2001; Zhang and Liang 2018).

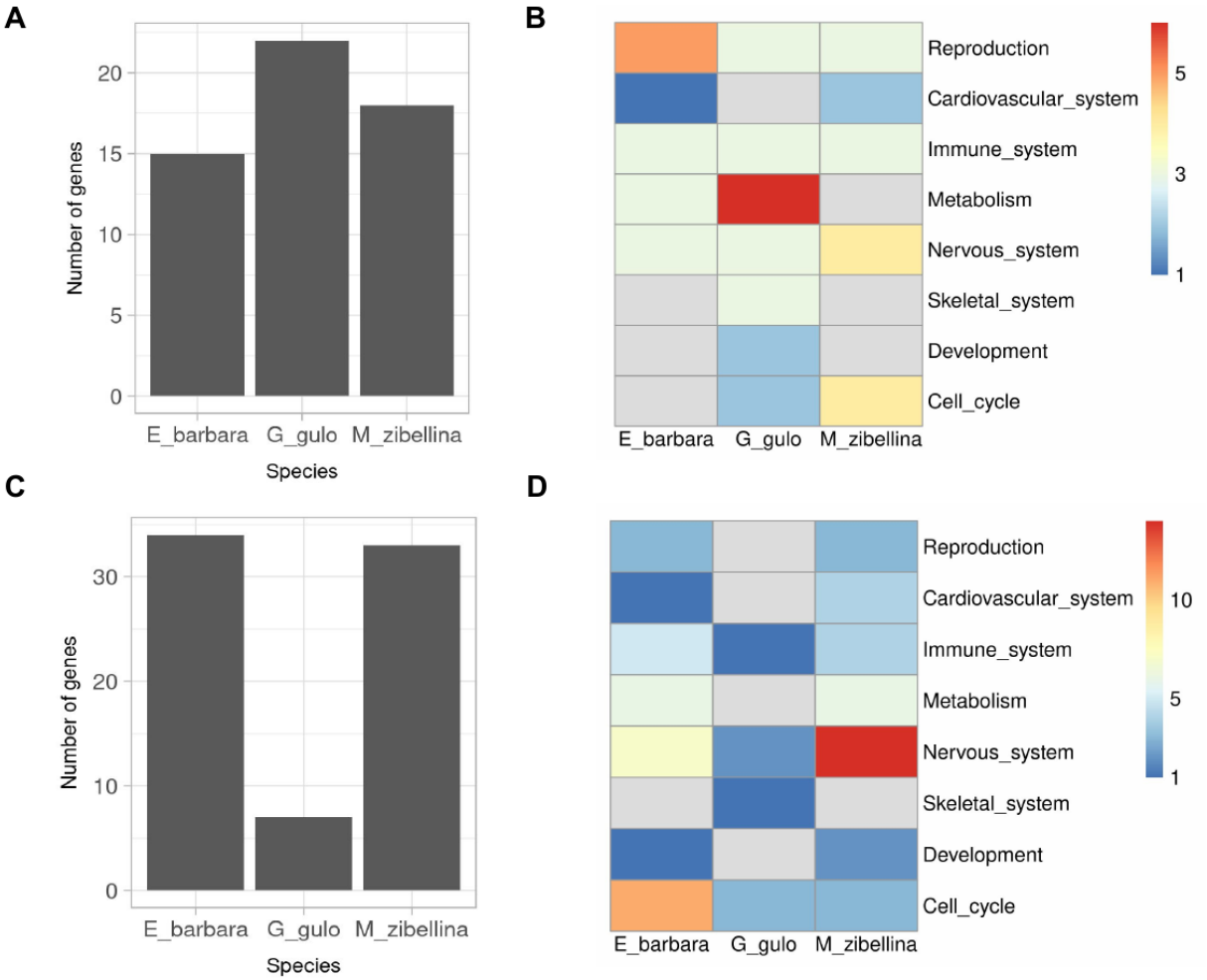

Figure 4. Number of candidate genes and their functional groups.
Genes identified from analyses of (A,B) positive selection on single genes (PSG), and (C,D) gene family expansions. Heatmap scale indicates the number of genes.

Structural variation

Structural variants (SVs) modify the structure of chromosomes and can affect gene synteny, repertoire, copy number and/or composition (e.g. gain or loss of exons), create linkage-blocks, and modify gene expression (Chiang et al. 2017; Mérot et al. 2020), leading to complex variation in phenotypes and genetic diseases (Weischenfeldt et al. 2013). We investigated four types of SVs (deletions, duplications, insertions, inversions)

in the three Guloninae species utilizing reads mapped to the domestic ferret genome and called with an ensemble of three SV callers (Kosugi et al. 2019).

We identified the highest number of species-specific SVs in sable (22979), followed by tayra (8907), and wolverine (264) (Figure 5A). The most abundant SVs detected in all three species are deletions (> 50bp), ranging from 183 species-specific deletions in wolverine to 21713 in sable. Duplications were the least frequent SV type among the three species (Figure 5B). For all three species, the majority of SVs are located in intergenic regions (> 80%), with a smaller portion found in genic regions, completely or partially overlapping protein-coding genes (UTRs, exons, introns). According to Variant Effect Predictor (VEP) classification, SVs impacting genic regions are classified either as high-impact variants or modifiers (McLaren et al. 2016) with putative consequences on gene transcription ranging from transcript truncation to transcript ablation or amplification. The highest number of species-specific genic SVs is detected in tayra, with 330 (3.70% of species-specific SVs), followed by 156 (0.68%) in sable and 53 (20.08%) in wolverine (Figure 5C). The exact impact of inversions overlapping large sets of genes is still challenging to determine, as the largest effect is likely to be restricted to genes near SV breakpoints, other than the well documented impact of inversions on intra and interspecific gene flow (Wellenreuther and Bernatchez 2018; Porubsky et al. 2020). Therefore, we further inspected genes and gene blocks affected by deletions, duplications, and insertions for their putative function and significantly enriched biological processes, respectively (Figure 5D, SI Table S5).

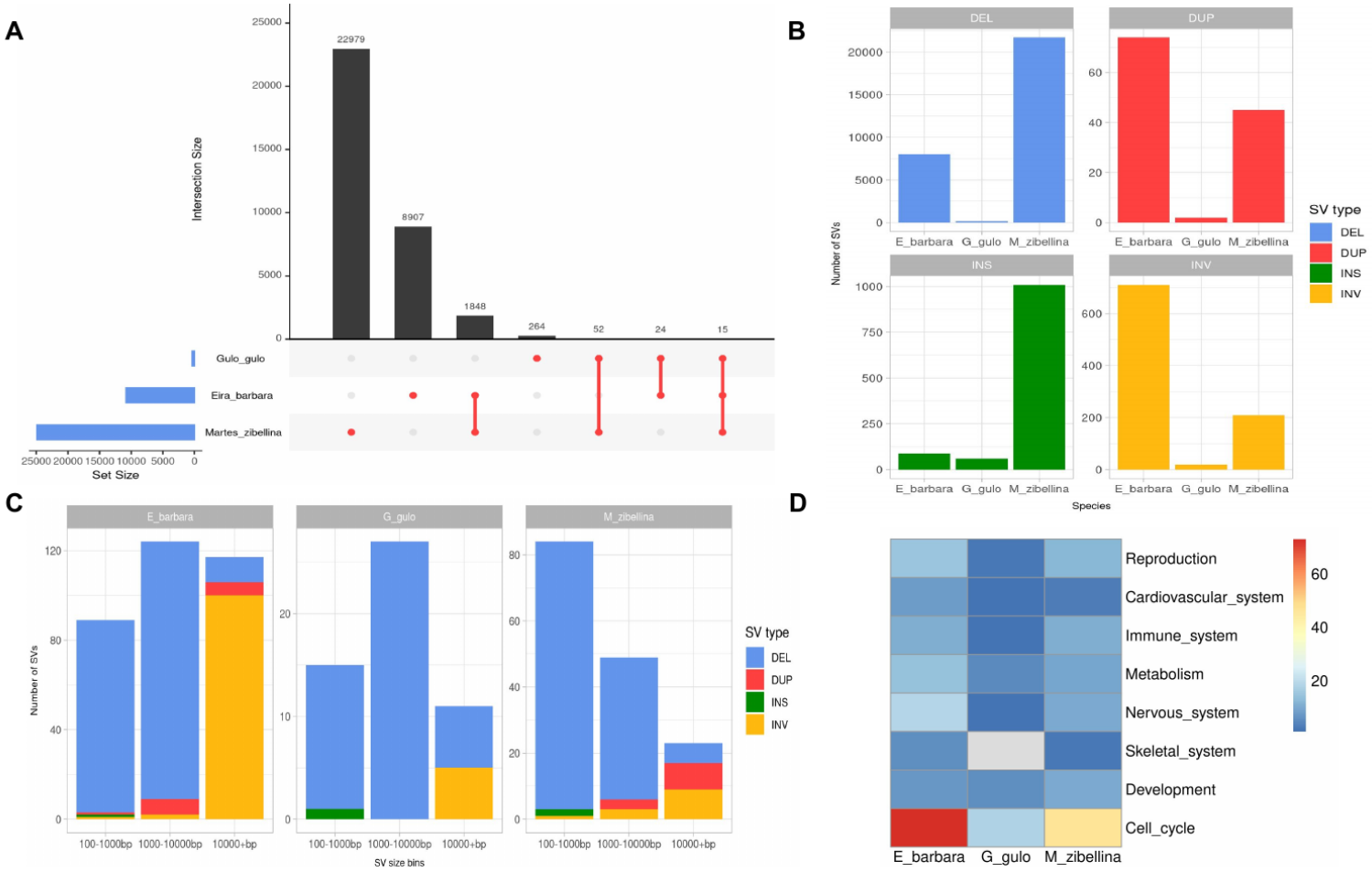

Figure 5. Structural variants detected in gulonine species.
A) Shared and species-specific structural variants detected in wolverine (*Gulo gulo*), tayra (*Eira barbara*), and sable (*Martes zibellina*), **B)** Counts of different types of species-specific structural variants detected in tayra (E_barbara), wolverine (G_gulo), and sable (M_zibellina), **C)** Length distribution of species-specific structural variants overlapping genic regions detected in tayra (E_barbara), wolverine (G_gulo), and sable (M_zibellina), **D)** Functional groups of genes affected by species-specific structural variants in 3 gulonine species (SV types: DEL, DUP, INS). Heatmap scale indicates the number of genes.

In the tayra genome, we observed 14 duplications spanning a combined length of 2.92 Mb, putatively affecting 24 protein-coding genes. Duplicated genes and gene blocks are associated with olfaction, reproduction, metabolism and energy conversion. This included *RNASEH2B*, a gene involved in *in utero* embryo development (Yockey and Iwasaki 2018), and two genes involved in spermatogenesis, *DIAPH3* (Mironova and Millette 2008) and *PCNX1* (Geisinger et al. 2005), the latter being an example of a complex SV involving heterozygous duplication and deletion of an exon (SV ~2kb in length). We detected 212 deletions in the tayra genome in relation to the domestic ferret reference, comprising a total length of 2.08 Mb, and affecting 247 genes, which are associated with cell cycle processes, metabolism/ energy conversion, nervous system,

and reproduction, among other functional categories (SI Table S5). A majority of these genes are affected by partial (involving one or several exons) heterozygous deletions. Genes involved in placenta development and *in utero* embryogenesis include *HSF1*, *RSPO2*, and *DNMT3A*. Additionally, we detected *NLRP1* and *NLRP8*, both associated with preimplantation development, highly expressed in oocytes, but with low to no expression in embryos (McDaniel and Wu 2009). One short insertion was observed in exon 2 of *LIX1L*, a gene associated with anatomical structure morphogenesis (Nakamura et al. 2015).

In the wolverine genome, none of the species-specific duplications overlapped genic regions. However, 47 deletions spanning a combined length of 229 kb are putatively associated with transcript truncation or ablation in 48 genes. The majority of affected genes are associated with basic cell cycle processes, development and metabolism/energy conversion. This includes *GLUD1*, a gene involved in amino-acid induced insulin secretion (Luczkowska et al. 2020), also found to be affected by a shorter deletion in sable, and *NSDHL*, a gene regulating cholesterol biosynthesis (Bauer et al. 2017). Additionally, we detected deletions affecting *PARVA*, a gene associated with angiogenesis and smooth muscle cell chemotaxis (Montanez et al. 2009) and *DNAJC7*, involved in positive regulation of ATPase activity and regulation of cellular response to heat (Sonna et al. 2002). We also detected one insertion in a gene of unknown function.

In the sable genome, we detected eleven duplications spanning a combined length of 324 kb, overlapping 16 genes associated with cell cycle, sensory perception, development, and the immune system. The 130 detected deletions (combined length of 408 kb) overlap 125 protein-coding genes associated with cell cycle, reproduction, the immune system, development, metabolism and sensory perception. Deletions were identified in two genes involved in keratinocyte differentiation, *PPHLN1* (Larsen et al. 2017) and *IVL*, the latter of which is also associated with hair follicle development (de Viragh et al. 1994; Kitchener et al. 2018). Additionally, two short insertions were found disrupting exon 2 of *NCOA4* and exon 7 of *YIPF5*, genes associated with mitochondrial iron homeostasis (hem synthesis) and protein transport, respectively.

Discussion

We present a highly contiguous genome for the tayra (*Eira barbara*), based on 10x Genomics linked-read data. Contiguity of the tayra genome assembly and its gene completeness are similar to or higher than those of other carnivoran species using the

same technology (African wild dog: Armstrong et al. 2019, European polecat: Etherington et al. 2020, Southern elephant seal: Kim et al. 2020), confirming the utility of short linked-reads for genome assembly of wildlife species.

The phylogenomic relationships among the investigated mustelids were reconstructed using more than 900 orthologous CDS, and resulted in a tree topology and divergence time estimates in agreement with previous studies using fewer loci (Koepfli et al. 2008; Sato et al. 2012; Li et al. 2014; 2018). We estimated the split between *Mustela* and Guloninae occurred 11.2 million years ago (Mya) (HPDI 13.1 - 9.5 Mya), followed by the split between *Eira* and the *Gulo-Martes* group 7.5 Mya (HPDI 9 - 6.1 Mya), and the split between *Gulo* and *Martes* at 5.9 Mya (HPDI 7.4 - 4.7 Mya).

We did not observe a positive relationship between variation at the nucleotide level (heterozygous SNPs) and variation at the structural level (SVs) within the gulonine species. The tayra displayed the highest nucleotide diversity (1.89 SNPs per kbp, SI Table S3), but only the second highest amount of heterozygous SVs (2543, 23.6% of the total SVs, SI Figure S8). The sable had the second highest nucleotide diversity (1.44 SNPs per kbp), but the highest number of heterozygous SVs (14823, 59.5% of total). The wolverine displayed the lowest variation for both (0.28 SNPs per kbp, and 153 or 43.1% heterozygous SVs in total).

Assessment of variation among genome assemblies of closely related species strongly relies on the contiguity and completeness of analysed assemblies (Gurevich et al. 2013; Totikov et al. 2021). This needs to be accounted for when examining variation among discontiguous genome assemblies generated from short-read sequencing data. Here, the low contiguity of the wolverine assembly (Table 1; SI Figure S2) has likely impacted the number of PSGs and gene family expansions/contractions detected, and multiple, short insert size libraries sequenced at low coverage have likely resulted in lower SV detectability. However, even with the improved assembly contiguity, low diversity in the Scandinavian wolverine population is expected given previous results (Ekblom et al. 2018) and the species' historical demography (SI Figure S4).
For the sable, analysis of the heterozygosity distribution along chromosomes revealed that the ends of many pseudochromosomes had nearly double the heterozygosity than the median (> 2.5 SNPs per kbp vs median of 1.44 SNPs per kbp; Figure 2B, dark red color), while at least eight of the pseudochromosomes had very long stretches of low diversity (Figure 2B, blue color) that might be considered as runs of homozygosity (ROHs). Such distributed ROHs are often interpreted to be a consequence of recent inbreeding (Ceballos et al. 2018). This sable was sampled in the Greater Khingan mountains (Heilongjiang Province, China), very close to the edge of the species' range

(Liu et al. 2020). The usual decline in abundance at the periphery coupled with partial isolation from the main part of the species' range might have resulted in recent inbreeding explaining the observed pattern. Such a positive relationship between intraspecific SV counts and census (population) size has also been demonstrated for other species (Weissensteiner et al. 2020). The sable displayed the highest historical effective population size of the three gulonines (SI Figure S4), which may account for the high number of SVs we detected in this species.

Adaptive genomic variation

Among positively selected genes, gene family expansions and coding regions impacted by SVs, we found numerous candidate loci related to species-specific traits in tayra, wolverine and sable. In particular, SVs featured genes related to traits of adaptive significance, strongly arguing for an inclusion of SV analysis in genome comparisons of wildlife species.

The three gulonine species differed with respect to which reproduction-related processes were associated with candidate genes. In the aseasonally breeding tayra, candidate genes detected in three analyses (PSGs, gene family expansions, SVs) were frequently pregnancy-related, while in the two seasonal breeders, sable and wolverine, candidate genes were involved in a greater diversity of reproduction-related processes, primarily in gametogenesis (Figure 6A, SI Tables S3, S4B, S5). This may reflect the transition from seasonal to aseasonal breeding in the tayra lineage, the only extant aseasonal breeder among the Guloninae.

Shifts in dietary preferences have been linked to positive selection in single genes (Kosiol et al. 2008) and to copy number variation in metabolism-related gene families in mammals (Hecker et al. 2019; Rinker et al. 2019). Among Guloninae, the dietary gradient from omnivory in the neotropics to (hyper)carnivory in the northern Palearctic is reflected in the proportion of metabolism-related candidate genes observed (Figure 6B). The highest proportion of candidate genes involved in carbohydrate metabolism ("omnivorous diet") were detected in tayra, followed by sable, and none detected in wolverine. However, the highest number of candidate genes involved in maintaining a stable body condition through shifts in energy sources (autophagy, fat storage and bone resorption) was observed for the wolverine, potentially reflecting this species' adaptive response to unfavourable environmental conditions in its circumpolar habitat.

We note that in two analyses (positive selection and gene family evolution), our study did not consider the entire gene repertoire of these species but only variation in genes found as single-copy orthologs among mammalian species. Thus, the proportional differences observed in diet, body condition and reproduction related genes reported here are likely only an incomplete reflection of the genes involved in these traits.

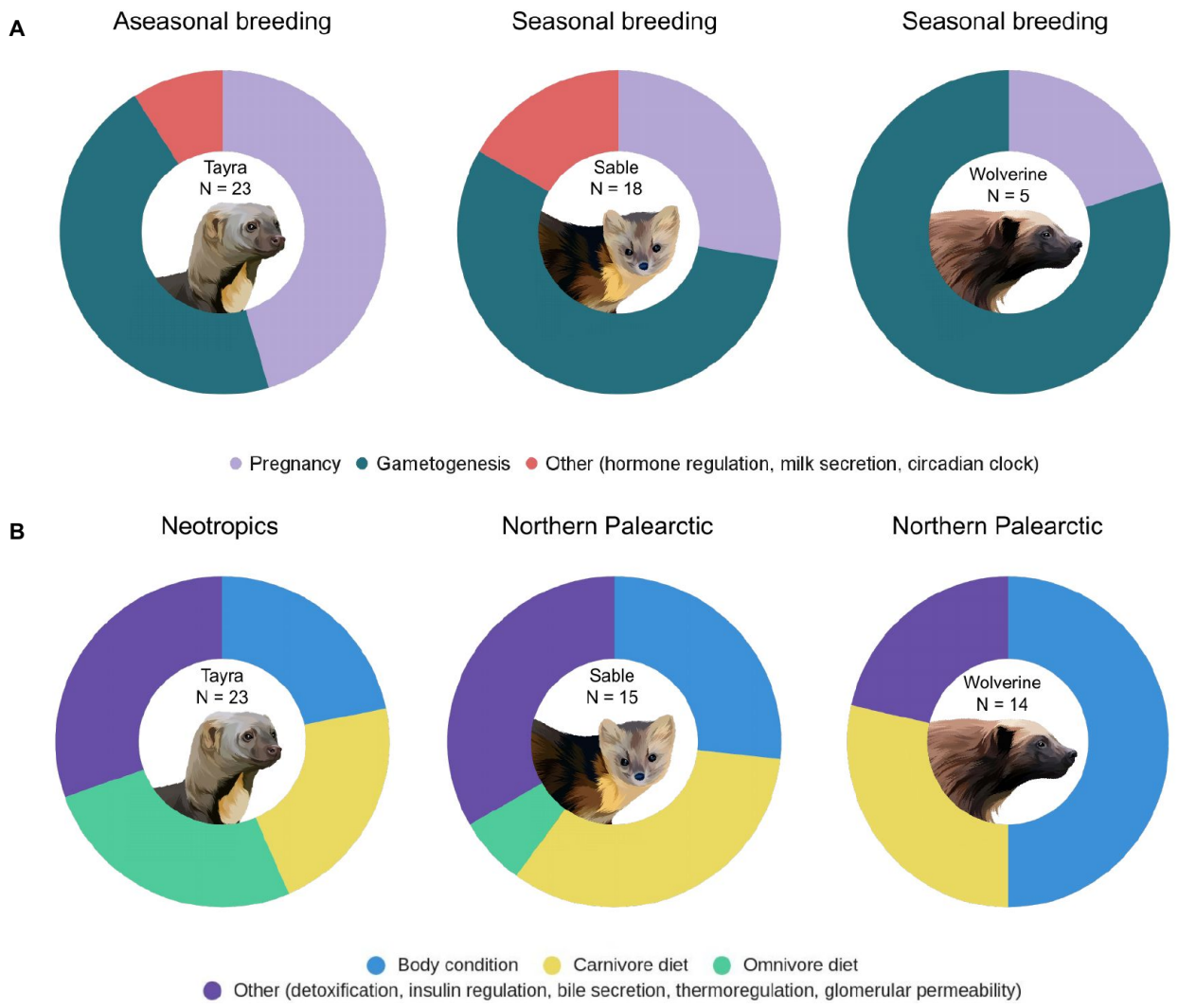

Figure 6. Summary of functional categories of (A) reproduction and (B) metabolism-related genes derived from PSG, gene family expansion and SV analyses. N represents the total number of detected genes. Vector graphics of species are created based on royalty-free images (source: Shutterstock).

Seasonal breeders in the north palaearctic: wolverine & sable

Obligate embryonic diapause or the delayed implantation of the blastocyst is a widespread reproductive strategy among mustelids and other carnivorans. The majority of mustelids in the Northern Hemisphere are seasonal breeders, which includes wolverines and sables that undergo a prolonged period of a delayed implantation lasting several months (Mead 1981; Svishcheva and Kashtanov 2011). This trait is also observed in fishers (*P. pennanti*) and martens (Mead 1989). Many environmental factors are associated with latitude, including photoperiod, temperature, seasonal changes in precipitation, all of which influence food abundance and availability. Optimal timing of ovulation and conception is crucial, and thus day length determines the onset of the breeding season in many species (Amstislavsky and Ternovskaya 2000). At higher latitudes, the mating season is even shorter, and there is a strong selection pressure for short birthing periods (Heldstab et al. 2018). As the breeding season represents one of the most energetically demanding periods, its timing in relation to when prey is abundant has a critical impact on the fitness of mustelids (Inman et al. 2012).

Candidate genes potentially involved in seasonal breeding that we detected in wolverine and sable are not restricted to those associated with pregnancy (SI Tables S3, S4B, S5). These mustelids occupy large home ranges, display territoriality and low population density, leading to infrequent encounters between males and females (Inman et al. 2012; Kashtanov et al. 2015). Thus, a mechanism that facilitates induced ovulation during the encounter would be an adaptive advantage (Larivière and Ferguson 2003). We detected signals of positive selection in *ANAPC7* in wolverine, a gene involved in progesterone-mediated oocyte maturation and release from cell arrest prior to fertilization (Papin et al. 2004; Reis et al. 2006), that might have a role in increasing progesterone secretion and renewed embryonic development, as observed in skunks and mink (Mead 1989). As previously noted, delayed implantation serves as an important adaptation to ensure maximal survival chances of offspring depending on the environmental conditions (Heldstab et al. 2018). Previous studies in mink (Lopes et al. 2003; Murphy 2012) showed increased levels of vascular endothelial growth factors (VEGF) and their receptors, correlating with the implantation process. *VEGFC*, primarily associated with angiogenesis and regulation of permeability of blood vessels during embryogenesis, was positively selected in sable, suggesting its possible involvement in embryo implantation regulation in this species.

Changes in testicular activity and spermatogenesis strongly correlate with season in mink (Blottner et al. 2006; Persson et al. 2011), and have been noted in lynx (Jewgenow et al. 2006), red deer (Pintus et al. 2015) and roe deer (Wagener et al. 2003). We observed spermatogenesis-related genes affected by different types of variation in the three gulonine species. In the wolverine, candidate genes showing signals of positive selection involved in spermatogenesis include *IZUMO3* and *RNF212B*. Testes-expressed *IZUMO3*, a sperm membrane protein, is essential for gamete fusion during fertilization (Ellerman et al. 2009) and *RNF212B* is critical for successful crossing over in gametes. Knockout of *RNF212* caused sterility in both male and female mice, with males not producing spermatocytes and having 70% smaller testes than those of wild-type animals (Reynolds et al. 2013). The IZUMO gene family most likely underwent expansion prior to the diversification of vertebrates, and several gene family members show signs of positive selection and indication of subfunctionalization (Grayson 2015). However, unlike other gene family members, positive selection of *IZUMO3* is driven by a more recent mammalian-specific diversification and is suggested to be linked to species-specific adaptations rather than sexual selection (Grayson and Civetta 2012).

In sable, genes involved in spermatogenesis were *UBQLNL* (Marín 2014) and *SEPT12*, which show signals of rapid evolution, with the latter also being duplicated (i.e. gene family expansion). Moreover, *MEIKIN* and *CDK2*, both involved in meiosis, show signals of positive selection and rapid evolution through gene family expansion, respectively. *MEIKIN* has been found to be consistently rapidly evolving in other eutherian mammals (Pontremoli et al. 2021).

Seasonal breeding in many mammals is largely under photoperiod regulation, suggesting that the circadian system and pineal gland play an important role in measuring day length. Regulation of pineal melatonin secretion is influenced by a neural pathway that includes the circadian oscillators (Goldman 1999). Moreover, seasonal diapause is observed to be predominant among carnivores (Renfree and Fenelon 2017), and maintaining elevated melatonin in mink and spotted skunks has been shown to prolong embryonic diapause (Murphy and Fenelon 2020). *FBXL3*, associated with maintenance of circadian clock oscillation in mammals (Siepka et al. 2007; Shi et al. 2013; Fenelon et al. 2017) is duplicated and rapidly evolving in sable, indicating an important role in regulating both daily and seasonal activity and possibly onset of diapause.

Aseasonal breeder in the neotropic: tayra

In tropical regions, reproductive seasonality is less pronounced as environmental conditions are relatively stable throughout the year (Dubost and Henry 2017; McNutt et al. 2019). Tayras inhabit tropical and subtropical forests of Central and South America, are aseasonal breeders with multiple estrous cycles per year (Proulx and Aubry 2017) and do not exhibit embryonic diapause (Poglayen-Neuwall et al. 1989). The tayra represents the most basal taxon of the Guloninae, and is an exception among these mustelids regarding its reproductive strategy.

Genes that may be involved in the aseasonal breeding of tayra include *ETV2*, *MUC15*, *SLC38A2*, *HSD17B10*, *RBP2* and *RNASEH2B*. *ETV2* and *MUC15* are involved in placental and embryo development and regulation of embryo implantation (Shyu et al. 2007; Singh et al. 2019). The *MUC15* protein has been shown to be present in the zona pellucida of preimplantation rat blastocyst, likely performing an anti-adhesive function, and preventing premature blastocyst attachment. Following the increase of progesterone levels, *MUC15* levels are reduced, suggesting its removal may be required for a successful implantation (Denker 2000; Poon et al. 2014). Increased expression of the neutral amino acid transporter *SLC38A2* has been detected in the endometrium of cattle during the preimplantation period of pregnancy (Forde et al. 2014) and in mice placentas during late gestation, maintaining fetal growth when maternal growth is restricted by undernutrition during pregnancy (Coan et al. 2010). *SLC38A2* is a duplicated and rapidly evolving gene in tayra, based on our analysis, suggesting its potential role in supporting multiple pregnancies during the year. *HSD17B10*, involved in mitochondrial fatty acid metabolism, cell growth and cell resistance in response to stress (Liu et al. 2020) is highly expressed in the fetal and maternal liver, and has a role in metabolism of steroids that influence the maintenance of human pregnancy and provide protection against excitotoxicity following acute hypoxic stress (Hill et al. 2011). Duplication of this gene in tayra might indicate a gene dosage modulation in steroid hormone-regulated pregnancy in tayra. Beside being associated with vision, retinol binding protein *RBP2* has a significant role in regulating retinoids during oogenesis and embryogenesis, and positively impacts oocyte maturation in mice, cattle, pigs and sheep, leading to improved embryonic survival (Harney et al. 1993; Brown et al. 2003). A partial duplication was detected in *RNASEH2B* in tayra. Mutations in this gene involved in pregnancy and embryogenesis have been shown to cause interferonopathies, leading to inflammation disrupting fetal brain development (Crow et al. 2015; Yockey and Iwasaki 2018). In tayra, duplication of

this gene potentially increases gene expression and may play a role in maintenance of early embryo development. Furthermore, genes involved in placental development, implantation and embryogenesis (*HSF1*, *RSPO2*, *NLRP1*,*NLRP8* and *DNMT3A*) have been affected by partial deletions in tayra, suggesting further potential changes in dosage of pregnancy-related genes.

Resource availability in the northern Palaearctic: wolverine & sable

Overcoming demanding periods and staying active throughout the year is challenging for non-hibernating northern palearctic species and requires specific mechanisms to cope with seasonal food scarcity. Responses to harsh environmental conditions aim to reduce the energy spent searching for food, and include physiological adaptations such as accumulation of fat reserves and adaptive fasting (Martinez and Ortiz 2017), as well as behavioural adaptations, like food caching (Mustonen et al. 2006) and flexible adjustment to alternative dietary sources (Zhou et al. 2011). For example, to successfully forage in a cold, low-productivity environment with scarce food resources, wolverines have evolved several adaptations to efficiently exploit food resources and overcome constraints of this niche (Inman et al. 2012). Wolverines both hunt and scavenge for the most energy-efficient food sources available in their habitat (Koskela et al. 2013). As it was demonstrated for female wolverines in Scandinavia, their reproduction is limited by food availability (Persson 2005). Scavenging from other predators such as gray wolf and Eurasian lynx facilitates food caching, leading to decreased unpredictability in food availability during winter and enhanced reproductive success of wolverines (Mattisson et al. 2017; Aronsson and Persson 2018).

A critical metric of body condition is the amount of stored fat, representing an important energy source between feeding opportunities and providing thermal insulation in cold environments. Undernutrition is a known cause affecting reproduction, and smaller energy reserves may lead to lower survival rates (Brown and Lasiewski 1972; Schulte-Hostedde et al. 2005). However, wolverines from Yukon, Canada, had no significant differences in fat deposits related to gender, season, body size or age although fat content was considerably higher in wolverines compared with other mustelids (Robitaille et al. 2012). Three PSGs detected in the wolverine are involved in adipose tissue formation, *MTPAP* (Han et al. 2012), *OIP5* (Inoue et al. 2014), *ZADH2*

(Yu et al. 2013) may be associated with lipid metabolism and selective fatty acid mobilization stimulated by fasting periods in this species (Krebs et al. 2004; Inman et al. 2012), as observed in mink (Nieminen et al. 2006), and raccoon dog (Mustonen et al. 2007).

One of the responses to prolonged periods of nutrient deprivation and extreme environmental conditions is suppressed bone resorption and formation, especially pronounced in hibernating species (Lennox and Goodship 2008; McGee-Lawrence et al. 2015). Beside regulating survival of blastocysts during delayed implantation (Lee et al. 2011; Lim and Song 2014), it has been demonstrated that autophagy plays a critical role in osteoclast differentiation and maintenance of bone homeostasis (DeSelm et al. 2011; Montaseri et al. 2020). This adaptation might be facilitated in wolverines by genes involved in bone mass regulation, including resorption (*PPP1R18*, *TMEM38B*) and autophagy (*NBR1*). Moreover, we detected a duplication of the muscle growth regulating gene *MTM1*. While a lack of *MTM1* will lead to muscle hypertrophy through unbalanced autophagy in humans and mice (Al-Qusairi et al. 2013), a gene duplication may facilitate muscle growth.

In sable, fatty acids are uniformly mobilized from anatomically distinct fat deposits (Nieminen and Mustonen 2007), whereby the fatty acid metabolism is regulated by positively selected genes of the ACSL family, maintaining a low body fat content of ~8% (Zhao et al. 2019). In our analyses we did not detect changes in the *ACSL* gene family, but we observed duplications of *ASB6*, *SLC25A10*, *RNF186* and *BORCS6*, which have been implicated in effective regulation of fat storage usage and response to nutrient availability (Wilcox et al. 2004; Mizuarai et al. 2005; Schweitzer et al. 2015; Okamoto et al. 2020). Moreover, partial deletions of *APOD*, *PDHB*, *LDLR*, and *CERS5*, associated with lipid metabolic processes (Carmo et al. 2009; Serão et al. 2011; Tavori et al. 2015; Gosejacob et al. 2016), indicate a possible association with adaptive fasting and energy conservation.

We observed partial deletions in *DNAJC7*, a gene involved in thermoregulation and response to heat (Sonna et al. 2002) in both sable and wolverine, but not in tayra, indicating its potential significance for gulonines inhabiting colder environments. Furthermore, we detected partial deletions in *GLUD1* in sable and wolverine. *GLUD1* regulates insulin secretion (Fahien and Macdonald 2011) and might play a role in mobilizing lipids, causing intermittent states of reversible insulin resistance as an adaptive response during prolonged periods of nutrient deprivation, as has been observed in some carnivorans (Viscarra et al. 2013; Martinez and Ortiz 2017).

In sable and tayra, we observed a partial deletion of *PPP1CC*, associated with glycogen metabolism (Li et al. 2021), tentatively facilitating a more omnivorous diet in these species compared to hypercarnivory in wolverines (Sharma et al. 2018; Lopes-Marques et al. 2020).

Despite the notable difference in hair follicle structure and fur density between palearctic and neotropic species (Kitchener et al. 2018), we did not detect any type of variation affecting genes related to these traits in wolverine. However, we observed two gene copy gains in sable, *TCHHL1*, involved in hair morphogenesis (Wu et al. 2011), and *CDC42*, required for differentiation of hair follicle progenitor cells (Wu et al. 2006).

Resource availability in the Neotropics: tayra

Tayras exploit diverse food sources and experience relatively stable resource availability all year round, as (sub)tropical habitats have higher primary productivity compared to habitats at higher latitudes (Zhou et al. 2011; Heldstab et al. 2018). We found species-specific genes associated with regulation of fructose metabolism, consistent with dietary preferences of tayra involving a variety of fruit and honey (Kratzer et al. 2014). The uricase (*UOX*) gene, which is involved in regulation of purine metabolism and conversion of fructose to fat (Johnson and Andrews 2010) was under positive selection in tayra. Old World monkeys show low levels of the enzymatic activity while uricase is pseudogenized in humans, great apes, and New World monkeys due to silencing mutations (Oda et al. 2002; Johnson et al. 2009). Gradual loss of uricase activity in primates may have been an evolutionary adaptation to more rapidly convert fructose into fat storage during periods of progressively cooler climates.

High rates of lineage-specific variation in gene family size, especially those families involved in immune response, and those involved in detoxification of xenobiotic molecules from the environment (Thomas 2007), are likely associated with environmental changes during speciation (Lynch and Conery 2000; Zhang 2003). We found a duplication of *N6AMT1*, a member of a gene family implicated in environmental stress response. *N6AMT1* plays a role in detoxification of xenobiotic compounds, more specifically, converting the arsenic metabolite monomethylarsonous acid to the less toxic dimethylarsonic acid (Ren et al. 2011). Chronic arsenic exposure through water, soil and crops, has been monitored in the neotropics, as it represents a severe public health issue, leading to various diseases including cancer (Zhang et al. 2015). This duplication event indicates putative local adaptation of tayra to this xenobiotic compound.

Furthermore, we also found candidate genes associated with vision and cognition, which may be associated with the tayra's primarily diurnal foraging activity. Tayras supposedly detect prey primarily by smell, as their eyesight has been described as being relatively poor (Galef et al. 1976; Wilson and Mittermeier 2009). This is contradictory to the observed behaviour of caching of unripe but mature stages of both native and non-native fruit by tayras (Soley and Alvarado-Díaz 2011). We detected variation in several genes implicated with lens fiber formation and retina vascularization, including gene expansions of *ANKRD13A* (Avellino et al. 2013) and *RBP2* (D'Ambrosio et al. 2011), along with the inversion of *PDC* (Pandya et al. 2016), suggesting that tayras might not in fact exhibit poor eyesight. The caching behavior mentioned above (Soley & Alvaro-Diaz, 2011) indicates remarkable sensory perception, especially olfaction (Presley 2000) and memory and recognition of different stages of fruit development, likely evolved as a response to avoid competition with other species during seasons when fruit becomes ripe. We observed candidate genes related to memory and learning such as *SLC38A1* (Qureshi et al. 2019) and *CRBN* (Higgins et al. 2010) that may have been involved in the evolution of this type of caching behavior.

Materials and Methods

Sample, Sequencing, and Genome Assembly

Whole blood from a captive male tayra was collected by the veterinary staff of the "Wildkatzenzentrum Felidae", Barnim (Germany), during a routine medical checkup. High molecular weight (HMW) genomic DNA extraction was performed using the Qiagen MagAttract HMW DNA Kit, following the manufacturer's protocol. We used 1ng of DNA and the Chromium Genome Reagents Kits Version 2 and the 10X Genomics Chromium Controller instrument with a microfluidic chip for library preparation (10x Genomics). This library was then sequenced on an Illumina NovaSeq 6000 instrument with 300 cycles on an S1 lane at the Max Delbrück Center for Molecular Medicine, Berlin.

Due to uncertainty regarding the optimum number of reads for genome assembly, we generated three *de novo* genome assemblies using the 10x Genomics Supernova assembler v2.1.1 (Weisenfeld et al. 2017) with default parameters, each with a different read input: 900 million, 1.3 billion and 1.7 billion paired reads, respectively. Based on Supernova assembly metrics (contig, scaffold, and phase block N50 sizes), we chose the assembly generated using 1.3 billion paired reads for further analysis (metrics for the chosen assembly given in SI Table S1).

Assessment of gene completeness

The assemblies of tayra, wolverine, sable and domestic ferret were assessed for gene completeness with BUSCO v4.1.2 using the mammalian lineage dataset mammalia_odb10 (Simão et al. 2015), which included 9226 single-copy orthologs.

Repetitive Elements

To accurately identify repeat families, we used RepeatModeler v2 (Flynn et al. 2020) with the option "-LTRstruct" option, followed by Repeatmasker v4.1.2 (Smit 2004) to identify and mask the modeled repeats in the tayra genome assembly.

Mapping to reference

For the purpose of demographic history and structural variation analyses, reads from all three Guloninae species were aligned to the domestic ferret (*Mustela putorius furo*) genome (MusPutFur1.0_HiC; Peng et al. 2014; Dudchenko et al. 2017, 2018) in local mode with Bowtie2 v2.3.5.1 (Langmead and Salzberg 2012). The proportion of reads mapping to the reference genome for all three samples was above 96%. Duplicated reads were removed with Picard Toolkit v2.23 (MarkDuplicates, http://broadinstitute.github.io/picard). Insert size distributions for each sample library (SI Figure S9) were generated with Svtyper v0.7.1 (Chiang et al. 2015). Trimmed tayra reads were downsampled to ~38x with seqtk v1.3 (https://github.com/lh3/seqtk) prior to mapping to maintain uniformity among libraries and to avoid bias in variant calling.

Pre-processing of sequencing data

Prior to mapping, linked-read barcodes were trimmed from tayra sequencing reads with proc10xG (filter_Reads.py, https://github.com/ucdavis-bioinformatics/proc10xSC). For the other two species, we used the reads used for generating the respective genome assemblies of Scandinavian wolverine (*Gulo gulo*, NCBI accession: GCA_900006375.2, PRJEB10674; Ekblom et al. 2018), and sable (*Martes zibellina*, NCBI accession: GCA_012583365.1, PRJNA495455; Liu et al. 2020). Adapter clipping and quality trimming (Q30, min. length 80 bp) were performed on all samples with TrimGalore v0.6.4 (Krueger et al. 2021). Additionally, trimmed reads were further used in the nucleotide diversity analysis.

Demographic reconstruction

Analysis of demographic history was performed with PSMC v0.6.5 (Li and Durbin 2011) using the following parameters (repeated 100 times for bootstrapping): *psmc -N25 -t15 -r5 -b -p '4+25*2+4+6' -o round-${ARRAY_TASK_ID}.psmc ${name}.split.psmcfa*
Results for each genome were plotted with psmc_plot.pl, and the mutation rate and generation time were set to 1e-08 substitutions per site per generation and 4 years respectively (Cahill et al. 2016; Dobrynin et al. 2015).

Reference-based scaffolding

For better visualization of heterozygosity (see below), we generated pseudochromosome assemblies for tayra, wolverine and sable using as reference the chromosome-length domestic ferret (*Mustela putorius furo*) genome assembly published by DNA Zoo (https://www.dnazoo.org/assemblies/Mustela_putorius_furo). Scaffolding was performed using RaGOO v1.1 (Alonge et al. 2019). The X chromosome in the domestic ferret assembly was identified via whole genome alignment to the domestic cat (*Felis catus*) Felis_catus_9.0 assembly (Buckley et al. 2020) and ZooFISH data available from the *Atlas of Mammalian Chromosomes* (Cavagna et al. 2000; O'Brien et al. 2020). Whole genome alignment was performed using LAST v971 (Frith and Kawaguchi 2015).

Alignment to pseudochromosome assemblies and sex verification

Trimmed reads were aligned to the pseudochromosome assemblies of corresponding species using BWA version 0.7.17 (Li and Durbin 2009). Read duplicates were marked using the markdup utility from Samtools version 1.10 (Li 2011). To verify the sex of the tayra, sable and wolverine genomes, two approaches were applied: marker-based and coverage-based. For the marker approach, we used the Y-chromosome-specific SRY gene (sex determining region Y). The amino acid sequence of the *Martes melampus* SRY (Genbank ID BAJ05096.1; Yamada and Masuda 2010) was downloaded from the NCBI protein database and aligned to the pseudochromosome assemblies using Exonerate v 2.2.4 (Slater and Birney 2005) in protein2genome mode to identify orthologous sequences. For the second approach, a per-base genome coverage was estimated using Bedtools v2.29 (Quinlan and Hall 2010). Mean and median values for both non-overlapping sliding windows of 1Mbp and whole genomes were calculated and visualized using scripts from the MACE package (https://github.com/mahajrod/MACE).

Visualization of heterozygosity distribution

Variant calling followed by quality filtration was performed using the BCFtools pipeline v1.10 (Poplin et al. 2018). Variant filtration was performed in several stages. Low-quality variants were removed using the BCFtools filter with the following thresholds: 'QUAL < 20.0 || (FORMAT/SP > 60.0 || FORMAT/DP < 5.0 || FORMAT/GQ < 20.0)'. Then, variant coverage was investigated. In each sample, positions with coverage lower or higher than 50-250% of the whole genome median value were removed, and out of the

remaining positions only those common to all samples were retained. Finally, SNPs with uncalled genotypes in any sample and variants with the same genotypes for all samples were removed. For visualization, heterozygous SNPs were counted in non-overlapping sliding windows of 1 Mbp and counts were scaled to SNPs per kbp. Indels were not included due to the low quality of calls from short reads. SNP density plots were created using the MACE package (https://github.com/mahajrod/MACE).

Phylogenomic data preparation, analysis and dating

We performed sequence alignments and filtering of highly divergent alignment segments for 6020 coding genomic regions of single-copy orthologs shared across eight species of carnivores, using the software MACSE v2 (Ranwez et al. 2011). These alignments were further trimmed for highly divergent regions, excessive missing data, and substitution model adequacy (further details in Supplementary information). Gene trees were then estimated from acceptable gene regions by first selecting the best substitution model from the GTR+F+Γ+I+R family (Kalyaanamoorthy et al. 2017) and calculating approximate likelihood-ratio test (aLRT) branch supports (Anisimova and Gascuel 2006), as implemented in IQ-TREE v2 (Minh et al. 2020).

Species tree estimates were performed using (i) concatenated sequence alignments for maximum likelihood inference using IQ-TREE v2, and (ii) gene trees for inference under the multi-species coalescent using the summary coalescent method in ASTRAL-III (Zhang et al. 2018). The maximum likelihood estimate of the species tree was accompanied by aLRT branch supports, while summary coalescent inference was accompanied by local posterior probabilities (Sayyari and Mirarab 2016). The decisiveness of the data regarding the phylogenetic signals was examined using gene- and site-concordance factors, calculated in IQ-TREE v2 (Minh et al. 2020).

Bayesian molecular dating analysis was performed using MCMCtree in PAML v4.8 (Yang 2007), assuming the reconstructed species tree from ASTRAL-III and using the genomic regions with gene trees concordant with the species tree (see Supplementary information for further details). Data were partitioned by codon positions, each modelled under individual GTR+Γ substitution models. We used an uncorrelated gamma prior on rates across lineages and a birth-death prior for divergence times. Fossil calibrations included (i) the split between Caniformes and Feliformes using the age of the oldest known fossil of the family Viverravidae (65 – 50Mya; Wang and Tedford 2008; (ii) the split between Canidae and other Caniformes using a fossil of the genus *Amphicticeps* (32.8 – 30.4Mya; Wang et al. 2005; (iii) the split between Pinnipedia and Musteloidea using fossils of stem musteloids of the genus *Mustelictis* (32.8 – 23.3Mya; Wang et al.

2005; Rybczynski et al. 2009; and (iv) the split between the pinnipeds *Odobenus* and *Mirounga*, using a fossil of the genus Proneotherium (20.4 – 13.8Mya; Deméré et al. 2003). The posterior distribution was sampled every $1x10^3$ MCMC steps over $1x10^7$ steps, after a burn-in phase of $1x10^6$ steps. We verified convergence to the stationary distribution by comparing the results from two independent runs, and confirming that the effective sample sizes for all parameters were above 1000 using the R package coda (Plummer et al. 2006).

Positive selection on single-copy orthologs

To investigate genes under positive selection, the CDS sequences corresponding to 1:1 orthologs were aligned for the eight aforementioned carnivoran species. Multiple sequence alignments (MSAs) were constructed with PRANK v120716 (Löytynoja 2014), and 17 MSAs were subsequently filtered out due to the alignments being too short. The CODEML module in the PAML v4.5 package was used to estimate the ratio of non-synonymous to synonymous substitutions, also called d_N/d_S or ω (Yang 2007). We applied the one-ratio model to estimate the general selective pressure acting among all species, allowing only a single d_N/d_S ratio for all branches. A free-ratio model was also used to estimate the d_N/d_S ratio of each branch. Furthermore, the CODEML branch-site test for positive selection was performed on 6003 ortholog alignments for three separate foreground branches: *Eira barbara*, *Gulo gulo* and *Martes zibellina* (Zhang et al. 2005). Statistical significance was assessed using likelihood ratio tests (LRT) with a conservative 10% false discovery rate (FDR) criterion (Nielsen et al. 2005). Orthologs with a free-ratio > 2 in the branch model were considered for further analysis of signatures of positive selection.

To account for differences in genome assembly quality, we evaluated the alignments of selected orthologs based on the transitive consistency score (TCS), an extension to the T-Coffee scoring scheme used to determine the most accurate positions in MSAs (Chang et al. 2014). Additionally, alignments were visually inspected for potential low-scoring MSA portions. Orthologs passing all the filters and inspection were further explored for their putative functional and biological roles using literature sources and online databases, including OrthoDB v10 (Kriventseva et al. 2019), Uniprot (The UniProt Consortium 2017), and NCBI Entrez Gene (Maglott et al. 2011).

Gene family evolution

In order to make inferences regarding changes in gene family sizes, we constructed a matrix with counts of complete single-copy, complete duplicated, and missing orthologs identified through the BUSCO genome assembly completeness assessment of all eight carnivoran genomes. Orthologs were retained if they were detected in at least four species (including *Felis catus* as an outgroup) to obtain meaningful likelihood scores for the global birth and death (λ) parameter.

We used CAFE v4.2.1. (Han et al. 2013) to analyse gene gains ('birth') and losses ('death') accounting for phylogenetic history. First, we estimated the error distribution in our dataset, as genome assembly and annotation errors can result in biased estimates of the average rate of change (λ), potentially leading to an overestimation of λ.

Following the error distribution modelling, we ran the CAFE analysis guided by the ultrametric tree estimated earlier, calculating a single λ parameter for the whole species tree. The CAFE results were summarized (SI Table 4A) with the python script *cafetutorial_report_analysis.py* (https://github.com/hahnlab/CAFE). All identified expansions were in the form of gene duplications, with one putative triplication detected in tayra (SI Table S4B). Functional and biological roles associated with gained gene copies for each ortholog in the gulonine species were assessed using literature sources and online databases, including OrthoDB v10 (Kriventseva et al. 2019), Uniprot (The UniProt Consortium 2017), and NCBI Entrez Gene (Maglott et al. 2011).

Structural variation

We applied an ensemble approach for structural variant (SV) calling, encompassing three SV callers: Manta v1.6.0 (Chen et al. 2016), Whamg v1.7.0 (Kronenberg et al. 2015) and Lumpy v0.2.13 (Layer et al. 2014). SV calls originating from reads mapping in low complexity regions and having poor mapping quality were removed from all three call sets. We retained Manta calls with paired-read (PR) and split-read (SR) support of PR>=3 and SR>=3, respectively. To reduce the number of false positive calls, the Whamg call set was filtered for potential translocation events, as Whamg flags but does not specifically call translocations. We further removed Whamg calls with A < 10 (total pieces of evidence supporting the variant: PR, SR). We removed Lumpy calls with a low number of reads supporting the variant (SU) of SU < 10. All SV call sets were filtered based on genotype quality (GQ $\geq$ 30). Whamg and Lumpy SV call sets were genotyped

with Svtyper v0.7.1 (Chiang et al. 2015) prior to filtering. Only scaffolds assigned to chromosomes were included in further analyses. Survivor v1.0.7 (Jeffares et al. 2017) was used to merge and compare SV call sets within and among samples. The union set of SV calls among the three gulonine species containing species-specific and shared variants (Figure 1.) was annotated. First, Liftoff v1.5.1 (Shumate and Salzberg 2020) was used for preparation of reference genome annotation and Ensembl Variant Effect Predictor v101.0 (McLaren et al. 2016) for identifying variants affecting protein-coding genes.

Functional and biological roles of genes affected by SVs was explored using literature sources and online databases, including OrthoDB v10 (Kriventseva et al. 2019), Uniprot (The UniProt Consortium 2017), and NCBI Entrez Gene (Maglott et al. 2011). Gene ontology analysis was performed with Shiny GO (Ge et al. 2020) with an FDR < 0.05 for each SV type (excluding inversions) overlapping multiple protein-coding genes (> 5 genes).

Data availability

This whole genome shotgun project has been deposited in GenBank under the accession JAHRIG000000000-JAHRIH000000000. The version described in this paper is version JAHRIG01000000-JAHRIH010000000.

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Competing interests

Authors declare no competing interests.

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